Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med 2015;372:2087-96. DOI: 10.1056/NEJMoa1501184

EFFICACY OF AN ADJUVANTED HERPES ZOSTER SUBUNIT VACCINE IN OLDER ADULTS: A PHASE III RANDOMIZED CONTROLLED TRIAL

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This supplement contains the following items:

1. Original protocol (page 2), final protocol (including summary of changes) (page 144).
2. Original statistical analysis plans for safety (page 395) and efficacy (page 452), final statistical analysis plans for safety (page 421) and efficacy (including summary of changes) (page 476)

Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals
Rue de l'Institut 89, 1330 Rixensart, Belgium

Primary Study vaccine	GlaxoSmithKline Biologicals' Lyophilized formulation of the Herpes Zoster (HZ) vaccine (GSK1437173A)
eTrack study number and Abbreviated Title	110390 (ZOSTER-006)
Investigational New Drug (IND) number	BB-IND 13857
EudraCT number	2008-00367-42
Date of protocol	Final: 07 April 2010
Title	Efficacy, safety, and immunogenicity study of GSK Biologicals' Herpes Zoster vaccine GSK1437173A in adults aged ≥ 50 years.
Detailed Title	A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' gE/AS01$_B$ vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older.
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Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	110390 (ZOSTER-006)
IND number	BB-IND 13857
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Sponsor signatory	[redacted] Vice President, Global Clinical Development
Signature	_____
Date	_____

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Protocol Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational product(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorised representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	110390 (ZOSTER-006)
IND number	BB-IND 13857
EudraCT number	2008-00367-42
Date of protocol	Final: 07 April 2010
Detailed Title	A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' gE/AS01$_B$ vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older.
Investigator name	_____
Signature	_____
Date	_____
Leiter der klinischen Prüfung' (LKP) name	
Signature	_____
Date	_____

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SYNOPSIS

Detailed Title	A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' gE/AS01$_B$ vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older.
Indication	Primary immunization of subjects ≥ 50 years of age (YOA) against Herpes Zoster (HZ). The study population includes males and females without severely immunocompromising conditions in the age ranges 50-59 YOA, 60-69 YOA, 70-79 YOA and ≥ 80 YOA. The 70-79 YOA and ≥ 80 YOA strata will be combined for primary analyses.
Rationale for the study and study design	Two studies (ZOSTER-006 enrolling subjects ≥ 50 YOA and ZOSTER-022 enrolling subjects ≥ 70 YOA) will be conducted concurrently to evaluate efficacy of GlaxoSmithKline (GSK) Biologicals' gE/AS01$_B$ vaccine. Study ZOSTER-006 will provide pivotal data on the overall efficacy in prevention of HZ in subjects ≥ 50 YOA. The primary endpoint of this study will be overall HZ vaccine efficacy (VE) across all age cohorts. To this end, ZOSTER-006 will evaluate VE of the gE/AS01$_B$ vaccine compared to placebo in reducing the risk of developing HZ in subjects ≥ 50 YOA. This study will enrol subjects in the age ranges 50-59 YOA, 60-69 YOA, 70-79 YOA and ≥ 80 YOA in an 8:5:3:1 ratio to achieve comparable numbers of HZ in the 3 main age strata (50-59 YOA, 60-69 YOA and ≥ 70 YOA) so that a balanced estimate of the overall VE in persons ≥ 50 YOA can be determined. Apportionment of 25% of the ≥ 70 YOA cohort to persons ≥ 80 YOA ensures that this particularly vulnerable population is adequately represented. Assessment of Postherpetic Neuralgia (PHN) VE would require a large sample size of subjects ≥ 70 YOA due to a relatively lower incidence of PHN in younger adults. This cannot be achieved in study ZOSTER-006 without impacting the intent of the study, since a large overrepresentation of subjects ≥ 70 YOA in the ZOSTER-006 study would not allow an accurate assessment of HZ VE across the entire ≥ 50 YOA age range enrolled in the trial and may potentially underestimate overall efficacy of the gE/AS01$_B$ vaccine, since

HZ VE may diminish with age.

Study ZOSTER-022 will address VE against PHN in subjects ≥ 70 YOA, in addition to providing a robust estimate of HZ VE in that age stratum.

After each study (ZOSTER-006 and ZOSTER-022) is analyzed separately, a pooled analysis of HZ and PHN data from both studies combined is planned and will be described prospectively.

A saline solution is included as a negative control (placebo) in this study to evaluate the efficacy and safety profile of the candidate HZ vaccine. Use of the placebo control and the observer-blind, randomized study design, will allow to control for potential biases in the conduct of the study.

Objectives

Primary

- To evaluate VE in the prevention of HZ compared to placebo in adults ≥ 50 YOA, as measured by the reduction in HZ risk.

Secondary

- To evaluate VE in the prevention of HZ compared to placebo in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, as measured by the reduction in HZ risk;
- To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;
- To evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate VE in the reduction of overall and HZ-related mortality and hospitalizations compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;
- To evaluate VE in the reduction in incidence of HZ-associated complications compared to placebo in subjects ≥ 50 YOA and in subjects within each of the

following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;

- To evaluate VE in the reduction in use of pain medications compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate vaccine safety and reactogenicity.

Exploratory objectives

- To evaluate VE in reducing the severity of acute HZ-associated pain compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate VE in improving Quality of Life (QoL) compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate VE in the mitigation of Burden-Of-Illness (BOI) caused by HZ compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;
- To evaluate vaccine induced cell mediated and humoral immune responses and the persistence of each type of response after two injections of study vaccine in subjects ≥ 50 YOA, and by age strata;
- To evaluate anti-varicella-zoster virus (VZV) neutralizing antibody (Ab) titres in a subset of subjects at Month 0 (pre-vaccination), and at Months 3, 14, 26 and 38, in subjects ≥ 50 YOA, and by age strata.

Study design

- Experimental design: multicentre, parallel group
- Control: placebo (NaCl solution)
- Vaccination schedule: 0, 2 months
- Treatment groups: Treatment groups: 2 groups of subjects
  - Vaccine group (gE/AS01$_B$ vaccine)
  - Placebo group (NaCl solution as control)

- Study allocation: Eligible subjects 70-79 YOA and ≥ 80 YOA will be randomly assigned to ZOSTER-006 or ZOSTER-022 at Visit 1.
- Treatment allocation: Eligible subjects will be randomized to investigational vaccine/placebo according to a 1:1 ratio (vaccine:placebo). Subjects will be stratified by age: 50-59 YOA; 60-69 YOA; 70-79 YOA and ≥ 80 YOA in an 8:5:3:1 ratio. The 70-79 YOA and ≥ 80 YOA strata will be combined for primary analyses.
- Blinding: observer-blind
- Biological samples to be collected:

– Blood samples will be collected from all subjects at Visit 1 and 3 to contribute to the correlate of protection assessment should the subject experience a HZ episode or be selected as a case control.

– Blood samples will be collected from a subset of subjects at Visit 4, 5 and 6 to assess persistence of humoral immune response. In these subjects, the blood samples from Visit 1 and 3 will also be assessed for humoral immune response.

– Blood samples will be collected from a subset of subjects at Visit 1, 3, 4, 5 and 6 to assess cell-mediated immunogenicity (CMI) response.

– Clinical specimens of HZ lesions will be collected from subjects clinically diagnosed as having a suspected case of HZ.

- Type of study: Self-contained, and will be combined with study ZOSTER-022 for some analyses.
- Data collection: Remote Data Entry (RDE) on electronic Case Report Form (eCRF).
- Duration of the study: Each subject will be followed for at least 30 months after Dose 2. The cut-off date for final analysis will occur when both of the following conditions are met:

– The prespecified number of confirmed HZ and PHN cases in the modified Total Vaccinated cohort (mTVc) required for final analyses of both ZOSTER-006 and ZOSTER-022 are accrued;

– 75% of subjects (for both ZOSTER-006 and ZOSTER-022) have completed at least 36 months follow-up after Dose 2, and the remaining subjects

have completed at least 30 months follow-up after Dose 2.

All subjects will continue in the study at least until the cut-off date for final analysis regardless of their date of enrolment. Study end will take place when both conditions for final analysis are met and a minimum 90 days follow-up is completed for each HZ case that occurs up to the cut-off date for final analysis.

The exact duration of the study for individual subjects will vary. The maximum total study duration for each subject is expected to be 4 to 5 years.

If a delay of approximately 6 months or more is predicted prior to the simultaneous end dates for the two studies based on the rates of accumulation of HZ and PHN cases, then the first study that reaches the criteria for final analysis may be continued until the second study reaches the criteria for final analysis so that the two studies end concurrently.

Number of subjects

Target enrolment will be 15,980 eligible subjects (7,990 in the vaccine group and 7,990 in the placebo group).

Endpoints

Primary

- Confirmed HZ cases.
  - Confirmed HZ cases during the study in the mTVc.

Secondary

- Occurrence of overall PHN
  - Incidence of PHN calculated using the mTVc;
- Duration of severe 'worst' HZ-associated pain
  - Duration of severe 'worst' HZ-associated pain following the onset of a confirmed HZ rash over the entire pain reporting period as measured by the Zoster Brief Pain Inventory (ZBPI) in subjects with confirmed HZ;
- Incidence of overall and HZ-related mortality
  - Incidence of overall and HZ-related mortality during the study;
- Incidence of HZ complications
  - Incidence of HZ complications during the study in subjects with confirmed HZ;
- Incidence of overall and HZ-related hospitalizations

- Incidence of overall and HZ-related hospitalizations during the study;

- Duration of pain medication administered for HZ
  - Duration of pain medication administered for HZ during the study in subjects with confirmed HZ;

- Solicited local and general symptoms in a subset of subjects
  - Occurrence, intensity of each solicited local symptom within 7 days (Days 0-6) after each vaccination, in subjects included in the 7-day diary card subset;
  - Occurrence, intensity and relationship to vaccination of each solicited general symptom within 7 days (Days 0-6) after each vaccination, in subjects included in the 7-day diary card subset;

- Unsolicited adverse events (AEs)
  - Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days (Days 0 – 29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification in all subjects;

- Serious Adverse Events (SAEs)
  - Occurrence and relationship to vaccination of all SAEs from Month 0 to Month 14 in all subjects;
  - Occurrence of SAEs related to study participation or to a concurrent GSK medication/vaccine during the entire study period in all subjects;
  - Occurrence of any fatal SAEs during the entire study period in all subjects;

- Occurrence of pre-defined AEs
  - Occurrence and relationship to vaccination of any new onset of autoimmune diseases (NOADs) and other immune mediated inflammatory disorders during the entire study period in all subjects;

- Occurrence of medically attended visits
  - Occurrence and relationship to vaccination of medically attended visits (defined as hospitalizations, emergency room visits or visits to or from medical personnel), other than routine health care visits, from Month 0 to Month 8 in all subjects.

Exploratory endpoints

- Acute HZ severity
  - Acute HZ severity as determined by the mean Area Under Curve (AUC) of the severity-by-duration of HZ-associated pain as measured by the ZBPI during a 4-week period following the onset of confirmed HZ in subjects with confirmed HZ;
- Interference of HZ with QoL
  - Interference of HZ with QoL as measured by ZBPI in subjects with confirmed HZ;
  - Interference of HZ with QoL as measured by EQ-5D in subjects with confirmed HZ;
  - Interference of HZ with QoL as measured by SF-36 in subjects with confirmed HZ;
- HZ BOI
  - HZ BOI as determined by the mean AUC of the severity-by-duration HZ-associated pain during a 26 week period following the onset of the HZ rash in the mTVc;
- CMI in terms of frequencies of antigen-specific CD4 T cells at Months 0, 3, 14, 26 and 38
  - Frequencies of CD4 T cells with antigen-specific Interferon gamma (IFN-γ) and/or Interleukin-2 (IL-2) and/or Tumour Necrosis Factor alpha (TNF-α) and/or CD40 Ligand (CD40L) secretion/expression to glycoprotein E (gE) and VZV as determined by intracellular cytokine staining (ICS) in a subset of subjects at Months 0, 3, 14, 26 and 38;
- Antigen-specific Ab concentrations at Months 0, 3, 14, 26 and 38.
  - Anti-gE and anti-VZV Ab concentrations as determined by Enzyme-linked Immunosorbent Assay (ELISA), in a subset of subjects at Months 0, 3, 14, 26 and 38;
- Anti-VZV neutralizing Ab titres at Months 0, 3, 14, 26 and 38
  - Anti-VZV neutralizing Ab titres as determined by the neutralization assay in a subset of subjects at Months 0, 3, 14, 26 and 38.

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LIST OF ABBREVIATIONS

Ab	Antibody
AE	Adverse Event
$AS01_B$	MPL, QS21, liposome based Adjuvant System (50 µg MPL and 50 µg QS21)
$AS01_E$	MPL, QS21, liposome based Adjuvant System (25 µg MPL and 25 µg QS21)
ATPc	According To Protocol cohort
AUC	Area Under Curve
BOI	Burden-Of-Illness
CD40 L	CD40 Ligand
CI	Confidence Interval
CMI	Cell-Mediated Immunogenicity/immunity
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked Immunosorbent Assay
FDA	Food and Drug Administration, United States
GCP	Good Clinical Practice
gE	Glycoprotein E
GMC/T	Geometric Mean Concentration/Titres
GM	Geometric Mean
GSK	GlaxoSmithKline
HRPO	Horseradish Peroxidase
HSV	Herpes Simplex Virus
HZ	Herpes Zoster
HZAC	HZ Ascertainment Committee
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Intracellular Cytokine Staining
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	Interferon Gamma
IL-2	Interleukin-2

IM	Intramuscular/Intramuscularly
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine System
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimal Important Difference
mIU	Milli-International Unit
MPL	3-*O*-desacyl-4'-Monophosphoryl Lipid A
mTVc	Modified Total Vaccinated Cohort
NOAD	New Onset of Autoimmune Disease
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PHN	Postherpetic Neuralgia
PRNT	Plaque Reduction Neutralization Test
QALY	Quality Adjusted Life Years
QoL	Quality of Life
QS21	*Quillaja saponaria* Molina, fraction 21 (Antigenics, New York, NY, US)
RAP	Reporting and Analysis Plan
RDE	Remote Data Entry
SAE	Serious Adverse event
SAS	Statistical Analysis System
SBIR	Simply Better Internet Randomisation
SD	Standard Deviation
SDAC	Statistical Data Analysis Centre
SDRRA	Study Determination (Recruitment/Randomisation) Agreement
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPM	Study Procedures Manual
TNF-α	Tumour Necrosis Factor Alpha
TVc	Total Vaccinated Cohort
US	United States

VAS	Visual Analog Scale
VE	Vaccine Efficacy
VZV	Varicella-Zoster Virus
YOA	Years Of Age
ZBPI	Zoster Brief Pain Inventory

GLOSSARY OF TERMS

Adequate contraception: Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly (when applicable, as mentioned in the product label) for example abstinence, combined or progestogen oral contraceptives, injectable progestogen, implants of levonorgestrel, oestrogenic vaginal ring, percutaneous contraceptive patches or intrauterine device (IUD) or intrauterine system (IUS), vasectomy with documented azoospermia of the sole male partner or male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository) or male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

For azoospermia, 'documented' refers to the laboratory report of azoospermia, required for acceptable documentation of successful vasectomy in the subject's male partner.

Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Blinding: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an observer-blind study, the subject and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment allocation (see Section 5.4 for details on observer-blinded studies).

Burden-of-illness score: The HZ "Burden-Of-Illness (BOI) score" represents the average severity of illness among all subjects in the vaccine or placebo groups. It is calculated according to

	the "modified" scale described by Coplan [Coplan, 2004] as the sum of the HZ "severity-of-illness" scores of all members of the treatment group divided by the total number of subjects in the group.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 6.6.1 and 10.5 for details on criteria for evaluability).
Investigational vaccine/product: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. A NaCl solution, also referred to as saline is used as placebo in this study.
Menopause:	Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.
Protocol amendment:	ICH defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.

Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. NB Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Quality of Life	Quality of Life is measured, using three questionnaires (ZBPI, EQ-5D and SF-36) to be completed by the subject. ZBPI specifically assesses HZ-associated pain and discomfort during an HZ episode. EQ-5D and SF-36 provide multi-dimensional evaluation of the health status.
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	Adverse events (AEs) to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Study determination number:	A unique number that assigns subjects aged 70 years and older to either study ZOSTER-006 or ZOSTER-022.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the product(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.
Treatment number:	A number identifying a treatment to a subject, according to the study randomisation or treatment allocation.
Unsolicited adverse event:	Any adverse event (AE) reported in addition to those solicited during the clinical study. Also any ‘solicited’ symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

TRADEMARKS

The following trademarks are used in the present protocol.

Note: In the body of the Protocol (including the synopsis), the names of the vaccines/products and/or medications will be written in italic font and without the subscript symbol ™ or ®.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Varilrix™	Varicella vaccine consisting of live attenuated Varicella-zoster virus (Oka strain)

Trademarks not owned by the GlaxoSmithKline group of companies	Generic descriptions
Varivax® (Merck & Co)	Varicella vaccine consisting of live attenuated varicella-zoster virus (Oka strain)
Zostavax® (Merck & Co)	Herpes zoster vaccine consisting of high-titre live attenuated Varicella-zoster virus (Oka strain)
Enzygnost® (Dade Behring)	ELISA kit

1. INTRODUCTION

1.1. Background

Varicella-zoster Virus (VZV) causes two distinct diseases. Varicella (chickenpox) shortly occurs after primary VZV infection and is characterised by systemic illness and a widely disseminated rash. Herpes zoster (shingles) occurs when VZV reactivates from latency and typically manifests as a localised, dermatomal rash.

The typical herpes zoster (HZ) rash usually lasts 2 to 4 weeks and is usually accompanied by pain that is often described as burning, shooting, or stabbing. In some patients, even touching the affected area lightly may cause pain, a phenomenon known as allodynia. This HZ-associated pain may be severe, and pruritus, which can also be severe, may be as common as pain.

The most common complication of HZ is postherpetic neuralgia (PHN). PHN is defined as pain that persists after the resolution of the HZ rash. Affected patients typically report constant burning, throbbing, intermittent sharp or electric shock-like pain, or allodynia. Older age is a clear risk factor for PHN. Other risk factors may include a severe HZ rash and a painful HZ prodrome. PHN tends to improve over a period of months. About 70-80% of cases resolve within 1 year, however, in some persons PHN persists for many years [Dworkin, 2007].

Other complications of HZ include ophthalmologic, neurological, cutaneous and visceral disease, which can result in severe disability. The most common ocular complications of HZ are keratitis and uveitis; other ophthalmologic complications include ptosis, episcleritis/scleritis, retinitis, secondary glaucoma and cataract [Schmader, 2008; Carter, 2008]. Neurologic complications associated with HZ include myelitis, motor neuropathy, ischaemic infarction of the brain and spinal cord, aneurysm, and subarachnoid and cerebral haemorrhage [Gilden, 2009; Schmader, 2008].

Age is the most common risk factor for developing HZ. The incidence of HZ is relatively constant at 2-3 cases per 1000 persons per year until age 40, and then increases progressively with age: At 50-59 years of age (YOA) the incidence is about 5 cases per 1000 persons per year, and it increases to 10 cases per 1000 persons per year in people ≥ 60 YOA [CDC, 2008; Oxman, 2005]. While most HZ incidence data come from the United States (US) and Europe, available data indicate similar incidences of HZ in other parts of the world including Japan, Korea, Australia and Latin America [Araújo, 2007; Garcia Cenoz, 2008; Kang, 2008; Toyama, 2009].

Half of all HZ cases occur in patients over the age of 60, and individuals who reach 85 years old have a 50% chance of having HZ during their lifetime [Oxman, 2005]. The risk for PHN is also highest in older people with HZ, occurring in 18-50% of those aged 70 years and older [Oxman, 2005; Scott, 2006]. Patients with impaired cell-mediated immunity (CMI) due to disease, drug treatment, medical interventions or advanced age are at increased risk for the development of HZ [Cohen, 2007]. Since the loss of VZV-specific T cell responses as a result of aging or immunosuppression leads to heightened

susceptibility to HZ, vaccination is considered as a means to reduce the risk of HZ in older adults and immunocompromised persons [Oxman, 2005; Sperber, 1992].

The potential of vaccination to protect against HZ was evaluated in a large efficacy study in which *Zostavax* (a live attenuated HZ vaccine that is a high titre preparation of the varicella vaccine, *Varivax* [both manufactured by Merck & Co]) partially protected immunocompetent older adults against HZ [Oxman, 2005]. In the overall population (≥ 60 YOA), *Zostavax* reduced the incidence of HZ by 51.3% (p-value < 0.001), although its effectiveness decreased with the age of the vaccinee. In particular, vaccine efficacy (VE) diminished to 37.6% among persons in older age groups (≥ 70 years of age) [Oxman, 2005]. Based on the data from this study, *Zostavax* was licensed in the US and other countries. In the US, *Zostavax* is indicated for prevention of HZ in individuals ≥ 60 YOA and older [CDC, 2008]. In Australia, *Zostavax* is indicated for the prevention of HZ, PHN and for reduction of acute and chronic HZ-associated pain in individuals ≥ 60 YOA, and for the prevention of HZ in individuals 50-59 YOA [TGA, 2009]. In Europe, *Zostavax* is indicated for prevention of HZ and PHN in individuals ≥ 50 YOA [EMEA, 2009]. Z*ostavax* is contraindicated in persons with immunodeficiency due to malignancy, human immunodeficiency virus (HIV) infection or immunosuppressive medical therapy.

Although no immunological correlate for protection against HZ has been identified, current knowledge suggests that VZV-specific CMI is of primary importance in preventing HZ [CDC, 2008]. The role of humoral immune responses in preventing HZ is less clear. However, VZV-specific antibodies (Abs) may help control viral dissemination in immunocompromised persons and may thereby help limiting the severity of HZ. Furthermore, a correlation between post-vaccination anti-VZV Ab concentrations and protection against HZ was observed in the *Zostavax* efficacy study [Levin, 2008]. While VZV-specific Abs may not be directly protective against HZ, they may represent a "downstream" measure of the CMI response to vaccination.

GlaxoSmithKline (GSK) Biologicals is developing a candidate HZ vaccine consisting of VZV glycoprotein E (gE) and an adjuvant. The VZV gE was chosen as the subunit vaccine antigen because of both its prominence as a target for host immune responses [Cohen, 2007] and its functional significance during viral infection. Since the vaccine does not contain live virus, it is expected that this vaccine will prove safe in all populations including highly immunocompromised persons. Adjuvant System $AS01_B$ used in combination with the gE antigen was developed at GSK Biologicals, and contains the immunostimulants MPL (3-O-desacyl-4'-monophosphoryl lipid A) and QS21 (*Quillaja saponaria* Molina, fraction 21; Antigenics, New York, NY, US) formulated in combination with liposomes. MPL is a chemically detoxified form of the parent lipopolysaccharide from the gram negative bacterium *Salmonella minnesota*. QS21 is a natural saponin molecule (triterpene glycoside) obtained from the tree bark of *Quillaja saponaria* Molina.

Three recently completed trials in healthy older adults have provided clinical evidence for the immunogenicity and tolerability of GSK Biologicals' candidate HZ vaccine, $gE/AS01_B$.

- In a phase I/II exploratory trial (Explo CRD-004), 155 subjects received two doses of either gE/AS01$_B$, gE/AS01$_B$ and *Varilrix* (a live attenuated varicella vaccine similar to *Zostavax*), or *Varilrix* alone. Of the 110 subjects who received gE/AS01$_B$, 90 were 50-70 YOA (the other 20 subjects were 18-30 YOA). Subjects in the gE/AS01$_B$ groups developed significantly higher CD4 T cell responses to gE and VZV than those in the *Varilrix* alone group. Immune responses persisted up to 40 months after administration of the second vaccination in older adults receiving gE/AS01$_B$ alone (the latest timepoint evaluated). Reactogenicity was higher in the gE/AS01$_B$ groups than in the group that received *Varilrix* alone; however, the incidences of grade 3 local and general symptoms were low. Based on the results of this study, gE/AS01$_B$, without *Varilrix*, was selected for further clinical evaluation.

- In a phase II dose finding trial (ZOSTER-003), gE/AS01$_B$ was administered to 714 adults ≥ 60 YOA. Subjects received either 2 doses of either 25 µg, 50 µg or 100 µg gE adjuvanted with AS01$_B$, one dose of 100 µg gE adjuvanted with AS01$_B$ and one of NaCl solution [Saline], or 2 doses of 100 µg gE/Saline (no adjuvant). Subjects in all gE/AS01$_B$ dose groups (660 total) developed significantly higher CD4 T cell and humoral immune responses to gE than did those who received unadjuvanted gE. Also, 2 vaccinations with any of the gE/AS01$_B$ vaccine formulations elicited higher immunological responses than a single dose. Comparison between the 25 µg, 50 µg and 100 µg gE/AS01$_B$ vaccine formulations administered in a 2 dose schedule demonstrated that humoral immune responses to 50 µg gE/AS01$_B$ were significantly greater than those induced by 25 µg gE/AS01$_B$, whereas 100 µg gE/AS01$_B$ was not superior to 50 µg gE/AS01$_B$. In addition, cellular immune responses to gE/AS01$_B$ vaccines exhibited slight dose dependence in favour of higher gE doses. Reactogenicity was similar for 25 µg, 50 µg, and 100 µg gE/AS01$_B$ formulations, but greater than that induced by 100 µg gE/Saline. Overall, vaccine safety and tolerability were acceptable in all gE/AS01$_B$ vaccine groups. Based on these data, the antigen dose of 50 µg gE combined with AS01$_B$ and administered as two doses was selected for use in future trials.

- In a phase II adjuvant dose comparison trial (ZOSTER-010), 410 adults ≥ 50 YOA received two doses of 50 µg gE adjuvanted with AS01$_B$, AS01$_E$ (½ dose of AS01$_B$) or no adjuvant (gE/Saline), or saline alone, administered on a 2-dose schedule at months 0 and 2. The objective of this study was to compare the immunogenicity and safety of gE/AS01$_B$ and gE/AS01$_E$ groups. Analysis of data obtained up to Month 3 (one month after dose 2) is currently available; an extended safety follow-up is ongoing. Subjects in the gE/AS01$_B$ group had 30% superior cellular immune responses and 40% superior antigen-specific humoral immune responses compared to the gE/AS01$_E$ group, which were both statistically significant differences. Local and general reactogenicity were common in both the gE/AS01$_B$ and gE/AS01$_E$ groups; however, approximately 11% more doses of gE/AS01$_B$ were associated with local or general reactogenicity than gE/AS01$_E$ doses. The overall incidence of grade 3 local and general reactions was low for both vaccines, and similar between the gE/AS01$_B$ and gE/AS01$_E$ groups. No related serious adverse events (SAEs) were reported

in either the gE/AS01$_B$ or gE/AS01$_E$ groups. Based on these results, AS01$_B$ was chosen for the final vaccine formulation, in combination with 50 μg gE, to be used in future studies.

Please refer to the current Investigator Brochure (IB) for a review of the pre-clinical and clinical studies, and the potential risks and benefits of GSK Biologicals' candidate HZ vaccine.

1.2. Rationale for the study and study design

Two studies (ZOSTER-006 enrolling subjects ≥ 50 YOA and ZOSTER-022 enrolling subjects ≥ 70 YOA) will be conducted concurrently to evaluate efficacy of GSK Biologicals' gE/AS01$_B$ vaccine.

Study ZOSTER-006 will provide pivotal data on the overall HZ VE. The primary endpoint of this study will be overall HZ VE across all age cohorts. To this end, ZOSTER-006 will evaluate VE of the gE/AS01$_B$ vaccine compared to placebo in reducing the risk of developing HZ in subjects ≥ 50 YOA. This study will enrol subjects in the age ranges 50-59 YOA, 60-69 YOA, 70-79 YOA and ≥ 80 YOA in an 8:5:3:1 ratio to achieve comparable numbers of HZ cases in the 3 main age strata (50-59 YOA, 60-69 YOA and ≥ 70 YOA; the 70-79 YOA and ≥ 80 YOA strata will be combined for primary analyses) so that a balanced estimate of the overall VE in persons ≥ 50 YOA can be determined. Apportionment of 25% of the ≥ 70 YOA cohort to persons ≥ 80 YOA ensures that this particularly vulnerable population is adequately represented.

Assessment of PHN VE would require a large sample size of subjects ≥ 70 YOA due to a relatively lower incidence of PHN in younger adults. This cannot be achieved in ZOSTER-006 without impacting the intent of the study, since a large overrepresentation of subjects ≥ 70 YOA in the ZOSTER-006 study would not allow an accurate assessment of HZ VE across the entire ≥ 50 YOA age range enrolled in the trial and may potentially underestimate overall efficacy of the gE/AS01$_B$ vaccine, since HZ VE may diminish with age. Study ZOSTER-022 will address VE against PHN in subjects ≥ 70 YOA, in addition to providing a robust estimate of HZ VE in that age stratum. After each study (ZOSTER-006 and ZOSTER-022) is analyzed separately, a pooled analysis of HZ and PHN data from both studies combined is planned and will be described prospectively. Detailed information regarding study ZOSTER-022 and the pooled analysis of data of both studies combined will be included in the protocol of study ZOSTER-022.

A saline solution is included as a negative control (placebo) in this study and provides an objective baseline for the evaluation of the efficacy and safety profile of the candidate HZ vaccine. Use of the placebo control and the observer-blind, randomized study design, will allow to control for potential biases in the conduct of the study.

2. OBJECTIVES

2.1. Primary objective

- To evaluate VE in the prevention of HZ compared to placebo in adults ≥ 50 YOA, as measured by the reduction in HZ risk.

Refer to Section 10.1 for the definition of the primary endpoint.

2.2. Secondary objectives

- To evaluate VE in the prevention of HZ compared to placebo in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, as measured by the reduction in HZ risk;
- To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;
- To evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate VE in the reduction of overall and HZ-related mortality and hospitalizations compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;
- To evaluate VE in the reduction in incidence of HZ-associated complications compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate VE in the reduction in use of pain medications compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate vaccine safety and reactogenicity.

Refer to Section 10.2 for the definition of the secondary endpoints.

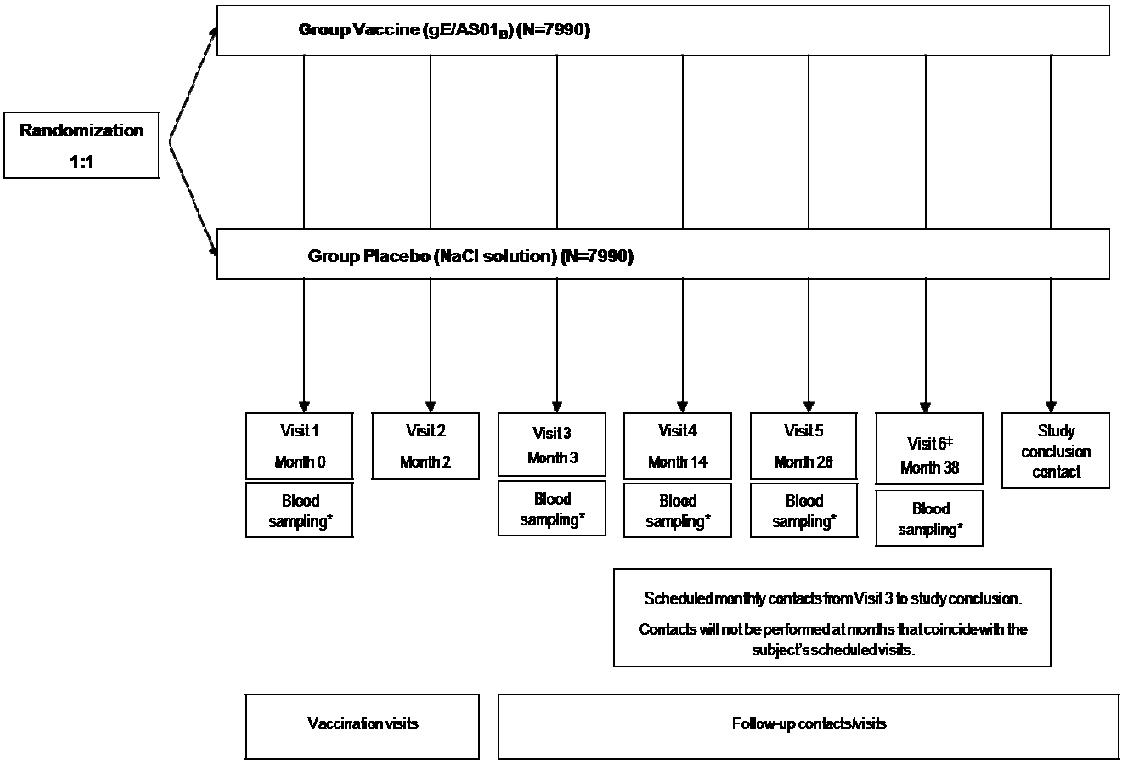
2.3. Exploratory objectives

- To evaluate VE in reducing the severity of acute HZ-associated pain compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;

- To evaluate VE in improving Quality of Life (QoL) compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate VE in the mitigation of Burden-Of-Illness (BOI) caused by HZ compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;
- To evaluate vaccine induced cell mediated and humoral immune responses and the persistence of each type of response after two injections of study vaccine in subjects ≥ 50 YOA, and by age strata;
- To evaluate anti-VZV neutralizing Ab titres in a subset of subjects at Month 0 (pre-vaccination), and at Months 3, 14, 26 and 38, in subjects ≥ 50 YOA, and by age strata.

Refer to Section 10.3 for the definition of the exploratory endpoints.

3. STUDY DESIGN OVERVIEW



* Blood samples will be collected from all subjects at Visit 1 and Visit 3, and from subsets of subjects additionally at the other visits to assess immune responses.
‡ If the conditions for final analysis and study end are met before Visit 6 is completed by all subjects and it is decided to conclude the study, Visit 6 may not take place in some subjects.
Note: In case of suspected HZ, the subject will have additional visits and contacts for follow-up of HZ (see Table 3).

- Experimental design: multicentre, parallel group
- Control: placebo (NaCl solution)

- Vaccination schedule: 0, 2 months
- Treatment groups: Treatment groups: 2 groups of subjects
  - Vaccine group (gE/AS01$_B$ vaccine)
  - Placebo group (NaCl solution as control)
- Study allocation: Eligible subjects 70-79 YOA and ≥ 80 YOA will be randomly assigned to ZOSTER-006 or ZOSTER-022 at Visit 1.
- Treatment allocation: Eligible subjects will be randomized to investigational vaccine/placebo according to a 1:1 ratio (vaccine:placebo). Subjects will be stratified by age: 50-59 YOA; 60-69 YOA; 70-79 YOA and ≥ 80 YOA in an 8:5:3:1 ratio. The 70-79 YOA and ≥ 80 YOA strata will be combined for primary analyses.
- Blinding: observer-blind
- Biological samples to be collected:
  - Blood samples will be collected from all subjects at Visit 1 and 3 to contribute to the correlate of protection assessment should the subject experience a HZ episode or be selected as a case control.
  - Blood samples will be collected from a subset of subjects at Visit 4, 5 and 6 to assess persistence of humoral immune response. In these subjects, the blood samples from Visit 1 and 3 will also be assessed for humoral immune response.
  - Blood samples will be collected from a subset of subjects at Visit 1, 3, 4, 5 and 6 to assess CMI response.
  - Clinical specimens of HZ lesions will be collected from subjects clinically diagnosed as having a suspected case of HZ.
- Type of study: Self-contained, and will be combined with study ZOSTER-022 for some analyses.
- Data collection: Remote Data Entry (RDE) on electronic Case Report Form (eCRF).
- Duration of the study: Each subject will be followed for at least 30 months after Dose 2. The cut-off date for final analysis will occur when both of the following conditions are met:
  - The prespecified number of confirmed HZ and PHN cases in modified Total Vaccinated cohort (mTVc) required for final analyses of both ZOSTER-006 and ZOSTER-022 are accrued;
  - 75% of subjects (for both ZOSTER-006 and ZOSTER-022) have completed at least 36 months follow-up after Dose 2, and the remaining subjects have completed at least 30 months follow-up after Dose 2.

All subjects will continue in the study at least until the cut-off date for final analysis regardless of their date of enrolment. Study end will take place when both conditions

for final analysis are met and a minimum 90 days follow-up is completed for each HZ case that occurs up to the cut-off date for final analysis.

The exact duration of the study for individual subjects will vary. The maximum total study duration for each subject is expected to be 4 to 5 years.

If a delay of approximately 6 months or more is predicted prior to the simultaneous end dates for the two studies based on the rates of accumulation of HZ and PHN cases, then the first study that reaches the criteria for final analysis may be continued until the second study reaches the criteria for final analysis so that the two studies end concurrently.

4. STUDY COHORT

4.1. Number of subjects/centres

Study ZOSTER-006 will be an international multicentre trial.

Target enrolment is approximately 16,000 eligible subjects using a 1:1 randomization ratio (vaccine:placebo).

Refer to Section 10.4 for a detailed description of the criteria used in the estimation of sample size.

The following subsets of subjects will be included in this study (see Table 1). Details regarding the number of subjects included in each of the subsets are described in Sections 10.4.5.5 and 10.4.5.6. The randomization of subjects to subsets is described in Section 5.3.4.

Table 1 Subsets in study ZOSTER-006

Subset name	Description
7-day diary card	Diary card completion for recording of solicited adverse events (AEs) (from Day 0 to Day 6 after each vaccination)
Immunogenicity	Blood samples (approximately 10 mL) collected at Visit 1, 3, 4, 5 and 6 will be analyzed to assess humoral immune response
CMI	Blood samples (approximately 20 mL) collected at Visit 1, 3, 4, 5 and 6 will be analyzed to assess CMI response

Note: Blood samples (approximately 10 mL) will be collected from all subjects at Visits 1 and 3, and will be used to assess correlate of protection.

Overview of the recruitment plan

Study ZOSTER-006 is planned to be conducted at sites in multiple countries in North America, Europe, Latin America and Australasia.

The recruitment rate will be monitored using a study specific central randomization system on internet (SBIR). Prior to randomization within each study, a SBIR distribution application will be used to assign subjects 70-79 YOA and ≥ 80 YOA to either ZOSTER-006 or ZOSTER-022.

Transfer of supplies will be tracked by the central randomization system. Monitoring visits frequency will be adapted to the pace of enrolment. Enrolment is estimated to last for approximately 12 months.

Vaccine doses will be distributed to each study site respecting the randomization block size. In addition, SBIR will account for the number of subjects in each age stratum (Section 5.3.3.2).

In case any countries would fall behind in subject recruitment (in a specific age group or overall), a redistribution of the enrolment target per country may be made to allow other participating countries to enrol additional subjects in an effort to ensure full and timely enrolment of the overall targeted number of subjects specified in this protocol.

4.2. Inclusion criteria for enrolment

All subjects must satisfy ALL the following criteria at study entry:

- Subjects who the investigator believes will comply with the requirements of the protocol (e.g. completion of the diary cards/questionnaires, return for follow-up visits, have regular contact to allow evaluation during the study);
- Written informed consent obtained from the subject;
- A male or female aged 50 years or older at the time of the first vaccination;
- Female subjects of non-childbearing potential may be enrolled in the study;

  For this study population, non-childbearing potential is defined as current tubal ligation, hysterectomy, ovariectomy or post-menopause.

  Please refer to the Glossary of Terms for the definition of menopause.

  OR

  Female subjects of childbearing potential may be enrolled in the study, if the subject has practiced adequate contraception for 30 days prior to vaccination, and has a negative urine pregnancy test on the day of vaccination, and has agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the vaccination series;

  Please refer to the Glossary of Terms for the definition of adequate contraception

4.3. Exclusion criteria for enrolment

The following criteria should be checked at the time of study entry. If **ANY** exclusion criterion applies, the subject must not be included in the study:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine, or planned use during the study period;

- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational product (pharmaceutical product or device);
- Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., malignancy, HIV infection) or immunosuppressive/cytotoxic therapy (e.g., medications used during cancer chemotherapy, organ transplantation or to treat autoimmune disorders);
- History of HZ;
- Previous vaccination against varicella or HZ (either registered product or participation in a previous vaccine study, and including previous vaccination with childhood varicella vaccine);
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine. Additionally, consider allergic reactions to other material or equipment related to study participation (such as materials that may possibly contain latex -gloves, syringes, etc). Please note, the vaccine and vials in this study do not contain latex;
- Significant underlying illness that in the opinion of the investigator would be expected to prevent completion of the study (e.g., life-threatening disease likely to limit survival to less than 4 years);
- Receipt of immunoglobulins and/or any blood products within the 90 days preceding the first dose of study vaccine or planned administration during the study period;
- Administration or planned administration of any other immunizations within 30 days before the first or second study vaccination or scheduled within 30 days after study vaccination. However, licensed non-replicating vaccines (i.e., inactivated and subunit vaccines, including inactivated and subunit influenza vaccines, with or without adjuvant for seasonal or pandemic flu) may be administered up to 8 days prior to each dose and/or at least 14 days after any dose of study vaccine;
- Any other condition (e.g., extensive psoriasis, chronic pain syndrome, cognitive impairment, severe hearing loss) that, in the opinion of the investigator, might interfere with the evaluations required by the study;
- Acute disease and/or fever at the time of enrolment;
  - Fever is defined as temperature ≥ 37.5°C (99.5°F) on oral, axillary or tympanic setting, or ≥ 38.0°C (100.4°F) on rectal setting. The preferred route for recording temperature in this study will be oral.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.
- Chronic administration (defined as > consecutive 15 days) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose. For corticosteroids, this will mean prednisone < 20 mg/day, or equivalent, is allowed. Inhaled and topical steroids are allowed.

- Pregnant or lactating female;
- Female planning to become pregnant or planning to discontinue contraceptive precautions (if of childbearing potential);

A list of criteria that will eliminate subjects from According To Protocol (ATP) analyses can be found in Section 6.6.1, Section 6.7 and Section 10.5.

5. CONDUCT OF THE STUDY

5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will also be conducted in accordance with the International conference on harmonisation (ICH) Guideline for Good Clinical Practice (GCP), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written (or witnessed thumb printed consent in case of an illiterate subject) informed consent must be obtained from each subject prior to participation in the study.

GSK Biologicals will prepare a model ICF which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to

GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

5.2. Study Determination (Recruitment/Randomisation) Agreement

Eligible subjects 70-79 YOA and ≥ 80 YOA will be randomly assigned to ZOSTER-006 or ZOSTER-022 at Visit 1. Prior to study assignment, these subjects must sign a Study Determination (Recruitment/Randomisation) Agreement (SDRRA). The signing of the SDRRA is not a consent or confirmation of the subject's participation in either study. The SDRRA allows the sponsor/study staff to collect limited personal information about a subject who has been contacted to participate in a clinical study. By signing the SDRRA, the subject enables the study staff to input age information into the SBIR system. The SBIR system will review current enrolment in the two age strata in both ZOSTER-006 and ZOSTER-022 and determine the study assignment for the subject. The subject will then be provided with the study specific informed consent to review and determine if they wish to participate in the assigned study. The first study related activity/procedure other than the study determination randomisation procedure may only be carried out after the subject has confirmed willingness to participate in the assigned study and signed an informed consent form.

5.3. Subject identification and randomization of treatment

All subjects 50-69 YOA will be randomized to vaccine or placebo in ZOSTER-006. Subjects 70-79 YOA and ≥ 80 YOA will be randomized to either ZOSTER-006 or ZOSTER-022, and then randomized to vaccine or placebo. This procedure ensures the compatibility of the ≥ 70 YOA subjects between the two studies and facilitates the pooled evaluation of both studies for HZ and PHN episodes. All subjects in ZOSTER-006 will be randomly assigned to two treatment groups in a 1: 1 ratio.

5.3.1. Study identification

ZOSTER-006 and ZOSTER-022 are similar studies, differing essentially in the age strata recruited. A SBIR study determination application will use a study determination number to assign subjects 70-79 YOA and ≥ 80 YOA to either ZOSTER-006 or ZOSTER-022. Subjects 50-69 YOA can only be assigned to ZOSTER-006.

5.3.2. Subject identification

Subject numbers will be assigned sequentially to subjects consenting to participate in the study, according to the range of subject numbers allocated to each study centre.

5.3.3. Randomization of treatment

5.3.3.1. Randomization of supplies

The randomisation will be performed at GSK Biologicals, Belgium, using MATEX, a program developed for use in SAS® (Cary, NC, US) by GSK Biologicals.

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centres in this multicentre study, and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.

The vaccine doses will be distributed to each study centre, respecting the randomization block size.

5.3.3.2. Treatment allocation to the subject

The treatment allocation at the investigator site will be performed using a central randomization system on the internet (SBIR). The treatment numbers will be allocated by kit. Within ZOSTER-006, the randomization algorithm will use stratification (preventing further randomization when a stratum is complete) and weighted minimization techniques for each parameter, below:

- By region: Stratification
- By age cohort within each region: Stratification
- By country within each region: Minimization
- By site within each country: Minimization

Note that as soon as the target number of subjects in a specific stratification group has been reached the recruitment will be frozen for that age group.

When SBIR is not available, please refer to SBIR user guide or Study Procedures Manual (SPM) for specific instructions.

After having checked the eligibility of the subject and obtaining the signed ICF, the site staff in charge of the vaccination will access SBIR.

Upon providing the subject identification number, the randomization system will use stratification and minimization algorithms to determine the treatment number to be used for the subject. The treatment number must be recorded in the eCRF on the Vaccine Administration screen (Randomization/Treatment Allocation Section).

5.3.4. Randomization of subjects to assay subsets

Subjects from 50-59 YOA and 60-69 YOA strata will be randomly allocated to be part of the 7-day diary card subset (note: all subjects from ≥ 70 YOA strata will be included in the 7-day diary card subset) according to criteria defined in Section 10.4.5.5. Subjects will be randomly allocated to be part of the Immunogenicity subset according to criteria

defined in Section 10.4.5.6. For operational reasons, the same subjects may be randomized to the various subsets.

The CMI analyses will be performed in the randomly selected Immunogenicity subset in three countries (Czech Republic, Japan and United States) at designated sites that have access to a Peripheral Blood Mononuclear Cells (PBMC) processing facility within the acceptable time window from sample collection to PBMC processing.

5.4. Method of blinding

Because the reconstituted gE/AS01$_B$ study vaccine differs in appearance from the NaCl solution placebo, the study will be conducted in an observer-blind manner.

Data will be collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccine/placebo recipient and those responsible for the evaluation of any study endpoint (e.g., safety, reactogenicity, and efficacy) will all be unaware of which vaccine/placebo was administered. To do so, vaccine/placebo preparation and administration will be done by authorised medical personnel who will not participate in the clinical evaluation of the subjects. Immunological data, which could lead to the unblinding of the treatment groups, will not be available during the course of the trial to any investigator or any person involved in the clinical conduct of the study (including data cleaning), until after the database is locked. Immunological data may however be available to the Statistical Data Analysis Centre (SDAC) and Independent Data Monitoring Committee (IDMC) in order to answer potential questions related to safety, efficacy or presence of correlate of protection during the interim analysis.

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

5.5. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

5.5.1. Data collection

Starting at Visit 3 monthly contacts between the subjects and the investigator and/or his delegate will take place to collect information on any event of interest that may have occurred [see Table 2 and Section 5.7.3.14 for details]. The contacts will not take place at months that coincide with the subject's scheduled study visits. Also, subjects with clinically diagnosed suspected HZ will be contacted periodically as outlined in Table 3. The contacts will take place using the most convenient method suited for the sites (e.g., telephone calls by site staff or designee, or SMS text messages through a call centre, or visit by the study staff to the subject's home). A guidance document outlining the

information that needs to be collected at each contact will be provided to each country, and will serve as a guidance to develop the local script. The logistic details on the set-up of the contacts will be documented by each site/country. At each contact, the subjects will respond to a standard set of questions in a language that is understandable to them. The investigator and/or his delegate will transcribe the relevant information on any event of interest in the appropriate section of the subject's eCRF, in English. In case of ongoing HZ, subjects will also be reminded to complete Zoster Brief Pain Inventory (ZBPI), EQ-5D and SF-36 questionnaires.

The diary cards and/or questionnaires to be completed will be distributed and explained by the investigator or his/her delegate. Any supplied diary cards or questionnaires should be preferably completed by the subject themselves. In case of difficulty in self-completion of the diary cards or questionnaires, an aide (such as a family member or care provider who is not involved in the study) may provide assistance with reading the questions and/or transcribing the subject's responses on the questionnaires and/or diary cards. When the completed diary cards and/or questionnaires are returned to the study staff, the study staff will ask the subject (at the time of return or at subsequent contact) if he/she received any assistance in completing diary cards or questionnaires. If the subject had assistance completing the diary card and/or questionnaires, it should be noted in the eCRF.

For all subjects:

- **30-day diary cards:** To be completed by all subjects for unsolicited AEs (from Day 0 to Day 29 after each vaccination) and any concomitant medication and vaccination taken from Day 0 to Day 29 after each vaccination.
- **EQ-5D and SF-36 questionnaires:** To be completed by all subjects at study entry. Also, to be completed by all subjects at Visits 4, 5 and 6 (subjects with an ongoing HZ episode will follow a weekly schedule and do not need to additionally complete the questionnaires at these visits).

EQ-5D and SF-36 will remain as source documents. The information from these questionnaires will only be transcribed into the eCRF for subjects who have confirmed HZ during the study.

For subjects in the 7-day diary card subset (in addition to the above):

- **7-day diary card:** To be completed by subjects to record solicited AEs (from Day 0 to Day 6 after each vaccination).

For all subjects in case of a suspected or confirmed case of HZ:

- **HZ-specific diary card:** To be completed by subjects who develop symptoms suggestive of HZ beginning immediately upon development of these symptoms and prior to visiting the study site for evaluation of the suspected HZ.
- **Zoster Brief Pain Inventory (ZBPI) questionnaire:** To be completed by subjects with clinically diagnosed suspected HZ on Day HZ-0 (Visit HZ-1) and daily from Day HZ-1 (day after the Visit HZ-1) up to Day HZ-28, and weekly

from Day HZ-29 onwards until the case of suspected HZ is disproved, OR until a 4-week pain-free period is documented, OR until the cut-off date for final analysis. For all subjects with HZ-associated pain, ZBPI data will be collected until at least Day HZ-90, regardless of the cut-off date for final analysis.

- **EQ-5D and SF-36 questionnaires**: To be completed weekly by the subjects with clinically diagnosed suspected HZ from Day HZ-0 onwards until the case of clinically diagnosed suspected HZ is disproved, OR until a 4-week pain-free period is documented, OR until the cut-off date for final analysis. For all subjects with HZ-associated pain, EQ-5D and SF-36 data will be collected until at least Day HZ-90, regardless of the cut-off date for final analysis.

5.5.2. Evaluation and confirmation of suspected and confirmed HZ cases

5.5.2.1. Definitions

A suspected case of HZ is defined as new unilateral rash accompanied by pain (broadly defined to include allodynia, pruritus or other sensations) and no alternative diagnosis.

Subjects clinically diagnosed as having a suspected case of HZ by the investigator will be referred to as a case of 'clinically diagnosed suspected HZ', and followed up. If a case is not clinically diagnosed as suspected HZ, the investigator should not progress further with evaluation of the case. Also refer to Section 5.5.2.2.

Determination of confirmed cases of HZ for efficacy analyses is provided in Section 5.5.2.3.

The HZ onset date is the earlier of the following two events: 1) the HZ rash start date; or 2) the date on which pain at the site of a subsequent HZ rash is first noted. The HZ onset date will be confirmed by the investigator and recorded in the eCRF.

PHN is defined by the presence of HZ-associated severe 'worst' pain persisting or appearing more than 90 days after onset of the HZ rash. Severe 'worst' pain is defined as HZ-associated pain rated as 3 or greater on the "worst pain" ZBPI question. Alternative definitions of PHN, based on duration of pain of 30, 60, 120 and 180 days will also be used for reporting purposes.

Cessation of pain to assess duration of HZ-associated pain: A 28-day pain-free period is used to confirm cessation of HZ-associated pain. If that pain-free period is not achieved or if pain did not cease, the time-to-event will be censored at the last day of HZ-associated pain.

Acute pain is defined as pain measured during the 4-week period following the onset of confirmed HZ.

5.5.2.2. Evaluation of suspected case of HZ

All HZ cases that occur during the study period up to the cut-off date for final analysis will be followed and evaluated. Any HZ cases that occur after the cut-off date for final analysis will be recorded in the study database and referred to the local physician for follow-up.

Any symptom/sign suggestive of HZ must be evaluated. At Visit 1, all subjects will be educated with regard to the signs and symptoms of HZ. The subjects are also given a HZ-specific diary card that they would complete with the date that rash and/or pain began. Subjects will be instructed to contact their study site immediately, and start completing the HZ-specific diary card if he/she develops any symptoms suggestive of HZ. The subjects will be asked to visit the study site (within 48 hours if possible) for evaluation of the "suspected case of HZ". The subject will be asked to bring the completed HZ-specific diary card when he/she visits the study site for evaluation of the suspected HZ. The investigator will perform a clinical examination when the subject visits the study site for the first evaluation of the suspected case of HZ [Visit HZ-1 at Day HZ-0]. If not considered a suspected HZ diagnosis, the investigator should not progress further with evaluation of this event as a HZ case for the purpose of this study. However, if meeting the definition of an AE/SAE (Section 8.1), the case should be handled as applicable (Section 8.3).

The schedule of visits/contacts that will take place for follow-up of clinically diagnosed suspected HZ cases is presented in Table 3.

For clinically diagnosed suspected HZ cases, the following will take place at Visit HZ-1:

- The investigator or his delegate will verify the completed HZ-specific diary card returned by the subject. The information from the diary card will be transcribed into the eCRF. The investigator or his delegate will record relevant information regarding the HZ episode in the eCRF (such as date of onset of pain and rash, date of clinical diagnosis of HZ, location and nature of HZ lesions, HZ-related complications if any). The HZ onset date will be confirmed by the investigator and recorded in the eCRF;
- The study staff/investigator will ask the subject to complete a ZBPI questionnaire at Visit HZ-1 to rate HZ-associated pain;
- The rash will be documented by digital photography;
- The study staff/investigator will record concomitant medication/vaccination, including concomitant medication for HZ treatment or any HZ-related complications (Section 6.6), and record intercurrent medical conditions (Section 6.7). If antiviral therapy is needed, it is recommended to use valacyclovir, acyclovir or famciclovir. Concomitant medication the subject has already received and/or will receive for HZ treatment will be recorded in the eCRF. The study staff/investigator will check if the subject received any medical attention [hospitalization, emergency room visit, or a visit to or from medical personnel (medical doctor)] for HZ or any HZ-related complication.

- Rash lesion samples (three replicate samples on the same day) will be collected from subjects clinically diagnosed as having a suspected case of HZ (Section 5.7.3.11);
- The subject will be given a supply of ZBPI, EQ-5D and SF-36 questionnaires. The ZBPI questionnaires will be used to collect information on the severity of HZ-associated pain, the duration of HZ-associated pain and rash, and the impact of the HZ episode on subject's QoL. The impact of HZ on subject's QoL will also be measured using the EQ-5D and SF-36 questionnaires (Section 7). The study staff/investigator will provide instructions to the subjects for completing the ZBPI, EQ-5D and SF-36 questionnaires and explain the importance of completing and returning the questionnaires to the site in order to provide more information on HZ.
- The subject will be asked to complete the ZBPI questionnaires daily from Day HZ-1 (day after the Visit HZ-1) up to Day 28, and weekly from Day HZ-29 onwards until:

– The case of clinically diagnosed suspected HZ is disproved; OR

– 28 days after HZ-associated pain ceases. The subject should continue to complete the ZBPI questionnaires weekly until a 28-day (or 4-week) pain free period is documented (i.e., '0' circled for item 3 of the ZBPI questionnaire at each assessment during that entire period); OR

– The cut-off date for final analysis. For all subjects with HZ-associated pain, ZBPI pain data will be collected until at least Day HZ-90, regardless of the cut-off date for final analysis;

If a subject with clinically diagnosed suspected HZ has not completed follow-up until at least Day HZ-90 at the cut-off date for final analysis, and the case is not disproved, follow-up for such a subject will continue until the Day HZ-90 follow-up is completed. The study conclusion for such a subject will thus occur after he/she completes Day HZ-90 follow-up.

The subjects will be asked to complete the EQ-5D and SF-36 questionnaires from Day HZ-0 and continued weekly during the entire period that the ZBPI questionnaires are completed.

After Visit HZ-1 until Visit HZ-7, visits/contacts will take place for follow-up of the HZ episode according to the schedule presented in Table 3.Follow-up of HZ-associated pain persisting beyond Visit HZ-7 or other complications will be done at monthly contacts between the subjects and the investigator and/or his delegate that are planned starting at Visit 3. If the case of clinically diagnosed suspected HZ is disproved, or if HZ-associated pain ceases (defined as a 28-day [or 4-week] pain free period), subsequent follow-up visits or contacts related to this case of HZ will be cancelled. The study staff/investigator will inform the subjects to stop completing the ZBPI, EQ-5D and SF-36 questionnaires and will provide instructions for the subject to return the completed questionnaires to the study site. Collection of subsequent HZ-related information will be stopped and no further information on that suspected HZ episode will be encoded in the clinical database. The following will take place at each visit or contact that occurs after Visit HZ-1:

- The study staff/investigator will: 1) record relevant information regarding the clinically diagnosed suspected HZ case (such as the location and nature of HZ lesions, HZ-related complications, if any); 2) record concomitant medications/vaccinations, including concomitant medication the subject has already received and/or will receive for HZ treatment or treatment of any HZ-related complications (Section 6.6); 3) record intercurrent medical conditions (Section 6.7); and 4) check if the subject received any medical attention [hospitalization, emergency room visit, or a visit to or from medical personnel (medical doctor)] for HZ or any HZ-related complication. Concomitant medication the subject has already received and/or will receive for HZ treatment will be recorded in the eCRF.
- The study staff/investigator will remind subjects to complete the ZBPI, EQ-5D and SF-36 questionnaires, and return the completed ZBPI, EQ-5D and SF-36 questionnaires to the study site according to the instructions given by the study staff/investigator. Once the completed ZBPI, EQ-5D and SF-36 questionnaires are available, the investigator will transcribe the information into the subject's eCRF. A new supply of ZBPI, EQ-5D and SF-36 questionnaires will be provided to the subjects as necessary.

5.5.2.3. Confirmation of suspected case of HZ

A suspected case of HZ can be confirmed in two ways:

- By Polymerase Chain Reaction (PCR):
  Rash lesion samples will be collected from subjects clinically diagnosed as having a suspected case of HZ. The samples will be transferred to GSK Biologicals or a validated laboratory designated by GSK Biologicals using standardised and validated procedures for laboratory diagnosis of HZ by PCR. Refer to Appendix A for details of PCR assay to be performed on HZ lesion samples. Refer to Appendix B for details of the PCR testing algorithm to classify suspected cases of HZ.
- By the HZ Ascertainment Committee:
  All cases of clinically diagnosed suspected HZ that cannot be confirmed or excluded by PCR [if the PCR specimen is inadequate (i.e., negative for both virus and β-actin DNA) or is missing] will be reviewed by the HZ Ascertainment Committee (HZAC). The HZAC will consist of three to five physicians with HZ expertise. HZAC members, participating as investigator in this study, will not evaluate cases from their own study site. HZAC members will be blinded to treatment assignments. For every such case, each reviewing HZAC member will be asked to make a clinical determination of whether the case is HZ based on review of the available clinical information (summary of the rash and pain evaluations, digital photographs of the subject's rash, and clinical progress notes). A unanimous diagnosis of "a confirmed case of HZ" or "not a case of HZ" will constitute a confirmed clinical diagnosis. HZAC members will discuss each non-unanimous case. A suspected case of HZ will be considered a "**clinically confirmed case of HZ**" if the majority of the HZAC members

concur; otherwise, it will be classified as "**not a case of HZ**". Further details will be provided in the HZAC charter.

5.5.2.4. Evaluation of severity of HZ-associated pain using the Zoster Brief Pain Inventory

The ZBPI is an assessment tool in the form of a questionnaire completed by the subject that is specifically designed to assess HZ-associated pain and discomfort during an HZ episode. The ZBPI also takes into account the effect of HZ treatment on subject's pain and the interference of HZ-associated pain with subject's QoL, and general health status. Previous studies have been shown that increasing HZ-associated pain scores are highly correlated with worsening of subject's QoL [Coplan, 2004; Schmader, 2007].

In each case of clinically diagnosed suspected HZ, the subjects will be asked to assess their HZ-associated pain and interference of HZ with their QoL by completing the ZBPI questionnaire either themselves or assisted, by an aide (Section 5.5.1) until the suspected case of HZ diagnosed is disproved, HZ-associated pain ceases (defined as a 28-day [or 4-week] pain free period) or until the cut-off date for final analysis (for all subjects with HZ-associated pain, ZBPI pain data will be collected until at least Day HZ-90, regardless of the cut-off date for final analysis). (Section 5.5.2.2).

Information on HZ-associated pain is derived from the ZBPI question: "Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours" (item 3), so called "worst pain" in this protocol.

The following outputs will be derived from the data recorded in the ZBPI: HZ Burden-Of-Illness (BOI) score and HZ severity score (Section 10.6.2).

5.5.2.5. HZ complications

The presence of HZ complications listed below will be documented in the eCRF at each contact/study visit, independently from the AE reporting. Any HZ complications, according to the definitions below, will be recorded by the investigator only in subjects with clinically diagnosed suspected HZ or confirmed HZ. If a recorded complication is associated with a case of clinically diagnosed suspected HZ, and that case of HZ is subsequently disproved, the associated complication will not be considered a complication of HZ.

HZ vasculitis	Vasculopathy or vasculitis (based on clinical, laboratory or radiologic findings) that is temporally associated with an episode of HZ and, in the opinion of the investigator, was caused directly by the VZV infection arising from the HZ episode.
Disseminated disease	Defined as ≥ 6 HZ lesions outside the primary dermatome as per the investigator's judgment.
Ophthalmic disease	Defined as HZ affecting any eye structure as per investigator's judgment.

Neurologic disease	Defined as cranial or peripheral nerve palsies, myelitis, meningoencephalitis, stroke, etc. that is temporally associated with an episode of HZ and, in the opinion of the investigator, was caused directly by VZV infection arising from the HZ episode.
Visceral disease	Defined as an abnormality of one or more internal organs (e.g., hepatitis, pneumonitis, gastroenteritis, etc.) that is temporally associated with an episode of HZ and, in the opinion of the investigator, was caused directly by VZV infection arising from the HZ episode.
Stroke	A diagnosis of stroke requires that criteria 1, 2 and 3 are fulfilled or criteria 1 and 4 and in the opinion of the investigator is temporally associated with an episode of HZ Criterion 1: Rapid onset of localising neurological deficit and/or change in level of consciousness; Criterion 2: Localising neurological deficit or change in level of consciousness that lasts greater than 24 hours; Criterion 3: No other cerebral process, peripheral lesion, or other disorder is the cause of the localising neurological deficit or change in level of consciousness; Criterion 4: CT scan or MRI scan evidence of an acute thrombotic or hemorrhagic lesion.

5.5.3. Independent Data Monitoring Committee

In order to ensure the safety of the subjects during the entire study period, an IDMC will be appointed to 1) monitor and follow-up the safety and tolerability of the subjects enrolled in the trial and 2) make recommendations to the sponsors concerning the continuation, modification, or termination of the trial.

An independent statistical team (i.e., not GSK employees), appointed by GSK Biologicals and not involved in the study management, will be unblinded to treatment assignment and provide all necessary tables, listings, figures and individual subject data to the IDMC. The IDMC will consist of four to six clinical experts, who are not participating in the study and an independent statistician.

The role of the IDMC will be to review the progress of the trial and the accumulating data to detect evidence of safety issues for the subjects while the trial is ongoing. The IDMC will be held to evaluate the safety assessments (e.g., AEs, SAEs, fatal events and withdrawals due to AEs) during the trial and make recommendations regarding continuation, modification or discontinuation of the study to the sponsor following each meeting.

The frequency of IDMC sessions and other operational details are described in the IDMC charter. The IDMC meetings will consist of an open session in which the conduct, recruitment and general baseline characteristics of the trial are presented, and a closed session in which the safety assessments by treatment group will be presented. The GSK Biologicals biostatistician and a member of the Zoster vaccine program will attend the IDMC meeting open sessions to immediately reply to any questions from the IDMC members. No GSK staff will participate in the closed sessions.

The IDMC may be also involved in evaluation of VE for futility analyses and prevent the continuation of a clinical study that already showed its inability to demonstrate the primary and main secondary endpoints. The futility rules will be described in the IDMC Charter.

The IDMC will review all safety parameters and efficacy data together before making a final recommendation. In case of a serious safety issue during the study, the sponsor will inform the IDMC expeditiously.

5.6. Outline of study procedures

Table 2 summarises the list of study procedures to be followed during the study visits and at the study conclusion contact. Table 3 summarises study procedures to be performed for the follow-up of each suspected HZ case.

Table 2 List of study procedures

Type of contact	VISIT 1	VISIT 2	VISIT 3	Monthly contacts[e]	VISIT 4	Monthly contacts[e]	VISIT 5	Monthly contacts[e]	VISIT 6[f]	Monthly contacts[e]	Study conclusion contact
Timepoints	**Day 0*/ Month0**	**Month 2**	**Month 3**		**Month 14**		**Month 26**		**Month 38**		
Sampling timepoints	**Pre-Vacc**	**Post-Vacc 1**	**Post-Vacc 2**		**Post-Vacc 2**		**Post-Vacc 2**		**Post-Vacc 2**		
SDRRA[a]	●										
Informed consent	●										
Check inclusion criteria	●										
Check exclusion criteria	●										
Check contraindications	●	●									
Medical history	●										
Physical examination	○										
Record demographic data	●										
Training on self-reporting by subjects[b]	○	○	○		○		○		○		
Urine pregnancy test[c]	●	●									
Pre-vaccination body temperature	●	●									
Blood sampling (approximately 10 mL) for Ab determination in all subjects	●		●								
Blood sampling (approximately 10 mL) for Ab determination in Immunogenicity subset subjects only					●		●		●		
Blood sampling (approximately 20 mL) for CMI response in CMI subset subjects only	●		●		●		●		●		
Randomization[d]	○										
Recording of treatment number	●										
Vaccination	●	●									
Dispensing of HZ-specific diary cards to all subjects	○										

Type of contact	VISIT 1	VISIT 2	VISIT 3	Monthly contacts[e]	VISIT 4	Monthly contacts[e]	VISIT 5	Monthly contacts[e]	VISIT 6[f]	Monthly contacts[e]	Study conclusion contact
Timepoints	**Day 0*/ Month0**	**Month 2**	**Month 3**		**Month 14**		**Month 26**		**Month 38**		
Sampling timepoints	**Pre-Vacc**	**Post-Vacc 1**	**Post-Vacc 2**		**Post-Vacc 2**		**Post-Vacc 2**		**Post-Vacc 2**		
Recording of intercurrent medical conditions according to guidelines in Section 6.7	●[d]	●	●	●	●	●	●	●	●	●	●
Reporting of all SAEs until Month 14	●[d]	●	●	●	●						
Reporting of SAEs related to study participation or to a concurrent GSK medication/vaccine, or any fatal SAE, after Month 14 until study conclusion						●	●	●	●	●	●
Reporting of new onset of autoimmune diseases (NOADs) and other immune mediated inflammatory disorders	●[d]	●	●	●	●	●	●	●	●	●	●
Follow-up of HZ	●[d]	●	●	●	●	●	●	●	●	●	●
Reporting of medically attended visits until Month 8	●[d]	●	●	●							
Recording of concomitant medication/vaccination by study staff/investigator according to guidelines in Section 6.6	●	●	●	●	●	●	●	●	●	●	●
Reporting of pregnancy	●[d]	●	●	●	●	●	●	●	●	●	●
Completion of EQ-5D and SF-36 questionnaires -by all subjects (subjects with an ongoing HZ episode will follow the weekly schedule and do not need to additionally complete the questionnaires at these visits)	○				○		○		○		

Type of contact	VISIT 1	VISIT 2	VISIT 3	Monthly contacts[e]	VISIT 4	Monthly contacts[e]	VISIT 5	Monthly contacts[e]	VISIT 6[f]	Monthly contacts[e]	Study conclusion contact
Timepoints	**Day 0*/ Month0**	**Month 2**	**Month 3**		**Month 14**		**Month 26**		**Month 38**		
Sampling timepoints	**Pre-Vacc**	**Post-Vacc 1**	**Post-Vacc 2**		**Post-Vacc 2**		**Post-Vacc 2**		**Post-Vacc 2**		
Transcription[g] by study staff/investigator of EQ-5D and SF-36 questionnaires completed - by all subjects - by subjects who do not have an ongoing HZ episode	●				●		●		●		
Dispensing of 7-day diary cards for solicited AEs to the 7-day diary card subset only and 30-day diary cards for unsolicited AEs and concomitant medication/vaccination to all subjects	○	○									
Daily post-vaccination recording by subjects of solicited symptoms (Days 0 – 6 after each vaccination) on the 7-day diary card by the 7-day diary card subset subjects	○	○									
Daily post-vaccination recording by subjects of unsolicited symptoms (Days 0 – 29 after each vaccination), and concomitant medication/ vaccination (Days 0 – 29 after each vaccination) on 30-day diary card by all subjects	○	○									
Returning by subjects of 7-day diary cards diary cards for solicited symptoms and 30-day diary cards for unsolicited AEs and concomitant medication and vaccination		○	○								

Type of contact	VISIT 1	VISIT 2	VISIT 3	Monthly contacts[e]	VISIT 4	Monthly contacts[e]	VISIT 5	Monthly contacts[e]	VISIT 6[f]	Monthly contacts[e]	Study conclusion contact
Timepoints	**Day 0*/ Month0**	**Month 2**	**Month 3**		**Month 14**		**Month 26**		**Month 38**		
Sampling timepoints	**Pre-Vacc**	**Post-Vacc 1**	**Post-Vacc 2**		**Post-Vacc 2**		**Post-Vacc 2**		**Post-Vacc 2**		
Transcription of 7-day diary cards for solicited symptoms and 30-day dairy cards for unsolicited AEs and concomitant medication and vaccination by study staff/investigator		●	●								
Study Conclusion											●

Note: Starting at Visit 3, monthly contacts between the subjects and the investigator and/or his delegate will be scheduled for the subject to respond to a standard set of questions, in a language that is understandable to the subject, to collect information on safety and the occurrence of HZ, and to follow-up ongoing HZ cases (Section 5.5.1).
Note: Futility analysis may occur (Section 10.4.5.3)
* Day of first vaccination
● is used to indicate a study procedure that requires documentation in the individual eCRF.
O is used to indicate a study procedure that does not require documentation in the individual eCRF.
[a] Subjects 70-79 YOA and ≥ 80 YOA will be randomly assigned to ZOSTER-006 or ZOSTER-022 at Visit 1. These subjects must sign a Study Determination (Recruitment/Randomization) Agreement (SDRRA) prior to study assignment, and will receive a study determination number to be recorded in the eCRF. Study assignment can be done prior to Visit 1 if needed.
[b] Subjects will be instructed to contact their study site immediately if he/she develops any symptoms suggestive of HZ, if he/she manifests any symptoms he/she perceive as serious and, in case of pregnancy for women of childbearing potential.
[c] Only for women of child-bearing potential.
[d] Study procedure to be assessed only after administration of vaccine at Visit 1.
[e] Monthly contact after Visit 3 until study conclusion, except at months that coincide with the subject's scheduled visits
[f] If the conditions for final analysis and study end are met before Visit 6 is completed by all subjects and it is decided to conclude the study, Visit 6 may not take place in some subjects.
[g] EQ-5D and SF-36 will remain as source documents. The information from these questionnaires will only be transcribed in the eCRF for subjects who have a zoster event during the study.

Table 3 Study procedures to be performed during the follow-up period for each suspected HZ case

	VISITS/CONTACTS IN CASE OF HZ						
Type of contact	**Visit HZ-1**	**Visit HZ-2**	**Contact HZ-3**	**Contact HZ-4**	**Visit HZ-5**	**Contact HZ-6**	**Visit HZ-7**
Timepoints	**Day HZ-0**	**Day HZ-7**	**Day HZ-14**	**Day HZ-21**	**Day HZ-28**	**Day HZ-56**	**Day HZ-91**
Perform clinical examination	○						
Return HZ-specific diary cards to study staff/investigator	○						
Transcription of the HZ-specific diary card by study staff/investigator	●						
Take digital photographs of HZ rash	●						
Recording of the HZ onset date by study staff/investigator	●						
Collect HZ lesion samples (3 replicate samples) for confirmation by PCR of a case of clinically diagnosed suspected HZ as specified in Section 5.7.3.11	●						
Record relevant information regarding HZ in eCRF by study staff/investigator	●	●	●	●	●	●	●
Record concomitant medication/vaccination according to guidelines in Section 6.6	●	●	●	●	●	●	●
Record intercurrent medical conditions according to guidelines in Section 6.7	●	●	●	●	●	●	●
Record any medical attention received for HZ or any HZ-related complication	●	●	●	●	●	●	●
Dispense ZBPI questionnaires to subjects	○						
Completion† of ZBPI questionnaires by the subjects until HZ is disproved, pain ceases or the cut-off date for final analysis (ZBPI pain data will be collected until at least Day HZ-90.)	○	○	○	○	○	○	○
Return completed ZBPI questionnaires to study staff/investigator according to instructions provided by the investigator/study staff to subjects		○	○	○	○	○	○
Transcription of ZBPI questionnaires by study staff/investigator	●	●	●	●	●	●	●
Dispense EQ-5D and SF-36 questionnaires to subjects	○						

	VISITS/CONTACTS IN CASE OF HZ						
Type of contact **Timepoints**	**Visit HZ-1** **Day HZ-0**	**Visit HZ-2** **Day HZ-7**	**Contact HZ-3** **Day HZ-14**	**Contact HZ-4** **Day HZ-21**	**Visit HZ-5** **Day HZ-28**	**Contact HZ-6** **Day HZ-56**	**Visit HZ-7** **Day HZ-91**
Completion‡ of EQ-5D and SF-36 questionnaires by the subjects until HZ is disproved, pain ceases or the cut-off date for final analysis (EQ-5D and SF-36 data will be collected until at least Day HZ-90)	○	○	○	○	○	○	○
Return completed EQ-5D and SF-36 questionnaires to study staff/investigator according to instructions provided by the investigator/study staff to subjects		○	○	○	○	○	○
Transcription of EQ-5D and SF-36 questionnaires by study staff/investigator	●	●	●	●	●	●	●

Note: If the case of clinically diagnosed suspected HZ is disproved, or if HZ-associated pain ceases (defined as a 28-day [or 4-week] pain free period), subsequent follow-up visits or contacts will be cancelled. When case of clinically diagnosed suspected HZ is disproved, collection of HZ-related information will be stopped and no further information on that suspected HZ episode will be encoded in the clinical database.

†Subjects with clinically diagnosed suspected HZ will be asked to complete the ZBPI questionnaire at Day HZ-0 (Visit HZ-1), daily from Day HZ- 1 to Day HZ-28, and weekly from Day HZ-29 onwards until a 4-week pain-free period is documented or until the cut-off date for final analysis. (ZBPI pain data will be collected until at least Day HZ-90)

‡Subjects with clinically diagnosed suspected HZ will be asked to complete the EQ-5D and SF-36 questionnaire weekly from Day HZ-0 onwards until a 4-week pain-free period is documented or until the cut-off date for final analysis. (EQ-5D and SF-36 data will be collected until at least Day HZ-90)

Each clinically diagnosed suspected HZ that occurs up to the cut-off date for final analysis will be followed at least until the study visit at Day HZ-91.

The study staff/investigator will dispense additional questionnaires and provide instructions for the subject to return the completed questionnaires to the study site. The subjects will be given a new supply of questionnaires as necessary. Follow-up of HZ-associated pain persisting beyond Day HZ-91 or other complications will be done at monthly contacts that are planned starting at Visit 3 between the subjects and the investigator and/or his delegate.

It is the investigator's responsibility to ensure that the intervals between study visits/contacts are strictly followed. These intervals determine each subject's evaluability in the ATP analyses.

Time intervals between study visits/contacts related to study procedures performed in subjects participating in the study are presented in Table 4. In addition; starting at Visit 3, monthly contacts between the subjects and the investigator and/or his delegate will be scheduled.

Follow-up for the occurrence of any SAEs will begin at Day 0 and continue until Month 14. Follow-up for the occurrence of SAEs related to study participation, or related to a concurrent GSK medication/vaccine or any fatal SAE, will continue until study conclusion. Follow-up for the occurrence of new onset of autoimmune diseases and other immune mediated inflammatory disorders will begin at Day 0 and continue until study conclusion.

Table 4 Intervals between study visits/contacts

Interval	Length of interval	Range (days)
Visit 1 → Visit 2	2 months	49-83
Visit 2 → Visit 3	1 month	30-48
Visit 2 → Visit 4	12 months	335-395
Visit 2 → Visit 5	24 months	700-760
Visit 2 → Visit 6*	36 months	1065-1125
Visit 2 → Study conclusion contact	Not fixed	Not fixed

Note: The date of Dose 1 (Visit 1) or Dose 2 (Visit 2), respectively, is used as reference date to define the interval between study visits/contacts.
* If the conditions for final analysis and study end are met before Visit 6 is completed by all subjects and it is decided to conclude the study, Visit 6 may not take place in some subjects

Time intervals between study visits/contacts to be performed for follow-up of HZ are presented in Table 5. Refer to the SPM for further guidance on data collection during follow-up of HZ.

Table 5 Intervals between contacts with subjects in case of suspected HZ

Interval between visits/contacts	Length of interval	Optimal Timing of contact (range of days)
Visit HZ-1 (Day HZ-0) → Visit HZ-2 (Day HZ-7)	7 days	Day HZ-7 (+/- 3 days)*
Visit HZ-2 (Day HZ-7) → Contact HZ-3 (Day HZ-14)	7 days	Day HZ--14 (+/- 3 days)*
Contact HZ-3 (Day HZ-14) → Contact HZ-4 (Day HZ-21)	7 days	Day HZ-21 (+/- 3 days)*
Contact HZ-4 (Day HZ-21) → Visit HZ-5 (Day HZ-28)	7 days	Day HZ-28 (+/- 3 days)*
Visit HZ-5 (Day HZ-28) → Contact HZ-6 (Day HZ-56)	28 days	Day HZ-56 (+/- 7 days)*
Visit HZ-1 (Day HZ-0) → Visit HZ-7 (Day HZ-91)	91 days	Day HZ-91 (+ 7 days)

Note: The date of the previous visit/contact is used as reference date to define the interval between the subsequent study visits/contacts
Note: If a case of clinically diagnosed suspected HZ is disproved or if pain ceases (i.e., after a 4-week pain-free period is documented), subsequent follow-up visits or contacts may be cancelled. Follow-up of HZ-associated pain persisting beyond Day HZ-91 or other complications will be done at monthly contacts between the subjects and the investigator and/or his delegate that are planned starting at Visit 3
* If contacted early in the window, then remaining days in the interval will need to be captured with the next contact.

5.7. Detailed description of study procedures

5.7.1. Procedures prior to study participation

5.7.1.1. Study Determination (Recruitment/Randomization) Agreement

Eligible subjects 70-79 YOA and ≥ 80 YOA will be randomly assigned to ZOSTER-006 or ZOSTER-022 at Visit 1. Prior to study assignment, subjects need to provide their signature/thumb print on the Study Determination (Recruitment/Randomisation) Agreement. Subjects will receive a study determination number to be recorded in the eCRF. Study assignment can be done prior to Visit 1 if needed.

5.7.1.2. Informed consent

Before performing any other study procedure, subjects need to provide their signature/thumb print on the study specific informed consent. Refer to Section 5.1 for the requirements on how to obtain informed consent, as appropriate.

5.7.2. Procedures prior to the first vaccination

5.7.2.1. Check inclusion and exclusion criteria

Check all applicable inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

If a subject is enrolled while not meeting all inclusion criteria or while meeting any of the exclusion criteria, this must be reported in the eCRF.

5.7.2.2. Collect demographic data

Record demographic data such as date of birth, gender, geographic ancestry and ethnicity in the subject's eCRF.

5.7.2.3. Medical history

Perform a history-directed medical examination and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study in the eCRF. Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

5.7.2.4. Physical examination

A history-directed physical examination according to local practice should be performed to ensure the subject is in good physical condition.

5.7.2.5. Urine pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test prior to any study vaccine administration. The study vaccine/placebo may only be administered if the pregnancy test is negative.

5.7.3. Procedures during the study

Note that some of the procedures to be performed during the vaccination visits, i.e., Visits 1 and 2, (such as history directed physical examination and urine pregnancy test) are performed prior to the first vaccination and are described in Section 5.7.2.

5.7.3.1. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant medication/vaccination must be recorded in the eCRF as described in Section 6.6. Refer to Section 6.6 for details on the medications/vaccinations that are forbidden or allowed during the study.

At each study visit or contact subsequent to the first vaccination, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition listed in Section 6.7. If it is the case, the condition(s) must be recorded in the eCRF.

Intercurrent medical conditions except HZ prior to one month after the second vaccination should be reported in the AE section of the eCRF.

Any subject with a clinically diagnosed HZ episode between Visit 1 and Visit 2 should not receive the second vaccination.

Antiviral and/or pain medications administered to subjects with a suspected or confirmed case of HZ for the purpose of treating the HZ or the associated pain will be recorded in order to establish the link between the medications and the indication.

In addition, any medication/vaccination taken from Day 0 to Day 29 after each vaccination will be recorded by the subjects on a 30-day diary card (Section 5.7.3.8).

5.7.3.2. Check contraindications to vaccination

Contraindications to vaccination are to be checked at the beginning of each vaccination visit. Refer to Section 6.5.

See Section 5.7.3.7 for an additional criterion to be checked prior to administration of the second vaccination dose.

5.7.3.3. Assess pre-vaccination body temperature

The axillary, rectal, oral or tympanic body temperature of all subjects will be measured prior to any study vaccine administration. The preferred route for recording temperature

in this study will be oral. All vaccines may be administered to persons with low-grade fevers, i.e., oral, tympanic on oral setting, or axillary temperature < 37.5°C/99.5°F, or < 38.0°C (100.4°F) on rectal setting (Section 4.3). If a subject has an axillary/oral/tympanic on oral setting temperature ≥ 37.5°C/99.5°F, or ≥ 38.0°C (100.4°F) on rectal setting, it will constitute a contraindication to administration of vaccine or placebo at that point in time (Section 6.5).

5.7.3.4. Randomization

At the first vaccination visit, randomization will occur as explained in Section 5.3.

5.7.3.5. Blood sampling for safety or immune response assessments

As specified in Table 2, blood samples will be taken during certain study visits. Refer to the Module on Biospecimen Management in the SPM for general handling of blood samples.

- A volume of approximately 10 mL of whole blood should be drawn from all subjects at Visits 1 and 3, and, from all subjects included in the Immunogenicity subset, at Visits 4, 5 and 6.
- An additional volume of approximately 20 mL of whole blood should be drawn from all subjects included in the CMI component of the Immunogenicity subset at Visits 1, 3, 4, 5 and 6.

5.7.3.6. Treatment number assignment

At the first vaccination visit, the subject will be assigned a treatment number defining the treatment he/she will be receiving. The treatment number must be recorded in the eCRF at the first vaccination visit.

If there is a need for a site to use a replacement vaccine at the subsequent visit, then that treatment number needs to be transcribed into the eCRF (see Section 6.4).

5.7.3.7. Vaccination

- After completing the prerequisite procedures prior to each vaccination, one dose of study vaccine/placebo will be administered intramuscularly (IM) in the deltoid of the non-dominant arm (refer to Section 6.3 for detailed description of the vaccine administration procedure). If the Investigator or delegate determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled within the interval for this visit.
- The vaccinees will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of anaphylaxis following the administration of vaccine.
- Any subject with clinically diagnosed HZ episode between Visit 1 and Visit 2 should not receive the second dose.

5.7.3.8. Recording of non-serious AEs and SAEs

- Refer to Section 8.3 for procedures for the Investigator to record AEs and SAEs and to Section 8.4 for guidelines on how to report these AEs/SAEs to GSK Biologicals.
- The subjects will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious or in case of pregnancy for women of childbearing potential.
- After each vaccination, 30-day diary cards will be provided to all subjects by study staff/investigator for daily recording by the subjects of:

– unsolicited symptoms from Days 0 to 29 after each vaccination

– any medication/vaccination taken from Days 0 to 29 after each vaccination.

- After each vaccination, 7-day diary cards will be provided to subjects who are part of the 7-day diary card subset by study staff/investigator for daily recording by the subjects of solicited symptoms from Days 0 to 6 after each vaccination
- The subjects will be instructed to return the completed diary cards to the investigator at Visit 2 and Visit 3, respectively.
- Collection and verification of completed diary cards will occur during discussion with the subject at Visit 2 and Visit 3. The investigator will transcribe the collected information into the eCRF in English.

5.7.3.9. Recording of new onset of autoimmune diseases (NOADs) and other immune mediated inflammatory disorders

As specified in the List of Study Procedures (Table 2, Section 5.6), NOADs and other immune mediated inflammatory disorders, occurring from administration of the first dose of vaccine/placebo onwards until end of the trial will be recorded.

Refer to Section 8.3.2.5 for information on recording of NOADs and other immune mediated inflammatory disorders.

5.7.3.10. Recording of data from completed EQ-5D and SF-36 questionnaires

- EQ-5D and SF-36 questionnaires will be completed by all subjects at Visit 1.
- EQ-5D and SF-36 questionnaires will be completed by all subjects at Visits 4, 5 and 6 (subjects with an ongoing HZ episode will follow the weekly schedule and do not need to additionally complete the questionnaires at these visits).

EQ-5D and SF-36 will remain as source documents. The information from these questionnaires will only be transcribed in the eCRF for subjects who have a confirmed episode of HZ during the study.

5.7.3.11. Follow up of suspected HZ cases and HZ-associated pain

Data will be collected on all clinically diagnosed suspected HZ cases that occur from administration of the first dose of vaccine/placebo until the cut-off date for final analysis (Section 5.7.3.16). For each suspected case of HZ that the investigator concludes is clinically consistent with HZ, data on HZ-associated pain (using ZBPI questionnaires completed by the subject) will be collected until:1) The case is disproved; 2) The subject has no HZ-associated pain for 4 consecutive weeks; or, 3) the cut-off date for final analysis. For all subjects with HZ-associated pain, ZBPI pain data will be collected until at least Day HZ-90, regardless of the cut-off date for final analysis. In addition, subjects with clinically diagnosed suspected HZ will be asked to complete EQ-5D and SF-36 questionnaires weekly.
At the first HZ evaluation visit (Visit HZ-1 at Day HZ-0 – The visit at which the suspected case of HZ is first evaluated by the investigator), rash lesion samples will be collected from the subject if the investigator considers the symptoms/signs to be consistent with HZ. If during clinical evaluation at Visit HZ-1, the investigator determines that adequate rash lesion samples cannot be collected, the subject may be asked to return to the study site for collection of suitable HZ lesion samples. Three replicate rash lesion samples (see Table 6) should be collected on the same day according to the guidelines provided in the SPM.

Refer to 5.5.2 for details on follow-up of HZ cases and HZ-associated pain.

5.7.3.12. Recording of medically attended visits

Refer to Section 8.3.2.4 for detailed information on recording of medically attended visits occurring up until Month 8.

5.7.3.13. Reminder for self-reporting by subjects

Subjects will be instructed at Visit 1 (and will be reminded at each subsequent visit) to contact their study site immediately

- should the subject develop any symptoms suggestive of HZ, and to start completion of the HZ-specific diary card immediately upon development of these symptoms prior to visiting the study site for evaluation of the suspected HZ;
- should the subject manifest any signs or symptoms he/she perceive as serious;
- should the subject become pregnant (for women of childbearing potential).

5.7.3.14. Reminder for monthly follow-up contacts/yearly follow-up visits

The subject will be reminded that, starting at Visit 3, monthly contacts between the subjects and the investigator and/or his delegate will take place (except at months that coincide with the subject's scheduled visits) in order to collect all relevant information on any event of interest that may have occurred [including SAEs (Section 8.3), NOADs and other immune mediated inflammatory disorders (Section 8.3.2.5), occurrence or follow up of a suspected episode of HZ (Section 5.5.2), intercurrent medical conditions (Section 6.7), medically attended visits (up to Month 8 only, Section 8.3.2.4), the use of

concomitant medications and/or vaccinations (Section 6.6) or pregnancy (Section 8.3)], and that information will be recorded in the appropriate section of the subject's eCRF.

The subject will be reminded that the current study still has yearly follow-up visits planned.

5.7.3.15. Invitation for a planned follow-up study

If study ZOSTER-006 is extended to include an additional long-term follow-up period beyond that currently mandated by the protocol, the investigator/study staff will ask all or a subset of subjects at the study conclusion contact if the subject would be willing to participate to a long-term follow-up study. If a subject declines to participate in a long-term follow-up study, refusal will be documented in the individual eCRF.

5.7.3.16. Study conclusion

Study end will take place when both conditions for final analysis are met and a minimum 90 days follow-up is completed for each case of confirmed or clinically diagnosed suspected HZ that occurs prior to the cut-off date for final analysis.

If it appears that there will be a large disparity in the study end date for study ZOSTER-006 and ZOSTER-022, respectively, then the first study that meets the criteria for final analysis may be continued until the second study reaches the criteria for final analysis so that the two studies end concurrently.

When the cut-off date for final analysis is established, the study sites will contact the subjects for the study conclusion contact. If a subject with clinically diagnosed suspected HZ has not completed follow-up until at least Day HZ-90 at the cut-off date for final analysis, and the case is not disproved, follow-up for such a subject will continue until the Day HZ-90 follow-up is completed. The study conclusion contact for such a subject will thus occur after he/she completes Day HZ-90 follow-up.

At the study conclusion contact, the study sites will provide instructions to the subjects for returning any outstanding ZBPI questionnaires.

At the study conclusion contact, the following procedures will take place:

- Follow-up of any cases of confirmed or clinically diagnosed suspected HZ and HZ-associated pain (Sections 5.5.2 and 5.7.3.10);
- Recording of any SAEs related to study participation or to a concurrent GSK medication/vaccine, or any fatal SAE (Section 5.7.3.8);
- Recording of NOADs and other immune mediated inflammatory disorders (Section 5.7.3.9);
- Check and record specific concomitant medication/vaccination and intercurrent medical conditions (Section 5.7.3.1);
- Study conclusion will be recorded in the eCRF.

At study conclusion, if the study vaccine demonstrates sufficient evidence of efficacy and safety such that a clinically important benefit may be reasonably expected, placebo recipients will be offered cross-over immunization with the study vaccine

5.8. Biological sample handling and analysis

Please refer to the SPM for details of biospecimen management (handling, storage and shipment).

Samples will not be labelled with information that directly identifies the subjects but will be coded with the identification number for the subject (subject number).

Collected samples may be used in other assays, for test improvement or test development of analytical methods related to the study vaccine and its constituents or the disease under study to allow to achieve a more reliable measurement of the vaccine response. Under these circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject.

Any human pharmacogenetic testing will require specific consent from the individual subjects and the ethics committee approval. Any anti-HIV testing will also require specific consent and ethics committee approval.

Refer also to the Investigator Agreement, where it is noted that the Investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking given in Section 5.8.4 may be changed.

Collected samples will be stored for up to 15 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.8.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (see Section 10.5 for the definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However,

when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used. Refer to the Module on Clinical Trial Supplies in the SPM.

5.8.2. Biological samples

The different biological samples collected in the study, the quantities needed, the units and the timepoints are described in Table 6.

Table 6 Biological samples

Sample type	Quantity (approximate volume)	Unit	Timepoint	Subset Name*
Blood (Cell-mediated immunology)	20	mL	Visit 1, 3, 4, 5, 6	CMI component of Immunogenicity subset
Blood (Humoral immunology)	10	mL	Visit 1, 3	All subjects
	10	mL	Visit 4, 5, 6	Immunogenicity subset
Clinical specimens of HZ lesions	3 replicate samples, taken on the same day, of the highest priority lesion type available (1) vesicle fluid; 2) crust; 3) crust swab; 4) papule swab)	NA	scheduled in case of suspected HZ for diagnosis	Subjects clinically diagnosed as having a suspected case of HZ

* Refer to Section 4.1 for description of the subsets

5.8.3. Laboratory assays

Please refer to Appendix A for a detailed description of the assays performed in the study.

Laboratory assays, which will be used in this study, are summarised in respectively Table 7 (Humoral Immunity), Table 8 (CMI) and Table 9 (Molecular Biology).

Table 7 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off	Laboratory
Serum	Varicella Zoster Virus Ab.IgG	ELISA	Enzygnost Dade Behring	mIU/mL	25	GSK Biologicals*
Serum	gE Ab.IgG	ELISA	NA	mIU/mL	18	GSK Biologicals*
Serum	Varicella Zoster Virus Neutralizing Ab.IgG	PRNT	NA	ED50	TBD	GSK Biologicals*

*GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals.
ELISA = Enzyme-linked Immunosorbent Assay; PRNT = Plaque Reduction Neutralization Test
mIU = milli international unit; ED50 = endpoint dilution 50%
NA = Not applicable; TBD = to be determined; Ab = antibody

Table 8 Cell-Mediated Immunity (CMI)

System	Component	Challenge	Method	Unit	Laboratory
Peripheral Blood Mononuclear Cells	Cells CD4.All double CD40 Ligand or Interleukin-2 or Tumor Necrosis Factor alpha or Interferon gamma	gE	ICS	Events/10E6	GSK Biologicals*
Peripheral Blood Mononuclear Cells	Cells CD4.All double CD40 Ligand or Interleukin-2 or Tumor Necrosis Factor alpha or Interferon gamma	VZV	ICS	Events/10E6	GSK Biologicals*

*GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals.
ICS = Intracellular cytokine staining

Table 9 Molecular Biology (PCR tests)

System	Component	Method	Unit	Laboratory
HZ lesion sample	Varicella Zoster Viirus.DNA	QPCR	No unit	GSK Biologicals*
HZ lesion sample	Herpes Simplex Virus.DNA	QPCR	No unit	GSK Biologicals*
HZ lesion sample	Actin Gene.DNA	QPCR	No unit	GSK Biologicals*

*GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals.

Collected samples will be used for purposes related to the quality assurance of data generated within the scope of this protocol, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

5.8.4. Biological samples evaluation

5.8.4.1. Immunological read-outs

The plan for immunogenicity testing on samples obtained is shown in Table 10. In case of insufficient blood sample volume to perform the assays, the samples will be analysed according to priority ranking provided in Table 10.

- For subjects included in the Immunogenicity subset (humoral immunity), anti-gE and anti-VZV Abs will be measured at specified timepoints. An anti-VZV neutralizing Ab assay may also be performed on the serum blood samples from a subgroup of subjects of the Immunogenicity subset.
- For a subgroup of subjects included in the CMI component of the Immunogenicity subset, CMI response will be measured at specified timepoints.
- For the correlates of protection analysis, analysis of the humoral immune responses at Month 3 will be performed on samples collected from vaccinated subjects who develop confirmed HZ and compared with the humoral immune responses at Month 3 from matched subjects that did not develop HZ. Additional blood samples may be analysed from other subjects to match more exactly with characteristics of those that developed HZ.

Table 10 Immunological read-outs

Blood sampling timepoint			Subset* Name	Marker	Components priority rank
Visit no	Timing	Month			
Visit 1	Pre-Vacc 1	0	Immunogenicity subset Immunogenicity subset Immunogenicity subset**	Ab gE ELISA Ab VZV ELISA anti-VZV neutralizing Ab	1 2 3
			CMI component of Immunogenicity subset CMI component of Immunogenicity subset	ICS gE ICS VZV	1 2
			Correlate of protection analysis‡ Correlate of protection analysis‡	Ab gE ELISA Ab VZV ELISA	1 2
Visit 3	Post-Vacc 2	3	Immunogenicity subset Immunogenicity subset Immunogenicity subset**	Ab gE ELISA Ab VZV ELISA anti-VZV neutralizing Ab	1 2 3
			CMI component of Immunogenicity subset CMI component of Immunogenicity subset	ICS gE ICS VZV	1 2
			Correlate of protection analysis‡ Correlate of protection analysis‡	Ab gE ELISA Ab VZV ELISA	1 2
Visit 4	Post-Vacc 2	14	Immunogenicity subset Immunogenicity subset Immunogenicity subset**	Ab gE ELISA Ab VZV ELISA anti-VZV neutralizing Ab	1 2 3
			CMI component of Immunogenicity subset CMI component of Immunogenicity subset	ICS gE ICS VZV	1 2
Visit 5	Post-Vacc 2	26	Immunogenicity subset Immunogenicity subset Immunogenicity subset**	Ab gE ELISA Ab VZV ELISA anti-VZV neutralizing Ab	1 2 3
			CMI component of Immunogenicity subset CMI component of Immunogenicity subset	ICS gE ICS VZV	1 2
Visit 6	Post-Vacc 2	38	Immunogenicity subset Immunogenicity subset Immunogenicity subset**	Ab gE ELISA Ab VZV ELISA anti-VZV neutralizing Ab	1 2 3
			CMI component of Immunogenicity subset CMI component of Immunogenicity subset	ICS gE ICS VZV	1 2

* Refer to Section 4.1 for description of subsets.
** Anti-VZV neutralizing Ab assay may be performed in a subgroup of the Immunogenicity subset.
‡ Refer also to Section 10.8.3.4 for details regarding correlate of protection analysis
Note: Test results obtained for the anti-gE and anti-VZV Ab ELISA assays will be used for correlate of protection analysis, if applicable.

Additional testing may be performed if deemed appropriate by GSK Biologicals should any findings in the present study, or in other studies, indicate that further investigation of the immunogenicity of the vaccine is warranted. In this case, the rankings above may also change.

5.8.4.2. Test for laboratory diagnosis of HZ

In case of a suspected HZ case diagnosis in any of the subjects, clinical specimens from HZ lesions will be collected to confirm the diagnosis of HZ by PCR. Please refer to Appendix A for or a detailed description of the PCR.

5.8.5. Immunological correlates of protection

No correlate of protection has been demonstrated so far for the antigen used as part of the candidate vaccine.

Study ZOSTER-006 will attempt to correlate humoral immune responses at Month 3 with protection. Additional evaluations to add precision to this assessment may be performed (see Section 10.8.3.4).

6. STUDY VACCINE AND ADMINISTRATION

6.1. Description of study vaccine

The Quality Control Standards and Requirements for the candidate vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccine is labelled and packed according to applicable regulatory requirements.

The study vaccine will be supplied in 2 vials, one containing the VZV gE antigen, and the other containing Adjuvant System $AS01_B$.

- The VZV gE antigen is provided in a lyophilized form in monodose vials. Each vial contains 62.5 µg of recombinant purified gE and formulation excipients. Therefore, when the 62.5 µg of VZV gE in each vial is reconstituted with the full volume of adjuvant, each vaccine dose will contain 50 µg of the VZV gE antigen per 0.5 mL of reconstituted vaccine.
- The $AS01_B$ Adjuvant System is provided as a liquid formulation in monodose vials, each vial containing at least 0.5 mL of adjuvant. One 0.5 mL dose of $AS01_B$ formulation contains 50 µg of MPL and 50 µg of QS21 mixed with liposomes.

When the VZV gE antigen is reconstituted in $AS01_B$ it appears as an opalescent, colourless liquid, free from visible particles.

After reconstitution, each 0.5 mL dose of study vaccine contains 50 μg of gE recombinant protein, 50 μg of MPL, 50 μg of QS21, and liposomes.

The NaCl solution is provided in monodose vials (0.5 mL/dose) containing 150 mM NaCl per 0.5 mL dose. The NaCl solution used as the placebo appears clear and colourless and is free from visible particles.

The method of preparation of the gE/AS01$_B$ study vaccine (reconstitution required) differs from that of the placebo (no reconstitution required for the NaCl solution placebo). The reconstituted gE/AS01$_B$ study vaccine differs in appearance from the NaCl solution placebo. To conduct the study in an observer-blind manner, the gE/AS01$_B$ vaccine and NaCl solution placebo doses will be prepared and administered by study staff not involved in the clinical evaluation of the subjects. In this way, neither the subject nor the investigator (or other study personnel) will know which treatment was administered. The method of blinding and the responsibilities of the study personnel in this regard will be documented by the investigator at each study site.

The SPM will include details of vaccine supplies.

6.2. Storage and handling of study vaccine

All study vaccines to be administered to the subjects must be stored in a safe and locked place with no access by unauthorised personnel.

The study vaccines will be stored at the defined temperature range (i.e. +2 to +8°C/36°F to 46°F) and must not be frozen. Please refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccine. The storage temperature of the vaccine will be monitored daily with validated temperature monitoring device(s) and will be recorded as specified in the SPM.

The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact.

Any temperature deviation, i.e. temperature outside the defined range (+2 to +8°C/36°F to 46°F of storage) , must be reported to the sponsor as soon as detected. Following an exposure to a temperature deviation, vaccines will not be used until written approval has been given by the Sponsor.

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the packaging and accountability of the study vaccine.

6.3. Dosage and administration of study vaccine

The vaccine should be reconstituted shortly after the vials are taken out of the refrigerator. The reconstituted vaccine is stable for up to two hours when kept at a temperature range of +2°C (36°F) to 30°C (86°F). .Therefore, reconstituted vaccines should be administered within a maximum of two hours after reconstitution.

To reconstitute gE/AS01$_B$ study vaccine, the entire content of one diluent vial (i.e. AS01$_B$) is aspirated into a syringe and injected into one vial of lyophilized gE antigen. The pellet is dissolved by gentle shaking of the vial (for a few seconds) until complete dissolution of the lyophilized cake.

Table 11 summarises how vaccine will be administered.

The entire volume of the reconstituted vaccine should be withdrawn, the needle can be replaced, and any solution in excess of 0.5mL should be expelled. After confirming that the needle is not in a blood vessel, the reconstituted vaccine should be administered by IM injection, preferably into the deltoid muscle of the non-dominant arm, using a standard aseptic technique. A 0.5 mL dose of the NaCl solution placebo should be injected IM. The injection site should be on the same arm for all injections for an individual subject. In rare situations when there is no other alternative, the second injection may be given on the different arm.

Table 11 Dosage and administration

Group	Visit	Vaccination	Treatment	Route	Site	Side
Vaccine	1, 2	1, 2	gE/AS01$_B$	IM	D	Non-dominant arm
Placebo	1, 2	1, 2	NaCl solution placebo	IM	D	Non-dominant arm

gE/AS01$_B$: lyophilized gE reconstituted in liquid AS01$_B$ Adjuvant System
Intramuscular (IM)
Deltoid (D) muscle of non-dominant arm

6.4. Replacement of unusable vaccine

Additional vaccine doses will be provided to replace those that are unusable (see the Module on Clinical Trial Supplies in the SPM for details).

In addition to the vaccine doses provided for the planned number of subjects (including over-randomization when applicable), at least 5% additional doses will be supplied to replace those that are unusable.

The investigator will use the central randomization system (SBIR) to obtain the replacement vial number. The system will ensure, in a blinded manner, that the replacement vial is of the same formulation as the randomized vaccine.

6.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of gE/AS01$_B$. If any of these events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 8.4.4).

- Anaphylaxis following the administration of vaccine(s);
- Pregnancy (Section 8.2.2);
- Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., malignancy, HIV infection) or

immunosuppressive/cytotoxic therapy (e.g., medications used during cancer chemotherapy, organ transplantation or to treat autoimmune disorders). However subjects who have received less than 15 days of immunosuppressants or other immune modifying drugs should not be contraindicated from receiving subsequent vaccinations. Also, for corticosteroids, prednisone < 20 mg/day, or equivalent, is allowed. Inhaled and topical steroids are allowed.

The following events constitute contraindications to administration of the gE/AS01$_B$ HZ vaccine at that point in time; if any one of these events occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (Section 5.6), or withdrawn at the discretion of the investigator (Section 8.4.4).

- Acute disease and/or fever at the time of vaccination.

– Fever is defined as temperature ≥ 37.5°C (99.5°F) on oral, axillary or tympanic setting, or ≥ 38.0°C (100.4°F) on rectal setting. The preferred route for recording temperature in this study will be oral.

Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines.

See Section 5.7.3.7 for an additional criterion to be checked prior to administration of the second vaccination dose.

6.6. Concomitant medication/vaccination

At each study visit/contact, the investigator should question the subject about any medication taken and vaccination received by the subject.

Concomitant medication administered for the treatment of NOADs or other immune mediated inflammatory disorders at any time during the study must be recorded in the eCRF. Refer to Section 8.3.2.5 for information regarding NOADs and other immune mediated inflammatory disorders.

Any concomitant medication administered for the treatment of confirmed or suspected HZ or any HZ-related complications (including pain) at any time during the study must be recorded in the eCRF and coded as ‘Treatment for HZ’.

Administration of any medications/vaccinations/products listed in Section 6.6.1 must be recorded in the eCRF respecting the time window as detailed in Section 6.6.2.

All concomitant medications, with the exception of vitamins and/or dietary supplements, administered at ANY time during the 30 days (Days 0 -29) after each vaccination are to be recorded in the eCRF. This also applies to concomitant medication administered prophylactically in anticipation of reaction to the vaccination and any medication intended to treat an AE.

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [oral/tympanic on oral

setting/axillary temperature < 37.5°C (99.5°F), or < 38.0°C (100.4°F) on rectal setting] and any other symptom, to prevent fever from occurring).

Similarly, concomitant medication administered for the treatment of a SAE must be recorded on the SAE screens in the eCRF, as applicable. Refer to Section 8.1.2 for the definition of a SAE and Section 8.3.1 for SAE reporting periods.

6.6.1. Medications/products that may lead to the elimination of a subject from ATP analyses

The following criteria should be checked at each visit subsequent to the first vaccination. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP analysis. See Section 10.5 for definition of study cohorts to be evaluated.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the study period;
- Administration of a vaccine not foreseen by the study protocol **within** 30 days prior to dose 2 of vaccine and/**or within** 30 days after any dose. However, licensed non-replicating vaccines (i.e., inactivated and subunit vaccines, including inactivated and subunit influenza vaccines, with or without adjuvant for seasonal or pandemic flu) may be administered up to 8 days prior to dose 2 and/or at least 14 days after any dose of study vaccine;
- Receipt of a vaccine against HZ other than the study vaccine during the study period;
- Prolonged use (> 14 consecutive days) of oral and/or parenteral antiviral agents that are active against VZV (acyclovir, valacyclovir, famciclovir etc.) during the study period for an indication other than to treat suspected or confirmed HZ or an HZ-related complication (topical use of these antiviral agents is allowed);
- Receipt of immunoglobulins and/or any blood products during the study period;
- Chronic administration (defined as > 15 consecutive days) of immunosuppressants or other immune-modifying drugs during the study period. For corticosteroids, this will mean prednisone < 20 mg/day, or equivalent, is allowed. Inhaled and topical steroids are allowed.

A detailed, comprehensive list of reasons for elimination from ATP analyses will be established at the time of data cleaning.

6.6.2. Time window for recording concomitant medication/vaccination in the eCRF

All concomitant medications administered for the treatment of all SAEs from Day 0 until Month 14, are to be recorded in the eCRF.

Concomitant medication, administered for the treatment of SAEs related to study participation or to a concurrent GSK medication/vaccine or any fatal SAE, from Day 0 until Study conclusion contact, must be recorded in the eCRF.

Concomitant medication, administered for the treatment of HZ or any related HZ-complications, or for the treatment of NOADs or other immune-mediated inflammatory disorders, from Day 0 until Study conclusion contact, must be recorded in the eCRF.

Oral and/or parenteral antiviral agents that are active against VZV (acyclovir, valacyclovir, famciclovir etc.) administered for > 14 consecutive days for an indication **other than** to treat suspected or confirmed HZ or an HZ-related complication from Day 0 until Study conclusion contact, are to be recorded in the eCRF;

Any vaccine not foreseen in the study protocol, administered from Day 0 until Month 3, is to be recorded in the eCRF.

Any investigational medication or investigational vaccine, administered from Day 0 through Study conclusion contact, must be recorded in the eCRF.

Any vaccine against HZ other than the study vaccine, administered from Day 0 until Study conclusion contact, is to be recorded in the eCRF.

Immunoglobulins and/or any blood products, administered from Day 0 until Study conclusion contact, are to be recorded in the eCRF;

Immunosuppressants or other immune-modifying drugs administered during the study period for > 15 consecutive days, are to be recorded in the eCRF. For corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent.

All concomitant medications, with the exception of vitamins and/or dietary supplements, administered at ANY time during the 30 days (Days 0 -29) after each vaccination are to be recorded in the eCRF.

6.7. Intercurrent medical conditions that may lead to elimination from an ATP cohort

Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition that has the capability of confounding their immune response to the study vaccine (i.e. a confirmed case of HZ prior to one month after the second vaccination); or they have any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g. malignancy, HIV infection). Intercurrent conditions except HZ prior to one month after the second vaccination should be reported in the AE section of the eCRF.

7. HEALTH ECONOMICS

The following questionnaires will be administered to the subjects:

- **EQ-5D questionnaire**

  The EQ-5D is a generic multi-attribute health classification system. The EQ-5D uses a 5-dimension (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) descriptive system, with each consisting of 3 response options (no problems, moderate problems or extreme problems). The EQ-5D also includes a Visual Analogue Scale (VAS) ranging from 0 to 100, with 100 representing the best imaginable health state and 0 representing the worst imaginable health state.

- **SF-36 health survey**

  The SF-36® is a multi-purpose health survey with 36 questions. It yields an 8-scale profile of scores (physical functioning, role physical, bodily pain, general health perceptions, vitality, social functioning, role emotional, and mental health) as well as a reported health transition score.

Both the EQ-5D and SF-36 questionnaires are international standards and have been extensively validated. They will generate Quality-Adjusted Life Years (QALY) weights in order to estimate the cost-effectiveness of an HZ vaccination strategy.

A standard algorithm has been developed for processing subjects' answers and producing QALY weights. These QALY weights will be generated for each age group: 50-59 YOA, 60-69 YOA and ≥ 70 YOA.

EQ-5D and SF-36 will be completed at Visit 1 for all subjects in order to generate a baseline measurement.

For subjects with clinically diagnosed suspected HZ, both questionnaires will be completed weekly from Day HZ-0 onwards until the case of clinically diagnosed suspected HZ is disproved, OR until a 4-week pain-free period is documented, OR until the cut-off date for final analysis. For all subjects with HZ-associated pain, data will be collected until at least Day HZ-90, regardless of the cut-off date for final analysis. For all subjects, the EQ-5D and SF-36 questionnaires will be completed at Visits 4, 5 and 6 (subjects with an ongoing HZ episode will follow the weekly schedule and do not need to additionally complete the questionnaires at these visits).

QALY weights measured for HZ cases in vaccine and placebo recipients will be compared and adjusted for their respective baseline values.

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator or site staff is/are responsible during the study for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol.

Each subject will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.

8.1. Safety definitions

8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

NB: AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs. (For subjects not included in the 7-day diary card subset, all AEs will be recorded as UNSOLICITED AEs.)

Example of events to be recorded in the medical history section of the eCRF:

- Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. prior to the first study vaccination).

The occurrence of HZ or PHN will not constitute an AE or SAE. However, complications or presentations of HZ or PHN that, in the opinion of the investigator, are not typical of these diseases may be AEs or SAEs.

8.1.2. Definition of a serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that:

a. Results in death.

b. Is life-threatening.

   NB: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation.

   NB: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition (known/diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, or

   NB: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an

emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

8.1.3. Solicited adverse events

Subjects in the 7-day diary card subset will be asked to report daily, from Day 0 to Day 6 (7-day follow-up period) after each dose, the occurrence of local or general solicited adverse experiences on a safety diary card provided by the sponsor. All clinical signs and symptoms will be recorded by the investigator on the appropriate section of the eCRF.

The following local (injection-site) AEs will be solicited (Table 12):

Table 12 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

The following general AEs will be solicited (Table 13):

General AEs are any experiences, which do not occur at the site of injection of a vaccine. They will be recorded as 'general' and include those events.

Table 13 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms †
Headache
Myalgia
Shivering

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain

NB: Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the eCRF.

8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

Safety laboratories are not collected in this study. Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments that come to the attention of, and are judged by, the investigator to be clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 8.1.1 or of a SAE, as defined in Section 8.1.2. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.2. Events or outcomes not qualifying as adverse events or serious adverse events

8.2.1. Disease-related events or outcomes not qualifying as serious adverse events

The occurrence of HZ or PHN will not constitute an SAE. However, complications or presentations of HZ or PHN that, in the opinion of the investigator, are not typical of these diseases may be SAEs.

8.2.2. Pregnancy

Any female subjects that are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccine/placebo but may continue other study procedures at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE, as described in Section 8.1.1 and 8.1.2, and will be followed as described in Section 8.4.4.

A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 8.4. Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related in time to the receipt of the investigational product will be reported to GSK Biologicals as described in Section 8.4. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

Information on pregnancies identified during screening/prior to vaccine administration is not required to be collected and communicated to safety.

8.3. Detecting and recording adverse events, serious adverse events and pregnancies

8.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies

Solicited AEs will be evaluated only in subjects who are part of the 7-day diary card subset. Unsolicited AEs will be evaluated in all subjects from Day 0 to Day 29 after each vaccination.

All AEs occurring from Day 0 to Day 29 after each vaccination must be recorded into the Adverse Event screen in the subject's eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

SAEs will be evaluated in all subjects. The standard time period for collecting and recording SAEs will begin at Day 0 and continue until Month 14 for each subject. See Section 8.4 for instructions on reporting and recording SAEs.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (e.g. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine or any fatal SAE will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

NOADs and other immune mediated inflammatory disorders will be evaluated in all subjects during the entire study period (Section 8.3.2.5).

Medically attended visits will be evaluated in all subjects from Day 0 until Month 8 (Section 8.3.2.4)**.**

Intercurrent medical conditions (Section 6.7) will be recorded in all subjects throughout the entire study period.

An overview of the protocol-required reporting periods for AEs and SAEs, NOADs and other immune mediated inflammatory disorders, medically attended visits, pregnancies, and intercurrent medical conditions in study ZOSTER-006 is shown in Table 14.

Table 14 Reporting periods for AEs, SAEs, new onset of autoimmune diseases, medically attended visits, pregnancies and intercurrent medical conditions in study ZOSTER-006

									CONTACT (monthly after Visit 3 until study conclusion, except at months that coincide with the subject's scheduled visits)				
Study activity	**VISIT 1 DOSE 1**				**VISIT 2 DOSE 2**			**VISIT 3**	**CONTACT**	**VISIT 4**	**VISIT 5**	**VISIT 6**	**Study conclusion contact**
Timing of reporting	**Day 0/ Month 0**	**Day 6 post Dose 1**	**Day 29 post Dose 1**		**Day 0/ Month 2**	**Day 6 post Dose 2**	**Day 29 post Dose 2**	**Month 3**	**Month 8**	**Month 14**	**Month 26**	**Month 38**	
Reporting of solicited AEs (only in 7-day diary card subset)													
Reporting of unsolicited AEs													
Reporting of all SAEs until Month 14													
Reporting of SAEs related to study participation or GSK concomitant medication/vaccine or any fatal SAE after Month 14 until study conclusion													
Reporting of NOADs and other immune mediated inflammatory disorders													
Reporting of medically attended visits until Month 8													
Reporting of pregnancies													
Recording of intercurrent medical conditions													

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 14. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.3.2. Evaluation of adverse events and serious adverse events

8.3.2.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of soliciting AEs, the subject should be asked a non-leading question such as:

'Have you felt different in any way since receiving the vaccine or since the previous visit?'

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE on the eCRF or SAE Report screens as applicable. It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals instead of the appropriate completed AE/SAE screens in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

8.3.2.2. Assessment of adverse events

8.3.2.2.1. Assessment of intensity

Intensity of the following AEs will be assessed as described:

Table 15 Intensity scales for solicited symptoms

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C/°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Gastrointestinal symptoms normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Myalgia	0	Normal
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Shivering	0	None
	1	Shivering that is easily tolerated
	2	Shivering that interferes with normal activity
	3	Shivering that prevents normal activity

*Fever is defined as: rectal temperature ≥38°C (100.4°F)/axillary temperature ≥37.5°C (99.5°F)/oral temperature ≥37.5°C (99.5°F)/tympanic temperature on oral setting ≥37.5°C (99.5°F)/tympanic temperature on rectal setting ≥38°C (100.4°F).The preferred route for recording temperature in this study will be oral.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals using GSK Biologicals' standard grading scale based on the US Food and Drug Administration (FDA) guidelines for Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers enrolled in Preventive Vaccine Clinical Trials" [FDA, 2007].

0 : < 20 mm diameter
1 : ≥ 20 mm to ≤ 50 mm diameter
2 : > 50 mm to ≤ 100 mm diameter
3 : > 100 mm diameter

Temperature (measured by oral, axillary or tympanic route) will be scored at GSK Biologicals as follows:

0	:	< 37.5°C
1	:	37.5°C to 38.0°C
2	:	38.1°C to 39.0°C
3	:	> 39.0°C

The investigator will assess of the maximum intensity that occurred over the duration of the event for all other AEs, i.e. unsolicited symptoms, including SAEs reported during the study. The assessment will be based on the investigator's clinical judgement.

The intensity of each AE and SAE recorded in the eCRF or SAE screens, as applicable, should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities. Such an AE would, for example prevent attendance at work and would necessitate the administration of corrective therapy.

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.2.

8.3.2.2.2. Assessment of causality

The investigator is obligated to assess the relationship between investigational vaccine and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship. Alternative plausible causes, based on natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational vaccine will be considered and investigated. The investigator will also consult the IB in the determination of his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccines administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational vaccine?

NO	:	The AE is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the AE.
YES	:	There is a reasonable possibility that the vaccine(s) contributed to the AE.

Non-serious and serious AEs will be evaluated as two distinct events. If an event meets criteria to be determined 'serious' (Section 8.1.2 for definition of serious adverse event), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors applicable to each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine, if applicable.
- Erroneous administration.
- Other cause (specify).

8.3.2.3. Assessment of outcomes

Outcome of any non-serious AE (i.e. unsolicited AE) occurring from Day 0 to Day 29 after each vaccination or any SAE reported during the entire study will be assessed as:

- Recovered/resolved.
- Not recovered/not resolved.
- Recovering/resolving.
- Recovered with sequelae/resolved with sequelae.

- Fatal (SAEs only).

8.3.2.4. Medically attended visits

The subject will be asked if the subject received medical attention defined as hospitalization, an emergency room visit or a visit to or from medical personnel (medical doctor) for any reason, other than routine health care visits, from the first vaccination until Month 8, and this information will be recorded in the eCRF.

8.3.2.5. AEs of specific interest

Adverse events of specific interest for safety monitoring include the NOADs and other immune mediated inflammatory disorders, such as those listed below.

Occurrences of AEs of specific interest will be reported throughout the entire study period, whether or not they are considered to be possibly related to the treatment administration. Medical documentation of the events will be reported in appropriate targeted follow-up forms included in the eCRF. These events have also to be reported as AE or SAE as appropriate in the eCRF.

AEs of interest to be reported and documented are the following**:**

- Neuroinflammatory disorders: cranial nerve disorders, multiple sclerosis, demyelinating disease, transverse myelitis, Guillain-Barré syndrome, myasthenia gravis, encephalitis, neuritis.
- Musculoskeletal disorders: systemic lupus erythematosus, cutaneous lupus, Sjogren's syndrome, scleroderma, dermatomyositis, polymyositis, rheumatoid arthritis, polymyalgia rheumatica, reactive arthritis, psoriatic arthropathy, ankylosing spondylitis, undifferentiated spondyloarthropathy.
- Gastrointestinal disorders: Crohn's disease, ulcerative colitis, ulcerative proctitis, celiac disease.
- Metabolic diseases: autoimmune thyroiditis, Grave's or Basedow's disease, Hashimoto thyroiditis, insulin-dependent diabetes mellitus (IDDM), Addison's disease.
- Skin disorders: psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases.
- Other: autoimmune haemolytic anemia, thrombocytopenias, antiphospholipid syndrome, vasculitis, pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune glomerulonephritis, autoimmune uveitis, autoimmune myocarditis, sarcoidosis, Stevens-Johnson syndrome.

Medical or scientific judgment should be exercised in deciding whether other disorders/diseases have autoimmune origin and should be reported as appropriate.

8.4. Reporting and follow-up of adverse events, serious adverse events and pregnancies

8.4.1. Prompt reporting of serious adverse events and other events to GSK Biologicals

SAEs will be reported promptly to GSK as described in Table 16 once the investigator determines that the event meets the protocol definition of an SAE.

Pregnancies will be reported promptly to GSK as described in Table 16 once the investigator becomes aware of a pregnancy in the time period defined in Section 8.3. The subject will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether that be full-term or premature, information on the status of the mother and child will be forwarded to GSK. Generally, follow-up should be no longer than 6 to 8 weeks following the estimated delivery date.

Table 16 Time frames for submitting SAEs and other events reports to GSK Biologicals

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours*	SAE screen	24 hours*	SAE screen
Pregnancy	24 hours*	Pregnancy Report Form	24 hours*	Pregnancy Report Form

* Time frame allowed after receipt or awareness of the information.

In case the electronic reporting system is temporarily unavailable, a back up system is in place. Please refer to Section 8.4.3 for a detailed description.

Please see the Sponsor Information Sheet for details on study contact for reporting SAEs.

Back-up Study Contact for Reporting SAEs
GSK Biologicals Clinical Safety & Pharmacovigilance
Fax: [redacted] or [redacted]
24/24 hour and 7/7 day availability

8.4.2. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.4.1. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a

SAE(s) that is both attributable to the investigational product and unexpected. The purpose of the report is to fulfil specific regulatory and Good Clinical Practice (GCP) requirements, regarding the product under investigation.

8.4.3. Completion and transmission of SAEs reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator will complete and submit the information in the SAE screens in eCRF within 24 hours. The SAE screens in eCRF will always be completed as thoroughly as possible with all available details of the event and will be submitted by the investigator. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the SAE screens in eCRF. The SAE screens in eCRF should be updated when additional relevant information is received WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report.

8.4.3.1. Back-up system in case the electronic SAE reporting system does not work

If the SAE reporting system has been down for 24 hours, the investigator or his/her delegate should fax an SAE report form directly to the GSK Central Safety department (please refer to Section 8.4.1) within 24 hours. The maximum timeline for reporting SAEs to central safety is therefore 48 hours.

NB. This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow.

As soon as the electronic reporting system is working again, the investigator or delegate must update the SAE screens in the eCRF within 24 hours.

The final valid information for regulatory reporting will be the information reported through the electronic system.

When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information is to be recorded on the paper SAE Report Form, with all changes signed and dated by the investigator. The updated SAE Report Form should be sent to GSK Biologicals WITHIN 24 HOURS of receipt of the follow-up information.

In rare circumstances, if the electronic system for reporting SAEs does not work and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by email or by mail. Initial notification via the telephone does not replace the need for the investigator to complete and submit SAE screens in the eCRF (or complete and sign the SAE Report Form if back-up system need to be used).

In the event of a death determined by the investigator to be related to vaccination, completion of SAE screens in the eCRF/sending of the fax (if electronic SAE reporting

system does not work or after freezing of the subject's eCRF) must be accompanied by telephone call to the Study Contact for Reporting SAEs.

8.4.4. Follow-up of adverse events and serious adverse events

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until study conclusion.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

Cases of new onset of autoimmune diseases and other immune-mediated inflammatory disorders documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until study conclusion.

Investigators will follow-up subjects:

- With SAEs or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.
- Or, in the case of other non-serious AEs, cases of new onset of autoimmune diseases, until study conclusion or they are lost to follow-up.

Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such abnormalities noted for any subject must be made available to the Site Monitor.

GSK Biologicals may request that the investigator perform or arrange for the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

8.5. Treatment of adverse events

Treatment of any adverse event is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF. Refer to Section 6.6.

8.6. Unblinding

GSK Biologicals' policy (incorporating ICH E2A guidance, EU Clinical Trial Directive and Federal Regulations) is to unblind any serious adverse event (SAE) report associated with the use of the investigational product, which is unexpected and attributable/suspected, prior to regulatory reporting. The GSK Biologicals' Central Safety physician is responsible for unblinding the treatment assignment in accordance with specified time frames for expedited reporting of SAEs (refer to Section 8.4.1).

8.7. Emergency unblinding

The investigator, or other physician managing the subject, should contact GSK Biologicals' Central Safety Physician to discuss the need for emergency unblinding. Alternatively the investigator may contact the local contact who will contact the GSK Central Safety Physician.

An investigator should request for unblinding of the subject's treatment code only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the investigational study vaccine(s)/product(s) is essential for the clinical management or welfare of the subject.

The GSK Biologicals' Central Safety Office will be allowed to access the individual randomisation code. The code will be broken by the GSK Biologicals' Central Safety physician (see below and Study Contact for Emergency Code Break in Sponsor Information) only in the case of medical events that the investigator/physician in charge of the subject feels cannot be treated without knowing the identity of the study vaccine(s)/product(s).

GSK Biologicals Central Safety Physician (Study Contact for Emergency Code Break)
Mobile phones for 7/7 day availability: Outside US/Canada: [redacted] (GSK Biologicals Central Safety Physician) For US/Canada only: [redacted] (Head Safety Evaluation and Risk Management North America) Back-up mobile phone contact (all countries): [redacted]

8.8. Subject card

Study subjects must be provided with the address and telephone number of the main contact for information about the trial.

Investigator/delegate should therefore provide a "subject card" to each subject. The aim of this card is to inform any physician having to deal with a subject in an emergency

situation that the subject is in a clinical trial and that he/she can contact the trial investigator for more relevant information.

Subjects must be instructed to keep these cards in their possession at all times.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for the concluding visit/is available for the concluding contact foreseen in the protocol is considered to have completed the study.

9.2. Subject withdrawal

Subjects who are withdrawn because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as result of a SAE/AE until resolution of the event (Section 8.4).

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not come back for the concluding visit/was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject himself/herself, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event.

- Moved from the study area.
- Lost to follow-up.
- Death.
- Other (specify).

9.2.2. Subject withdrawal from investigational vaccine

A 'withdrawal' from the investigational vaccine refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the investigational vaccine may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the investigational vaccine will be documented on the Vaccine Administration screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the subject himself/herself, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Other (specify).

10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

10.1. Primary endpoint

- Confirmed HZ cases

– Confirmed HZ cases during the study in the modified total vaccinated cohort (mTVc).

10.2. Secondary endpoints

- Occurrence of overall PHN

– Incidence of PHN calculated using the mTVc;

- Duration of severe 'worst' HZ-associated pain

– Duration of severe 'worst' HZ-associated pain following the onset of a confirmed HZ rash over the entire pain reporting period as measured by the ZBPI in subjects with confirmed HZ;

- Incidence of overall and HZ-related mortality

– Incidence of overall and HZ-related mortality during the study;

- Incidence of HZ complications
  - Incidence of HZ complications during the study in subjects with confirmed HZ;
- Incidence of overall and HZ-related hospitalizations
  - Incidence of overall and HZ-related hospitalizations during the study;
- Duration of pain medication administered for HZ
  - Duration of pain medication administered for HZ during the study in subjects with confirmed HZ;
- Solicited local and general symptoms in a subset of subjects
  - Occurrence, intensity of each solicited local symptom within 7 days (Days 0 – 6) after each vaccination, in subjects included in the 7-day diary card subset;
  - Occurrence, intensity and relationship to vaccination of each solicited general symptom within 7 days (Days 0 – 6) after each vaccination, in subjects included in the 7-day diary card subset;
- Unsolicited AEs
  - Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days (Days 0 – 29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification, in all subjects;
- Serious AEs
  - Occurrence and relationship to vaccination of all SAEs from Month 0 to Month 14 in all subjects;
  - Occurrence of SAEs related to study participation or to a concurrent GSK medication/vaccine during the entire study period in all subjects;
  - Occurrence of any fatal SAEs during the entire study period in all subjects;
- Occurrence of pre-defined AEs
  - Occurrence and relationship to vaccination of any NOADs and other immune mediated inflammatory disorders during the entire study period in all subjects;
- Occurrence of medically attended visits
  - Occurrence and relationship to vaccination of medically attended visits (defined as hospitalizations, emergency room visits or visits to or from medical personnel), other than routine health care visits, from Month 0 to Month 8 in all subjects.

10.3. Exploratory endpoints

- Acute HZ severity
  - Acute HZ severity as determined by the mean Area Under Curve (AUC) of the severity-by-duration of HZ-associated pain as measured by the ZBPI during a 4-

week period following the onset of confirmed HZ in subjects with confirmed HZ;

- Interference of HZ with QoL
  - Interference of HZ with QoL as measured by ZBPI in subjects with confirmed HZ;
  - Interference of HZ with QoL as measured by EQ-5D in subjects with confirmed HZ;
  - Interference of HZ with QoL as measured by SF-36 in subjects with confirmed HZ;
- HZ BOI
  - HZ BOI as determined by the mean AUC of the severity-by-duration HZ-associated pain during a 26 week period following the onset of the HZ rash in the mTVc;
- CMI in terms of frequencies of antigen-specific CD4 T cells at Months 0, 3, 14, 26 and 38
  - Frequencies of CD4 T cells with antigen-specific Interferon gamma (IFN-γ) and/or Interleukin-2 (IL-2) and/or Tumour Necrosis Factor alpha (TNF-α) and/or CD40 Ligand (CD40L) secretion/expression to gE and VZV as determined by ICS in a subset of subjects at Months 0, 3, 14, 26 and 38;
- Antigen-specific Ab concentrations at Months 0, 3, 14, 26 and 38
  - Anti-gE and anti-VZV Ab concentrations as determined by ELISA, in a subset of subjects at Months 0, 3, 14, 26 and 38;
- Anti-VZV neutralizing Ab titres at Months 0, 3, 14, 26 and 38
  - Anti-VZV neutralizing Ab titres as determined by the neutralization assay in a subset of subjects at Months 0, 3, 14, 26 and 38.

10.4. Estimated sample size

10.4.1. Sample size assumptions

Table 17 presents the assumptions used for the sample size calculations for both studies ZOSTER -006 and ZOSTER-022. Simulations were performed to estimate the sample size required as a consequence of unequal VE estimates by age strata. A drop-out rate of 5% per year and an incidence of 5% for non-compliance to vaccine schedule were taken into account for sample size calculations.

Table 17 Assumptions for incidences under placebo, and VE used for trial simulations

Age	HZ Incidence (% / Year)	HZ VE	PHN Incidence in HZ subjects (% /Year)	On top PHN VE in HZ subjects [2]	Overall PHN VE in HZ subjects
Overall[1]	~0.7	~68%	~11%	NA	~71%
50-59	0.5	82%	5%	5%	83%
60-69	0.8	72%	9.5%	5%	73%
70-79	1.1	58%	17%	35%	73%
≥80	1.1	36%	28%	25%	52%
≥70 [1]	1.1	~53%	~19%	NA	~71%

[1] The overall HZ incidence and the incidence in the ≥ 70YOA age strata depends on the age-stratification considered
[2] VE against PHN in people with HZ, i.e., a comparison of VE between placebo recipients with HZ who got PHN versus vaccine recipients with HZ who got PHN.

10.4.2. Significance level

The overall efficacy analyses will be performed at the 5% 2-sided significance level. No significance adjustment is planned in ZOSTER-006 or ZOSTER-022 for the efficacy analyses due to the futility analyses, since GSK has no current intention to submit the data to Regulatory Authorities for registration.

The scope of the statistical testing of ZOSTER-006, ZOSTER-022 and the pooling of the data from both studies are described in Section 10.4.4 and summarised in Table 18. The pooled analysis of studies ZOSTER-006 and ZOSTER-022 is planned provided the following conditions are met, as defined in Section 10.4.4:

1. Clinically meaningful overall HZ VE in subjects ≥ 50 YOA is reached in ZOSTER-006;
2. Clinically meaningful HZ VE is reached in subjects ≥ 70 YOA in ZOSTER-022;
3. Statistically significant PHN VE is reached in subjects ≥ 70 YOA in ZOSTER-022.

The pooled analysis of data in subjects ≥ 50 YOA accrued in study ZOSTER-006 and data in subjects ≥ 70 YOA collected in study ZOSTER-022 allows a more robust estimation of overall PHN VE, HZ VE in subjects ≥ 70 YOA and PHN VE in subjects ≥ 70 YOA. Both objectives, HZ VE in subjects ≥ 70 YOA and PHN VE in subjects ≥ 70 YOA, will be assessed in study ZOSTER-022. An estimation of the confidence interval (CI), based on pooled data will be provided in addition. The statistical evaluation of the other objectives of the pooled analysis, including the overall PHN VE primary objective and the PHN VE in subjects with HZ secondary objective, will only be performed on the pooled data from both studies. According to these restrictions in the testing sequence, the type 1 error is maintained at 2.5% (1-sided). Each statistical evaluation in the pooled analysis is either preceded by an evaluation in ZOSTER-006, ZOSTER-022, or both; or is only performed on the pooled database during the pooled analysis. As a consequence, there is no increase in the significance level of each objective due to a possible multiple testing problem.

Table 18 Summary of statistical evaluations of primary and secondary objectives for studies ZOSTER-006, ZOSTER-022 and the pooled analysis

Analysis	Endpoint	50-59 YOA	60-69 YOA	≥70 YOA	All age strata
ZOSTER-006	HZ VE	S	S	O	P
	PHN VE	-	-	-	-
	PHN VE in HZ subjects	-	-	-	-
ZOSTER-022	HZ VE	-	-	P	-
	PHN VE	-	-	P	-
	PHN VE in HZ subjects	-	-	-	-
Pooled analysis	HZ VE	-	-	R	-
	PHN VE	-	-	R	P
	PHN VE in HZ subjects	-	-	-	S*

P: Primary objective, well powered
R: Re-estimation of VE for an objective already demonstrated previously in ZOSTER-006 or ZOSTER-022.
S: Secondary objective, appropriately powered
S*: Secondary objective, low power
O: Study not well powered under current assumptions although may lead to significance
- : Estimates not relevant or not considered for a statistical evaluation

10.4.3. Success criteria

The ZOSTER-006 study is designed to demonstrate clinically meaningful overall HZ VE in subjects of ≥ 50 YOA. Clinically meaningful overall HZ VE will be demonstrated if the lower limit of the 95% CI is above 25%; however, the study has been powered for the more robust lower limit of 40%. That primary analysis will be supported by sensitivity analyses of the HZ VE in the 50-59 YOA and 60-69 YOA strata. Clinically meaningful HZ VE by age strata will be demonstrated if the lower limit of the 95% CI is above 10%. The ZOSTER-006 study is not powered to demonstrate significant HZ VE within the ≥ 70 YOA stratum. That objective is not within the scope of this study and is deferred to the analysis of ZOSTER-022 study data.

The ZOSTER-022 study is designed to demonstrate clinically meaningful HZ VE in subjects ≥ 70 YOA. Clinically meaningful HZ VE will be demonstrated in that age range if the lower limit of the 95% CI is above 10%. The ZOSTER-022 study is also powered to demonstrate statistical significant PHN VE. Statistical significance of PHN VE in ≥ 70 YOA randomized subjects will be demonstrated if the lower limit of the 95% CI is above 0%. The PHN VE co-primary objective will be tested provided the primary HZ VE is demonstrated and no adjustment of significance level will be made.

Both studies ZOSTER-006 and ZOSTER-022 will be performed in parallel, in similar centres and using essentially identical study designs (aside from the age distribution of the enrolled population). The pooled analysis of those 2 studies is therefore deemed acceptable and will provide additional precision in estimating VE. Homogeneity of relative risk between the 2 studies will be demonstrated. The pooled analysis of studies ZOSTER-006 and ZOSTER-022 is intended to provide consolidated estimations of the clinically meaningful HZ VE in all subjects ≥ 70 YOA and clinically meaningful overall PHN VE in mTVc subjects randomized to studies ZOSTER-006 and ZOSTER-022.

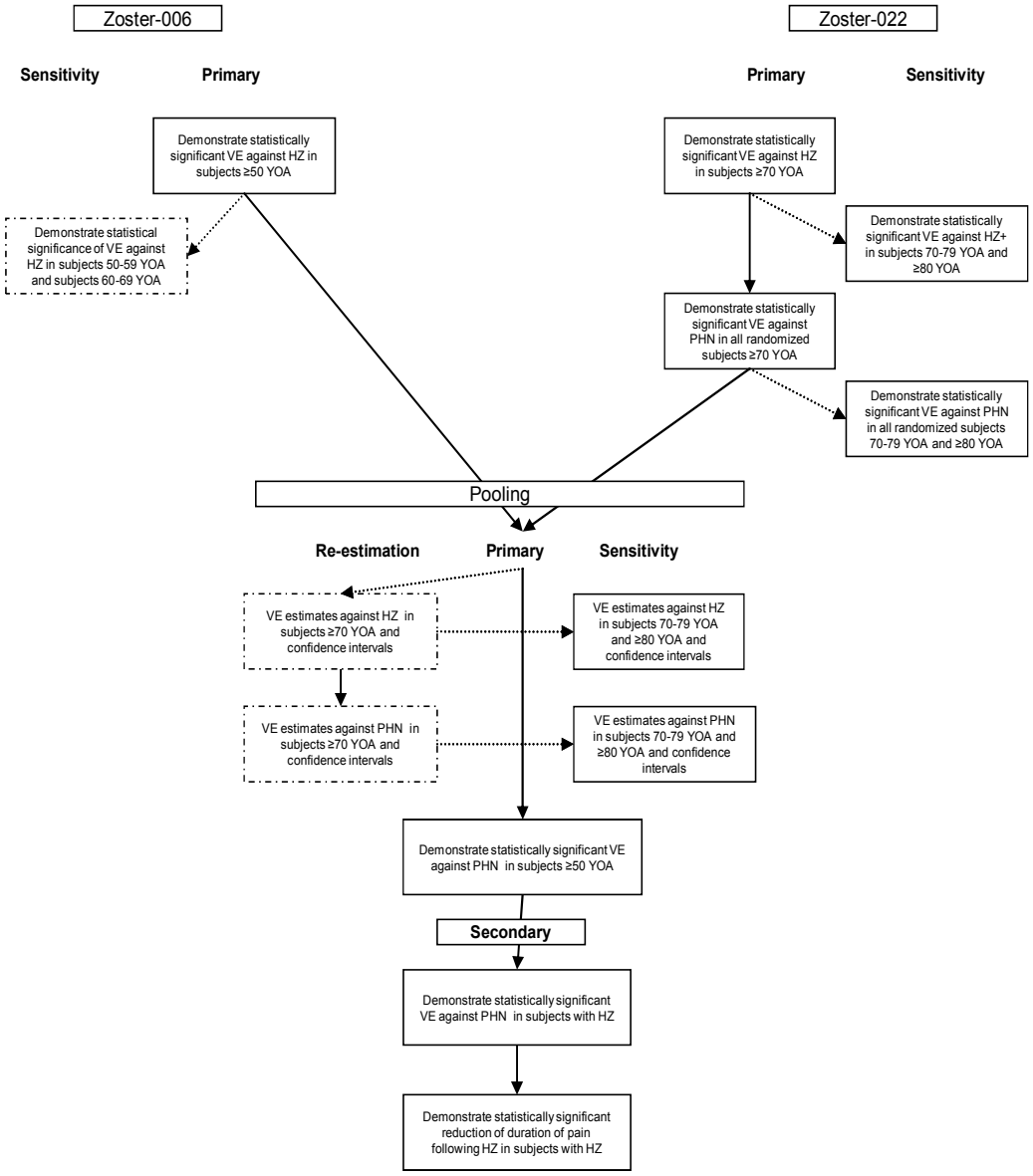
Clinically meaningful HZ VE in subjects ≥ 70 YOA will be demonstrated if the lower limit of the 95% CI is above 10% and clinically meaningful overall PHN VE will be demonstrated if the lower limit of the 95% CI is above 25%.

10.4.4. Gatekeeping strategy

The statistical testing for each study will proceed sequentially using an order for the gatekeeping families defined prospectively (see below). If more than one test is involved within the same family, the Hochberg's set up method [Hochberg, 1988] will be used to adjust the p-values for the multiple test schemes. All secondary objectives mentioned in protocols ZOSTER-006 and ZOSTER-022 will be evaluated within each report. However, the overall type 1 error of 5% two-sided can only be fully controlled for those objectives that are mentioned sequentially in the gatekeeping strategy presented below. If a gatekeeping family fails to be demonstrated, the remaining planned tests will be performed, but the type 1 error of the following families may not be fully controlled.

The enrolment of subjects ≥ 70 YOA in both studies and the need to provide an estimation of the HZ VE and PHN VE across the two studies, requires the gatekeeping strategy to be defined across the two studies and the pooling. The following pathway is proposed and will be confirmed prior to unblinding of the treatment assignment.

The primary objective of ZOSTER-006 and both co-primary objectives of ZOSTER-022 should be demonstrated prior to testing the primary objective of the pooling. The second co-primary of ZOSTER-022 will be tested at 5% 2-sided following demonstration of the first co-primary, also at 5%. Sensitivity analyses will be performed by age strata for each of the primary or co-primary objectives.


Zoster-006
Zoster-022
Sensitivity
Primary
Primary
Sensitivity
Demonstrate statistically significant VE against HZ in subjects ≥50 YOA
Demonstrate statistical significance of VE against HZ in subjects 50-59 YOA and subjects 60-69 YOA
Demonstrate statistically significant VE against HZ in subjects ≥70 YOA
Demonstrate statistically significant VE against HZ+ in subjects 70-79 YOA and ≥80 YOA
Demonstrate statistically significant VE against PHN in all randomized subjects ≥70 YOA
Demonstrate statistically significant VE against PHN in all randomized subjects 70-79 YOA and ≥80 YOA
Pooling
Re-estimation
Primary
Sensitivity
VE estimates against HZ in subjects ≥70 YOA and confidence intervals
VE estimates against HZ in subjects 70-79 YOA and ≥80 YOA and confidence intervals
VE estimates against PHN in subjects ≥70 YOA and confidence intervals
VE estimates against PHN in subjects 70-79 YOA and ≥80 YOA and confidence intervals
Demonstrate statistically significant VE against PHN in subjects ≥50 YOA
Secondary
Demonstrate statistically significant VE against PHN in subjects with HZ
Demonstrate statistically significant reduction of duration of pain following HZ in subjects with HZ

The primary objectives of the pooling include the re-estimation of HZ VE and PHN VE in subjects ≥ 70 YOA. Both hypotheses are planned to be already demonstrated in ZOSTER-022 and, as a consequence, do not affect the overall type 1 error and are not considered within the main path of the gatekeeping strategy.

The first hypothesis to be tested from the pooled dataset consists in the overall PHN VE in subjects ≥ 50 YOA. Further secondary objectives are then sequentially tested following demonstration of overall PHN VE.

1. Demonstrate statistically significant reduction in incidence of PHN (90 days or more) in subjects with HZ
2. Demonstrate statistically significant reduction of duration of severe 'worst' pain following HZ in subjects with HZ.

10.4.5. Sample sizes

The sections below describe the estimated number of subjects required to achieve the objectives of studies ZOSTER-006, ZOSTER-022 and the pooling of data from both studies. The country allocation and various subsets are also described. For operational reasons, the same subjects may be randomized to the more than one subset.

10.4.5.1. Primary objective

The final analysis of the ZOSTER-006 study is planned after the accumulation of at least 196 confirmed HZ cases across all age strata (primary condition) in the primary cohort for efficacy. Other conditions for triggering the analyses are described in Section 10.4.5.6. It is estimated that 196 confirmed HZ cases would provide ~97% power to demonstrate an overall HZ VE of at least 40% assuming a true HZ VE of 68% (including essential sensitivity analyses in 50-59 and 60-69 YOA strata). Table 19 presents the sample sizes overall and according to the age-stratification ratio 8:5:3:1 (50-59, 60-69, 70-79 and ≥ 80 YOA) using a randomization ratio 1:1 for vaccine or placebo. The sample size was selected in order to provide the required number of HZ cases within a follow-up time of ~3 years. The stratification ratios were selected in order to achieve similar numbers of HZ cases in the three main age strata. If large disparities in the total number of HZ cases (placebo and vaccine groups combined) are observed during the trial between the age strata, sample size reassessment or modification of the stratification ratios may be considered.

Table 19 Expected median number of HZ and PHN cases in ZOSTER-006

Age strata	Sample size	Median number of HZ cases		Median number of PHN cases	
		Placebo	All	Placebo	All
50-59 YOA	7520	48	57	3	3
60-69 YOA	4700	48	62	4	6
70-79 YOA	2820	40	56	6	8
≥ 80 YOA	940	13	22	4	5
All	15980	149	196	17	23

Median number of cases calculated based on 1000 trial simulations.

The final analysis of the ZOSTER-022 study is planned after the accumulation at least 65 PHN cases (expected median are approximately 40 PHN cases in 70-79 YOA and approximately 26 PHN cases in ≥ 80 YOA strata) are accrued from study ZOSTER-022 (primary condition for triggering analysis), and at least 278 confirmed HZ cases (expected median number of cases is 310 HZ cases) across both 70-79 YOA (median of 222 HZ cases) and ≥ 80 YOA (median of 87 HZ cases) strata. All PHN or HZ cases should be accrued in the primary cohort for efficacy. Other conditions for triggering the analyses are described in Section 10.4.5.6. This number of HZ cases would provide ~99% power to demonstrate HZ VE of at least 10% under the assumptions described above in subjects ≥ 70 YOA. This number of PHN cases would provide ~97% to demonstrate statistically significant PHN VE in all randomized subjects, in addition to the HZ objective above. Table 20 presents the sample sizes overall and according to the age-stratification ratio 3:1 (70-79 and ≥ 80 YOA) and a randomization ratio 1:1. The sample size was selected in order to provide the required number of HZ cases within a follow-up time of ~3 years. If the accrual rate of HZ or PHN cases is much lower than expected, a blinded sample size reassessment may be considered for which the details would be available prior to the first interim analysis.

Table 20 Expected median number of HZ and PHN cases in ZOSTER-022

Age strata	Sample size	Median number of HZ cases		Median number of PHN cases	
		Placebo	All	Placebo	All
70-79 YOA	10884	157	222	32	40
≥ 80 YOA	3628	54	87	17	26
All	14512	210	310	49	65

Median number of cases calculated based on 1000 trial simulations.

The number of HZ cases, PHN cases and the total sample size for each age strata for the **pooled** analysis are driven by the number of the cases and sample size in both the ZOSTER-006 and ZOSTER-022 studies (see Table 21). The total number of PHN cases and the number of PHN cases in subjects ≥ 70 YOA that each study (ZOSTER-006 and ZOSTER-022) will contribute to the pooled analysis may vary from what has been described above. It is estimated however that the median total number of PHN cases in ≥ 50 YOA subjects is approximately 88, among which at least ~79 PHN cases would be accrued in the ≥ 70 YOA age strata. A total of at least 88 PHN cases provide 93% power to demonstrate an overall PHN VE of at least 25%.

Table 21 Expected median number of HZ and PHN cases in pooled ZOSTER-006 and ZOSTER-022

Age strata	Sample size	Median number of HZ cases		Median number of PHN cases	
		Placebo	All	Placebo	All
50-59 YOA	7520	48	57	2	3
60-69 YOA	4700	48	61	4	6
70-79 YOA	13704	196	278	32	48
≥ 80 YOA	4568	57	110	17	31
All	30492	360	506	57	88

Median number of cases calculated based on 1000 trial simulations.

10.4.5.2. Secondary objectives

The ZOSTER-006 sample size is sufficient to demonstrate a HZ VE of at least 10% for the 50-59 YOA and 60-69 YOA age strata with powers of 99% and 98%, respectively.

The ZOSTER-022 sample size is sufficient to demonstrate a HZ VE of at least 10% for the ≥ 70 YOA stratum with a power of 99%.

The sample size of the pooled studies ZOSTER-006 and ZOSTER-022 provide 22% chance to demonstrate statistically significant PHN VE (LL above 0%) in those subjects presenting with an HZ episode.

10.4.5.3. Futility analyses and sample size re-assessment

The study may involve one (or more) unblinded futility analyses performed by the IDMC. One futility analysis is planned after approximately 25% of the total HZ cases are observed and/or when at least 20% of the total HZ cases are observed in each age stratum. The precise timing of that analysis may be triggered by a blinded review of the HZ accrual in ZOSTER-006 and/or ZOSTER-022. The futility decision rules will be described in the IDMC Charter and statistical analysis plan. Essentially, no increase in the type 1 error of the final analysis is incurred as no decision of early termination for efficacy will be made by GSK at any of those analyses. Adequate trial duration is required to accumulate enough PHN information and safety information necessary for regulatory purposes. Conversely, a slight reduction in the power of the study can be caused due to the futility rules. A conservative futility boundary or a predictive power threshold [Proschan, 2006] in the range of ~30% is anticipated but the actual functional form of the beta-spending function or the predictive power threshold used for the trial will be defined in the IDMC Charter. Information collected in both trials may be combined to calculate the predictive power for each trial separately and together.

Table 22 below provides information about the ZOSTER-006 conditional power with respect to the overall HZ VE LL 40% (i.e. without consideration for by-age HZ VE LL 10%) calculated following 25% of accrual and for different values of the observed HZ VE or futility boundaries. Irrespective to the futility boundary considered, the conditional power calculated under the sample size (alternative) assumptions remains very high

although the conditional power calculated under the observed HZ VE is close to zero. A more reasonable prediction for the power at the final analysis that will be implemented is the expected conditional power or Bayesian predictive power, following integration of the conditional power on the posterior distribution of the VE in each age strata and accounting for the proportion density of each stratum in the total number of HZ cases at the final analysis.

Table 22 Observed HZ VE at ZOSTER-006 Interim to trigger futility stopping and conditional power at the final analysis calculated under alternative hypothesis and current observed VE

						VE Confidence Interval[e]	
Futility analysis	Rho[a]	# HZ cases	Observed VE[b]	CP under alternative[c]	CP under observed VE[d]	Lower Limit	Upper Limit
1	1	49	33.6%	87.2%	0.0%	-102.6%	70.8%
2	1	98	46.9%	78.8%	1.8%	0.2%	69.5%
1	2	49	24.7%	81.5%	0.0%	-137.4%	71.8%
2	2	98	44.6%	71.5%	0.6%	-4.2%	69.7%
1	3	49	17.0%	76.1%	0.0%	-168.1%	72.5%
2	3	98	42.5%	64.3%	0.2%	-8.2%	69.9%
1	4	49	9.7%	69.7%	0.0%	-201.7%	73.2%
2	4	98	40.4%	56.5%	0.0%	-12.3%	70.1%

a: Rho defines the form of the futility boundary. A conservative (O'Brian-Fleming) boundary is defined for Rho=3 and a more aggressive (Pocock) boundary is defined for Rho = 1.
b: Observed HZ VE that triggers futility conditions at each futility analysis.
c: Conditional power at the final analysis calculated under the sample size (alternative) assumptions
d: Conditional power at the final analysis calculated under the observed HZ VE at the interim
e: HZ VE repeated confidence interval and approximate VE posterior distribution at the interim over which the mean (expected) conditional power may be calculated.

Table 23 below provides information about the ZOSTER-022 conditional power with respect to the HZ VE LL 40% in subjects of ≥ 70 YOA (i.e., without consideration for statistically significant PHN VE in subjects of ≥ 70 YOA) calculated following 25% of accrual and for different values of the observed HZ VE or futility boundaries. Irrespective to the futility boundary considered, the conditional power calculated under the sample size (alternative) assumptions remains very high although the conditional power calculated under the observed HZ VE is close to zero. A more reasonable prediction for the power at the final analysis that will be implemented is the expected conditional power or Bayesian predictive power, following integration of the conditional power on the posterior distribution of the VE in each age strata and accounting for the proportion density of each stratum in the total number of HZ cases at the final analysis.

Table 23 Observed HZ VE at ZOSTER-022 Interim to trigger futility stopping and conditional power at the final analysis calculated under alternative hypothesis and current observed VE

Futility analysis	Rho[a]	# HZ cases	Observed VE[b]	CP under alternative[c]	CP under observed VE[d]	VE Confidence Interval[e]	
						Lower Limit	Upper Limit
1	1	77	18.7%	79.6%	0.1%	-85.7%	53.2%
2	1	155	31.3%	71.4%	3.4%	-9.6%	52.7%
1	2	77	8.5%	71.7%	0.0%	-112.6%	53.7%
2	2	155	28.5%	62.1%	1.0%	-14.1%	52.8%
1	3	77	-0.2%	64.1%	0.0%	-136.3%	54.0%
2	3	155	26.0%	53.2%	0.3%	-18.1%	52.9%
1	4	77	-8.4%	56.3%	0.0%	-160.8%	54.3%
2	4	155	23.5%	44.5%	0.1%	-22.3%	53.0%

a. Rho defines the form of the futility boundary. A conservative (O'Brian-Fleming) boundary is defined for Rho=3 and a more aggressive (Pocock) boundary is defined for Rho = 1.
b. Observed HZ VE that triggers futility conditions at each futility analysis.
c. Conditional power at the final analysis calculated under the sample size (alternative) assumptions
d. Conditional power at the final analysis calculated under the observed HZ VE at the interim
e. HZ VE repeated confidence interval and approximate VE posterior distribution at the interim over which the mean (expected) conditional power may be calculated.

The futility approach, whether by futility boundary or conditional or predictive power implemented is not-bounding with regards to the decision actually taken at the time of the analysis. The IDMC recommendations with regards to futility of the study may not be endorsed by GSK Steering Committee without affecting the overall significance level.

Blinded sample size reassessment may be performed by GSK in one or more age strata in order to keep the same trial duration if accrual is much lower than expected. The sample size re-evaluation will be done independently from the data provided to the IDMC. Conditions for the sample size reassessment need to be defined further.

10.4.5.4. Provisional region and sub-population allocations

The provisional region allocation for study ZOSTER-006 is presented in Table 24. In study ZOSTER-006, eligible subjects will be randomized to investigational vaccine/placebo according to a 1:1 ratio.

Subjects will be stratified by age: 50-59 YOA; 60-69 YOA; 70-79 YOA and ≥ 80 YOA in an 8:5:3:1 ratio. The main ≥ 70 YOA stratum used for sample size calculation is subdivided into 70-79 and ≥ 80 YOA strata in order to demonstrate efficacy ≥ 80 YOA or in any of these 2 sub-strata taken separately. The study is however not powered to demonstrate efficacy in any of these 2 sub-strata taken separately. In addition, some small percentages of the sample will include frail elderly subjects.

Table 24 Provisional region allocation for study ZOSTER-006

Australasia		Europe		Latin America		North America	
Country	**Sample Size**	**Country**	**Sample Size**	**Country**	**Sample Size**	**Country**	**Sample Size**
Australia Hong Kong Japan S. Korea Taiwan	~3200	Czech Republic Estonia Finland France Germany Italy Spain Sweden United Kingdom	~7560	Brazil Mexico	~2620	Canada US	~2620

10.4.5.5. 7-day diary card subset

The number of subjects in this subset was defined based on the empirical rules that, in absence of a specific AE in a cohort of N subjects, the probability is 95% that the incidence of that AE is less than 1 / (N/3) [Hanley, 1983].

The provisional number of subjects in the 7-day diary card subset in study ZOSTER-006 is shown in Table 25.

Table 25 Provisional number of subjects in the 7-day diary card subset in study ZOSTER-006

Age cohort	50-59 YOA		60-69 YOA		70-79 YOA		≥ 80 YOA		All	
Treatment group	**Vaccine**	**Placebo**	**Vaccine**	**Placebo**	**Vaccine**	**Placebo**	**Vaccine**	**Placebo**	**Vaccine**	**Placebo**
ZOSTER-006	1410	1410	1410	1410	1410	1410	470	470	4880	4880

Note: In addition, study ZOSTER-022 will include a 7-day diary card subset of 1000 subjects (in each 70-79 YOA and ≥ 80 YOA strata, 250 subjects in each treatment group).

10.4.5.6. Immunogenicity Subset

10.4.5.6.1. Assumptions and background information for humoral immunity

Assumptions to estimate the number of subjects to be included in the immunogenicity subset in study ZOSTER-006 and ZOSTER-022 were based on gE-specific humoral immunogenicity data obtained in study ZOSTER-003 for subjects who received two doses of gE 50 µg/AS01$_B$.

10.4.5.6.2. Humoral immune response vaccine take

The humoral vaccine take is assessed in comparison to placebo group using anti-gE or anti-VZV Ab concentrations. The increase observed post dose 2 in study ZOSTER-003 in the gE 50µg/AS01$_B$ group as compared with placebo is about 10-fold for anti-gE Abs.

The CV is about 100% (or In-based variance = 0.693 = 0.832^2), accounting for higher variability in the current study as compared to study ZOSTER-003 due to, but not limited to, inter-country variations. A 4-fold increase in geometric mean over placebo as a lower bound for clinical relevance, in absence of other justification, adjusted for pre-vaccination level, is considered as a threshold for clinical relevance, and will be used as criteria to demonstrate vaccine take.

When expressed on the log-scale, the effect size for clinical significance is Ln(10) / 0.832 = 2.76. When accounting for the superiority requirement of a 4-fold increase over NaCl solution, the effect size is 2.76 – Ln(4) / 0.832= 1.10. Despite the number of blood samplings that should be administered in vaccine and placebo according to the study randomization ratio, it is also reasonable to analyze twice as much vaccine samples than placebo samples. The overall power of the test is conventionally set to ~95% and the type 1 error to 2.5%. Since we may be required to demonstrate that success criteria in all countries involved in the trial, accounting for ~15 countries, the power of the test in each country should be 0.95^(1/15) = 0.996.

Table 26 presents the number of subjects under vaccine (N1) and placebo (N2) required to demonstrate a 4-fold increase in anti-gE Ab concentration geometric means over saline. The number of evaluable blood samples required in each country at post dose 2 is ~55 for vaccine and ~28 for placebo for an overall power of 0.996^15 = 0.95. A slight increase in that number of subjects may be needed as the sample size should be a multiple of 3 for the age stratification. Overall, accounting for the same number of subjects to be sampled in vaccine and placebo groups in each of the 15 to 18 countries in order to maintain the blind, and to have a sufficiently large number of evaluable blood samples, the total number of subjects enrolled into the subset should be 18 x 60 x 2 = ~2160. No comparisons are planned within each age strata at the country level.

Table 26 Power calculations for a T-test for Relevant Superiority

Power	N1/N2	Equivalence margin (E)	Actual difference (D)	Significance level		Standard deviation	
				alpha	beta	SD1	SD2
0.99839	61/32	13.90	23.00	0.02500	0.00161	8.32	8.32
0.99648	**55/28**	**13.90**	**23.00**	**0.02500**	**0.00352**	**8.32**	**8.32**
0.99413	51/26	13.90	23.00	0.02500	0.00587	8.32	8.32
0.99245	49/26	13.90	23.00	0.02500	0.00755	8.32	8.32
0.99031	47/24	13.90	23.00	0.02500	0.00969	8.32	8.32
0.95043	34/17	13.90	23.00	0.02500	0.04957	8.32	8.32
0.90324	28/14	13.90	23.00	0.02500	0.09676	8.32	8.32

Means & SD were multiplied by a 10-fold coefficient in order to allow more precision in the outputs.
N1, N2: number of subjects receiving vaccine (N1) and placebo (N2)

10.4.5.6.3. Humoral immune response inter-region variability

Following the objective of vaccine take, the vaccine geometric mean responses between countries can be compared. This comparison consists of selecting two countries, or group of countries and comparing their means in order to demonstrate equivalence since defining the success criteria in terms of "statistical significance" is not meaningful in this situation. The absence of statistical significance would not support the absence of clinical relevance between regions or countries.

Using Ratio of Geometric Means – Region-wise

An equivalence criteria of 2-fold is considered acceptable when referring to the ratio of geometric means between regions. This threshold ensures that any differences between countries are not clinically relevant as it corresponds to half of the 4-fold increase over placebo, considered as the minimally clinically relevant difference.

The same assumptions as above are used for the calculations. ZOSTER-010 data showed a ratio of geometric means equal to 1.26 between EU and US. A pairwise comparison between each of the 4 main regions may be considered, leading to 6 comparisons. The power of each test should be ~99% for a global power of ~95%.

Table 27 presents the sample size for each individual comparison, assuming absence of true difference between regions, assuming ratio of geometric means equal to 0, 90% (Ln = -0.10) and 75% (Ln = -0.29). A sample size of approximately 60 subjects under vaccine within each region would allow demonstrating equivalence of the two geometric means within a non-clinically relevant range of 2-fold, provided absence of difference in means (true difference = 0). Since each region includes several countries, a pool of at least 3 countries is sufficient within each region to allow the comparison when the ratios of geometric means reach 75%.

Table 27 Power Testing Equivalence Using a Parallel-Group Design (Region)

	Reference Group	Treatment Group						
Power	Sample Size (N1)	Sample Size (N2)	Lower Equiv Limit	Upper Equiv Limit	True Difference	Standard Deviation	Alpha	Beta
0.7490	60	60	-6.93	6.93	-2.90	8.32	0.0250	0.2510
0.9630	120	120	-6.93	6.93	-2.90	8.32	0.0250	0.0370
0.9957	**180**	**180**	**-6.93**	**6.93**	**-2.90**	**8.32**	**0.0250**	**0.0043**
0.9996	240	240	-6.93	6.93	-2.90	8.32	0.0250	0.0004
0.9714	60	60	-6.93	6.93	-1.00	8.32	0.0250	0.0286
0.9998	120	120	-6.93	6.93	-1.00	8.32	0.0250	0.0002
1.0000	180	180	-6.93	6.93	-1.00	8.32	0.0250	0.0000
1.0000	240	240	-6.93	6.93	-1.00	8.32	0.0250	0.0000
0.9897	60	60	-6.93	6.93	0.00	8.32	0.0250	0.0103
1.0000	120	120	-6.93	6.93	0.00	8.32	0.0250	0.0000
1.0000	180	180	-6.93	6.93	0.00	8.32	0.0250	0.0000
1.0000	240	240	-6.93	6.93	0.00	8.32	0.0250	0.0000

Note: Means and Standard Deviation were multiplied by 10 to achieve sufficient precision

If those comparisons should be made within each age strata, leading to a total of 3*6 comparisons, the power of each comparison should be closer to 99.7% in order to maintain the overall power to 0.997^18 = 0.95. The number of countries to be involved in the comparisons should then be at least 4.

Using Ratio of Geometric Means – Country-wise

The same calculations may be performed on a country basis. The table below provides the power for a comparison of one country versus the rest of the world, assuming 15 countries and a ratio of geometric mean equal to 0.90 (LN = -0.10) and 75% (LN = -0.29). A sample of 60 subjects in the country selected is sufficient to allow the comparison versus 900 subjects with a power of at least 95%.

Table 28 Power Testing Equivalence Using a Parallel-Group Design (Country)

	Reference Group	Treatment Group						
Power	Sample Size (N1)	Sample Size (N2)	Lower Equiv Limit	Upper Equiv Limit	True Difference	Standard Deviation	Alpha	Beta
0.9553	**60**	**900**	**-6.93**	**6.93**	**-2.87**	**8.32**	**0.0250**	**0.0447**
0.9757	70	900	-6.93	6.93	-2.87	8.32	0.0250	0.0243
0.9868	80	900	-6.93	6.93	-2.87	8.32	0.0250	0.0132
0.9929	90	900	-6.93	6.93	-2.87	8.32	0.0250	0.0071
0.9962	100	900	-6.93	6.93	-2.87	8.32	0.0250	0.0038
0.9996	60	900	-6.93	6.93	-1.00	8.32	0.0250	0.0004
0.9999	70	900	-6.93	6.93	-1.00	8.32	0.0250	0.0001
1.0000	80	900	-6.93	6.93	-1.00	8.32	0.0250	0.0000
1.0000	90	900	-6.93	6.93	-1.00	8.32	0.0250	0.0000
1.0000	100	900	-6.93	6.93	-1.00	8.32	0.0250	0.0000

Note: Means and Standard Deviation were multiplied by 10 to achieve sufficient precision

Using Ratio of responder Rates – Country-wise

When comparing responder rate, a non-inferiority limit of 15% may be considered. Based on ZOSTER-010 data, the responder rates were ~97% in EU (N=95) and 100% in US (N=37) and a value of 97% will be used as the reference value worldwide. A ~3% - 4% difference in point estimate may be observe between countries [eq. 96% in CZ (N=49) and 100% in SP (N=46)], as observed between EU and US.

Table 29 provides power for a sample of 60 - 100 subjects from one country in comparison with the rest of the world, assuming 15 countries. When considering a difference of 4%, the sample should be at least equal to 100 to achieve a power of 90%.

Table 29 Sample Sizes for Non-Inferiority Tests (Responder Rates)

	Sample Size	Sample Size	Grp 2	Equiv Grp 1	Actual Grp 1	Equiv Margin	Actual Margin	
	Grp 1	Grp 2	Prop	Prop	Prop	Diff	Diff	Target
Power	N1	N2	P2	P1.0	P1.1	D0	D1	Alpha
0.6449	60	900	0.9700	0.8200	0.9300	-0.1500	-0.0400	0.0250
0.7364	70	900	0.9700	0.8200	0.9300	-0.1500	-0.0400	0.0250
0.8088	80	900	0.9700	0.8200	0.9300	-0.1500	-0.0400	0.0250
0.8641	90	900	0.9700	0.8200	0.9300	-0.1500	-0.0400	0.0250
0.9050	**100**	**900**	**0.9700**	**0.8200**	**0.9300**	**-0.1500**	**-0.0400**	**0.0250**
0.7642	60	900	0.9700	0.8200	0.9400	-0.1500	-0.0300	0.0250
0.8471	70	900	0.9700	0.8200	0.9400	-0.1500	-0.0300	0.0250
0.9041	80	900	0.9700	0.8200	0.9400	-0.1500	-0.0300	0.0250
0.9415	90	900	0.9700	0.8200	0.9400	-0.1500	-0.0300	0.0250
0.9652	100	900	0.9700	0.8200	0.9400	-0.1500	-0.0300	0.0250

Score test [Miettinen ,1985]

10.4.5.6.4. Number of subjects in the Immunogenicity subset

Table 30 provides the provisional number of subjects in the Immunogenicity subset in study ZOSTER-006. CMI analysis will be performed in the Immunogenicity subset of three countries (Czech Republic, Japan and United States). These countries will have approximately 156 subjects per country enrolled in the immunogenicity subset. Other countries will have approximately 138 subjects per country enrolled in the immunogenicity subset.

Subjects will be randomized to be part of the Immunogenicity subset (Section 5.3.4). Blood samples obtained from subjects included in the Immunogenicity subset will be used to assess humoral immune responses. The number of placebo subjects and vaccine subjects that will have their blood sampled will be equal in order to maintain the blind. However, only a fraction of the placebo samples will be analyzed as a reduced sample is sufficient to characterise the background gE or VZV-specific immunogenicity levels in the placebo group.

Table 30 Provisional number of subjects in the Immunogenicity subset in study ZOSTER-006

Age cohort	50-59 YOA		60-69 YOA		≥ 70 YOA		All	
Treatment group	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo
CMI countries[1]	26	26	26	26	26	26	78	78
Non-CMI countries[2]	23	23	23	23	23	23	69	69

[1] Czech Republic, Japan, United States

[2] Australia, Hong Kong, S. Korea, Taiwan, Estonia, Finland, Germany, Italy, Spain, Sweden, United Kingdom, France, Brazil, Mexico, Canada

10.4.5.7. CMI Subset

10.4.5.7.1. Assumptions and background information for CMI

Assumptions to estimate the number of subjects to be included in the CMI subset in study ZOSTER-006 were based on gE-specific CMI data obtained in study ZOSTER-003 for subjects who received two doses of gE 50 µg/AS01$_B$.

The cellular proportion of subjects achieving a cellular immune response to vaccination with gE/AS01$_B$ (cellular immunity take rate) will be compared to that of subjects in the Placebo group based on the frequency of gE specific CD4 cells, after adjustment for background and prevaccination gE-specific CD4 responses. The increase in CMI response observed post dose 2 following 50 µg gE/AS01$_B$ compared with saline is about 5.5 fold, and the coefficient of variation is about 100%. These figures were used for the sample size calculation.

When expressed on the log-scale, the effect size for clinical significance is Ln(5.5)/ 0.832 = 2.05. When accounting for a target of a 1.5-fold increase over saline, the effect size is 2.05 – Ln(1.5) /0.832 = 1.562. While the number of blood samplings will be collected in vaccine and placebo recipients according to the study randomization ratio, it is appropriate to analyze twice as many vaccine samples than placebo samples using an

immunogenicity sample-randomization ratio of 2. Although this endpoint is purely exploratory, the overall power of this test is set to ~95% and the type 1 error to 2.5% per convention.

Table 31 presents the number of subjects under vaccine (N1) and placebo (N2) required to demonstrate a 1.5-fold increase over saline in frequency of gE-specific CD4 cells producing at least 2 cytokines. If the test is performed for each of the 3 age-ranges, the power of each test should be 98.1% in order to maintain the overall power at 0.981^3 = 0.94 (i.e., 94%). Twenty-one subjects in each of the 3 main age strata equals will have received vaccine or placebo, respectively, for a total number of 3 * 21 * 2 = 126 subjects. For this exploratory objective, the comparison is based upon one country only and, for instance, does not account for comparison across multiple countries and regions.

Table 31 Power Calculations for CMI subset

Power	N1/N2	Equivalence margin (E)	Actual difference (D)	Significance level		Standard deviation	
				Alpha	beta	SD1	SD2
0.99320	25/14	4.05	17.00	0.02500	0.00680	8.32	8.32
0.98871	23/12	4.05	17.00	0.02500	0.01129	8.32	8.32
0.98145	**21/12**	**4.05**	**17.00**	**0.02500**	**0.01855**	**8.32**	**8.32**
0.97242	20/10	4.05	17.00	0.02500	0.02758	8.32	8.32
0.95163	17/10	4.05	17.00	0.02500	0.04837	8.32	8.32

10.4.5.7.2. Number of subjects in the CMI subset

The CMI analyses will be performed in the Immunogenicity subset in three countries (Czech Republic, Japan and United States) at designated sites that have access to a PBMC processing facility within the acceptable time window from sample collection to PBMC processing. The CMI subset in these countries will include 156 subjects to account for anticipated lost or non-evaluable samples, see Table 32.

Table 32 Provisional number of subjects in the CMI subset in study ZOSTER-006

Age cohort	**50-59 YOA**		**60-69 YOA**		**≥ 70 YOA**		**All**	
Treatment group	**Vaccine**	**Placebo**	**Vaccine**	**Placebo**	**Vaccine**	**Placebo**	**Vaccine**	**Placebo**
Each participating country	26	26	26	26	26	26	78	78

10.4.6. Conditions for triggering analyses

A comprehensive understanding of the extent to which the candidate vaccine prevents HZ in the various age strata involves the availability of results from both studies (ZOSTER-006 and ZOSTER-022). The database freeze and statistical analyses would then be triggered when **both** studies have achieved their conditions for triggering analyses. However, if one of the studies reached the conditions required for triggering the analyses and a delay of more than approximately 6 months is predicted prior to those conditions are reached for the second study, then GSK may decide to proceed with the analysis of the study that reaches its conclusion first. The conditions described below are minimum

requirements prior to unblinding. Additional HZ cases and/or PHN cases may be accrued as a result of the decision to wait for **both** studies to achieve the requirements simultaneously.

The following conditions are planned prior to final HZ analyses of study ZOSTER-006. The number of HZ and PHN cases mentioned refers to the cases in the primary cohort for efficacy.

1. At least 196 HZ cases across all age group for the overall HZ analysis;
2. ~75% of the initial sample size (not accounting for any sample-size reassessment) in each strata with at least 36 months follow-up and the remaining subjects have completed at least 30 months follow-up after Dose 2 in order to ensure enough safety data;
3. Approximately 60 HZ cases in subjects 50-59 YOA and approximately 60 HZ cases in subjects 60-69 YOA for the HZ analysis by-age in 50-59 and 60-69 YOA age strata respectively;
4. A total of at least 88 PHN cases when pooled with ZOSTER-022 PHN cases accrued.

The following conditions are planned prior to final HZ analyses of study ZOSTER-022. The number of HZ and PHN cases mentioned refers to the cases in the primary cohort for efficacy.

1. At least 65 PHN cases over both 70-79 and ≥ 80 YOA strata;
2. A total of at least 88 PHN cases when pooled with ZOSTER-006 PHN cases accrued;
3. At least 278 HZ cases accrue over both 70-79 and ≥ 80 YOA strata;
4. ~75% of the initial sample size (not accounting for any sample-size reassessment) in each stratum with at least 36 months of follow-up and the remaining subjects have completed at least 30 months follow-up after Dose 2 in order to ensure enough safety data.

10.5. Study cohorts to be evaluated

10.5.1. Total Vaccinated cohort

The Total Vaccinated cohort (TVc) will include all vaccinated subjects with respect to the vaccine actually administered.

The TVc for analysis of efficacy and immunogenicity will include vaccinated subjects for whom data related to efficacy and immunogenicity endpoints are available.

The TVc for analysis of safety will include all subjects with at least one vaccine administration documented.

10.5.2. Modified Total Vaccinated cohort

The mTVc will be the primary population for efficacy analysis, which excludes subjects in the TVc for efficacy analysis who were not administered with the second vaccination or who develop a confirmed case of HZ prior to 1 month after the second vaccination.

Rationale for using mTVc for primary analysis:
Although the TVc (Intent-to-treat [ITT] population) analysis of efficacy is the one recommended according to ICH, the true assessment of the VE, according to the recommended schedule, can only be performed based on the mTVc, where subjects not completing the vaccination schedule due to an HZ episode or withdrawal will be excluded, as was done in an earlier HZ vaccine efficacy study [Oxman, 2005]. The analysis on the TVc is planned for sensitivity analyses and is expected to provide consistent results with the primary analyses. A delay of 1 month was selected prior to which any subject with confirmed HZ would be excluded from mTVc.

For those reasons, GSK Biologicals believes that the VE estimate for registration purposes should be based on mTVc, provided there is no essential VE difference between the mTVc and TVc analyses. Our proposal is to compare VE analyses on mTVc and TVc, and review the frequency for exclusion from mTVc. If the results are consistent between both cohorts then the VE estimate based on mTVc would be considered for registration purposes.

10.5.3. According To Protocol cohort for analysis of efficacy

The According To Protocol cohort (ATPc) for analysis of efficacy will include all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom efficacy data concerning endpoint measures are available, i.e., excluding all subjects who developed a confirmed case of HZ prior to 1 month after the second vaccination. The list of criteria used to exclude subjects from ATP will be defined prospectively in the Reporting and Analysis Plan (RAP) prior to database freeze.

The ATPc will be the analysis set for supportive efficacy analysis, only including subjects who developed a confirmed case of HZ during the follow-up period starting from 1 month after the second vaccination (Month 3).

10.5.4. According To Protocol cohort for analysis of safety

The ATPc for analysis of safety will include all subjects:

- who have received at least one dose of study vaccine/placebo according to their random assignment;
- with sufficient data to perform an analysis of safety (at least one dose with safety follow-up);
- for whom administration site of study vaccine/placebo is known;

- who have not received other medication/vaccine forbidden in the protocol (Section 6.6.1);
- for whom the randomization code has not been broken.

10.5.5. According To Protocol cohort for analysis of immunogenicity

For study ZOSTER-006, the ATPc for analysis of immunogenicity will include all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom immunogenicity results are available at Month 3 for CMI and/or humoral immunogenicity.

10.6. Derived and transformed data

10.6.1. Handling of missing data

For a given subject and a given efficacy measurement, missing or non-evaluable measurements will not be imputed for the primary analysis. The missing endpoint and censoring are supposed to occur independently, and the pattern of the missingness being either Completely At Random (MCAR) or Missing At Random (MAR) only.

For the analysis of solicited symptoms, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVc will include only subjects/doses with documented safety data (i.e., symptom screen/sheet completed).

For the analysis of unsolicited AEs/SAEs/concomitant medication, all vaccinated subjects will be considered and subjects who did not report an event will be considered as subjects without an event.

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

The reasons for and timings of missing data will be reviewed and discussed. The likely patterns for missing data will be assessed and compared with the actual missing data pattern in light of CHMP /EWP/1776/99 and implementation recommendations.

Sensitivity analyses will be pre-specified prior to unblinding for each main efficacy endpoint in order to assess the sensitivity of the conclusions to missing-data pattern. When repeated measurements are planned, primary methodology will include mixed effect model for repeated measurement analysis [Mallinckrodt, 2008].

10.6.2. Efficacy

The HZ incidence rate is determined with reference to the first confirmed HZ case observed in the patient, should several HZ cases occur in the same subject.

The HZ-free period for a subject is calculated from HZ onset to time zero relative to the cohort considered: first vaccination for TVc and beyond the HZ-case exclusion period following the second injection for mTVc and ATP.

The number of Person-Years at risk over an interval of time is the sum of the confirmed HZ-free episodes over all subjects at risk during that interval, either up to the cut-off date for the analysis, the censoring date or the occurrence of the first HZ case for a subject.

The following outputs will be derived from the efficacy data recorded using the ZBPI:

HZ burden-of-illness score

For each confirmed case of HZ, responses to the "worst pain" question in the ZBPI are used to calculate a "HZ severity-of-illness" score, defined as the area under the curve (AUC) of HZ-associated pain plotted against time during the 182-day period after the onset of rash. Subjects developing HZ will present "severity-of-illness" scores ranging from 0 up to, theoretically, 1820. A score of 0 is recorded for subjects in whom HZ did not develop during the study period.

HZ severity score

The methodology described for the HZ burden-of-illness score will be applied to the 4 weeks during which a daily measure is taken and provide the HZ severity score. The HZ severity score will apply only to subjects with HZ. Subjects not infected with HZ will not take part in this analysis.

10.6.3. Humoral immune response

- The current cut-off values that apply for gE and VZV Ab responses are described in Table 7 of Section 5.8.3. Those values may changes as improvements are introduced to the analytical methods. The final cut-off values that are used for the analyses will be stated in the study report.
- A seronegative subject is a subject whose Ab concentration is below the cut-off value.
- A seropositive subject is a subject whose Ab concentration is greater than or equal to the cut-off value.
- The seropositivity rate is defined as the percentage of seropositive subjects.
- The VZV gE-specific humoral immune response to vaccine for subjects who are seropositive at baseline is defined as a 4-fold increase in the anti-gE Ab concentration at the endpoint as compared to the pre-vaccination anti-gE antibody concentration. The VZV gE-specific humoral immune response to vaccine for subjects who are seronegative at baseline is defined as a 4-fold increase in the anti-gE Ab concentration at the endpoint as compared to the anti-gE Ab cut-off value for seropositivity.
- The VZV-specific humoral immune response to vaccine for subjects who are seropositive at baseline is defined as a 4-fold increase in the anti-VZV Ab

concentration at the endpoint as compared to the pre-vaccination anti-VZV Ab concentration. The VZV-specific humoral immune response to vaccine for subjects who are seronegative at baseline is defined as a 4-fold increase in the anti-VZV Ab concentration at the endpoint as compared to the anti-VZV Ab cut-off value for seropositivity.

- The Geometric Mean Concentrations (GMCs) calculations are performed by taking the anti-log of the mean of the log concentration transformations. For descriptive statistics only, Ab concentrations below the cut-off of the assay will be given an arbitrary value equal to half the cut-off for the purpose of GMC calculation. For inferential analyses, those concentrations below the cut-off will be considered as missing to avoid potential influential data.

10.6.4. Cellular-mediated immune response

- The frequency of CD4 T cells producing at least 2 activation markers (cytokines: IFN-γ, IL-2, TNF-α and/or CD40L, termed "all doubles" or CD4[2+]) upon in vitro stimulation with the antigen (induction condition) is calculated by adding an offset of 0.5 to the number of activated CD4 T cells (numerator) divided by the total number of CD4 T cells involved (denominator). A similar calculation will be made for the frequency of CD4 T cells producing at least 2 cytokines ("all doubles", CD4[2+]) upon in vitro stimulation in medium only (background condition).

$$Freq_{Induction}^{CD4\,2+} = \frac{n_{Induction}^{2+} + 0.5}{N_{Induction}^{CD4}} \qquad Log_e\left(Freq_{Induction}^{CD4\,2+}\right) = Log_e\left(\frac{n_{Induction}^{2+} + 0.5}{N_{Induction}^{CD4}}\right)$$

$$Freq_{Background}^{CD4\,2+} = \frac{n_{Background}^{2+} + 0.5}{N_{Background}^{CD4}} \qquad Log_e\left(Freq_{Background}^{CD4\,2+}\right) = Log_e\left(\frac{n_{Background}^{2+} + 0.5}{N_{Background}^{CD4}}\right)$$

$n_{Induction}^{2+}$ = Number of antigen - specific CD4 T - cells expressing at least 2 cytokines

$n_{Background}^{2+}$ = Number of CD4 T - cells expressing at least 2 cytokines in the medium only

N^{CD4} = Total number of CD4 involved in the assay (induction or background)

- The frequency of **antigen-specific** (gE or VZV) CD4 T cells for each individual subject is calculated as the difference between the frequency of CD4 T cells producing at least 2 cytokines among IFN-γ, IL-2, TNF-α and/or CD40L, termed "all doubles" or CD4[2+], upon in vitro stimulation with the antigen (induction condition) minus the frequency of CD4 T cells producing at least 2 cytokines ("all doubles", CD4[2+]) upon in vitro stimulation in medium only (background condition). When the log-transformation is applied to that variable prior to analysis, differences less or equal to zero (0) are imputed to 1 gE or VZV-specific cytokine secreting CD4 T cell per 10^6 CD4 T cells.

$$Freq_{Specific}^{CD4\,2+} = \frac{n_{Induction}^{CD4\,2+} + 0.5}{N_{Induction}^{CD4}} - \frac{n_{Background}^{CD4\,2+} + 0.5}{N_{Background}^{CD4}}$$

$$Log_e\left(Freq_{Specific}^{CD4\,2+}\right) = Log_e\left(\frac{n_{Induction}^{CD4\,2+} + 0.5}{N_{Induction}^{CD4}} - \frac{n_{Background}^{CD4\,2+} + 0.5}{N_{Background}^{CD4}}\right) \quad if \ \frac{n_{Induction}^{CD4\,2+}}{N_{Induction}^{CD4}} > \frac{n_{Background}^{CD4\,2+}}{N_{Background}^{CD4}}$$

$$Log_e\left(Freq_{Specific}^{CD4\,2+}\right) = Log_e\left(\frac{1}{10^6\,cells}\right) \quad if \ \frac{n_{Induction}^{CD4\,2+}}{N_{Induction}^{CD4}} \leq \frac{n_{Background}^{CD4\,2+}}{N_{Background}^{CD4}}$$

- The Geometric Mean (GM) frequency calculations are performed by taking the anti-log of the mean of the log frequency transformations;
- The CMI vaccine response against gE is defined for all subjects as a 1.5 to 2-fold increase (see RAP for final threshold) in background-adjusted frequency of CD4 following induction with gE measured at endpoint as compared to pre-vaccination.
- The CMI vaccine response against VZV is defined for all subjects as a 1.5 to 2-fold increase (see RAP for final threshold) in background-adjusted frequency of CD4 following induction with VZV measured at endpoint as compared to pre-vaccination.
- A CMI responder is a subject with a CMI response greater than or equal to the cut-off value.

10.7. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in the protocol will be described and justified in the final study report.

10.7.1. Prior to Final Analysis

Blinded review of safety and efficacy data will be performed in order to anticipate any data issues and rate of accrual of HZ and PHN events within each age strata.

Unblinded evaluation of safety, efficacy and risk-benefit for the subjects will be performed by the IDMC on an ongoing basis. Operational details for IDMC will be provided in the IDMC Charter.

10.7.2. Statistical considerations for the interim futility analyses

The IDMC may be also involved in evaluation of VE at specified interim timepoints (futility analysis) and may recommend discontinuation of a clinical study that has demonstrated its inability to achieve its primary and main secondary endpoints. The futility rules will be described in the IDMC Charter.

GSK has no plan to proceed with early registration for efficacy (i.e., following an interim analysis) due to the expected low accrual rate of PHN cases and the need to collect a sufficient number of events to achieve robust estimation of PHN VE. If a futility analysis

occurs and leads to a recommendation by the IDMC to filing prior to study end for ethical reasons, it is mandated that, prior to final analysis, the significance level required during the course of the trial for considering early analysis by IDMC for all primary objectives but also key secondary objectives is 0.0001 for both HZ and PHN. As a consequence, the significance level of the final analysis will be adjusted to 4.9998% 2-sided. Practically speaking, however, that adjustment makes no essential difference as using a significance level of 5% 2-sided that will be referred to in other part of this document.

10.7.3. Final analysis

When the conditions for triggering the final analysis of efficacy have been reached, the final analysis cut-off date will be defined. Any HZ episode occurring prior to the final analysis cut-off data will be followed for a minimal duration of 90 days, as described in the RAP, in order to document potential PHN episodes.

Prior to unblinding, the third party responsible for generating immunogenicity data will communicate the results to the SDAC for review and consistency checks with the remaining database. SDAC will make sure than any feedback to that third party does not unblind the laboratory. Data issues on immunogenicity identified by the SDAC and that cannot be resolved beforehand unless unblinding a treatment assignment blind party, will be reviewed after efficacy and safety database lock.

Following achievement of criteria triggering analyses, final data collection and data cleaning, the write access to the clinical database will be removed and all eCRF data will become available for final analysis. The merging of immunogenicity data to the eCRF data will occur after that database lock. A first report will document efficacy and safety results and provide immunogenicity results using descriptive methodology. Analysis of correlate of protection may require extensive exploratory analyses and may be available as an annex report after completion of the primary report. Persistency data may be also provided in annex reports.

10.8. Statistical methods

All analyses will be presented overall and by age strata. The main age strata for reporting purposes are 50-59, 60-69 and ≥70 YOA. In addition, the results for the ≥ 70 YOA stratum will also be presented separately for 70-79 and ≥ 80 YOA subjects. The study is not powered prospectively to demonstrate efficacy in these 2 sub-strata taken separately. Another set of analyses in subjects ≥ 60 YOA will also be presented.

Any exploratory or sensitivity analysis may be performed in addition to the analyses described below on an ad-hoc basis. The significance level of those analyses may not however be fully controlled.

10.8.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age, gender, geographic ancestry and ethnicity) of each study cohort will be tabulated overall and by region.

The mean age (plus range and standard deviation) of the enrolled subjects, as a whole, and per treatment group and stratified by age group will be calculated.

The distribution of subjects enrolled among the study sites will be tabulated as a whole and per vaccine group.

No inferential analyses of demographic data or baseline characteristics are planned.

10.8.2. Analysis of efficacy

All efficacy analyses will be presented overall and by age strata.

When overall VE is presented, the age stratification factor will include the 3 main age levels. When VE by age is presented, the same model will be run using only the data pertaining to the strata under consideration.

Additional tables will present the overall VE by region and overall VE by time (e.g., using 1-year interval). The methodology will be described in the RAP.

All p-values reported are related to the null hypothesis test VE = 0 or absence of effect of the vaccine and will account for p-value adjustment for multiple testing scheme when applicable. Both raw-confidence intervals and confidence intervals adjusted for multiple testing or other kind of significance adjustment will be produced.

10.8.2.1. Reduction in HZ risk

Descriptive statistics

For each treatment group, the number of subjects at risk, person-time, number of confirmed events (HZ) and incidence rate, and incidence of confirmed HZ cases will be tabulated overall and by age strata. The results will be presented over the whole study and by visit interval. Similar tables will describe the median time-to-event and hazard rate.

Survival curves for each vaccine group will be calculated non-parametrically, tabulated and presented graphically overall and by age strata using the Kaplan-Meier (i.e., Product-Limit) method.

Primary Inferential Analyses

When the disease incidence is very low, large sample size is required together with longer trial duration. As a consequence, all participants cannot be expected to be followed for the same duration throughout the end of the trial. For sufficiently large sample size and small incidence of disease, the number of cases in the vaccine and placebo groups may be approximated by independent Poisson distributions. For such low incidence rates, both binomial and Poisson distribution are equivalent. Under that model, it can be demonstrated that the number of vaccine group, given the total number of cases, follows a binomial distribution and resolves into a single-parameter estimation problem [Chan, 2003].

Under that model, the primary analysis method of the vaccine VE will consider the exact inference on the relative risk stratified for age strata and regions conditionally to the total number of HZ cases observed and time at risk. The method is implemented in the Poisson procedure of the StatXact package provided by Cytel. Relative risks will be calculated overall and by age-strata. Stratification will include age and regions for the overall analysis and region alone when analysis by age strata. The stratification will account for possible differences in HZ incidence across strata and/or regions.

These analyses will adjust for the number of person-time in each vaccine group and strata when applicable. Similarity of the relative risks across the strata analyzed will be assessed graphically and by means of exact tests for homogeneity of the relative risks. Absence of clinically meaningful difference in relative risks across strata and p-values larger than 5% (2-sided) will justify assuming the relative risks are similar across the strata. In other situations, the impact of potential heterogeneity on the study conclusions will be assessed using sensitivity analyses.

Sensitivity analysis of the VE will be provided by region to support registration and for visual inspection of the consistency of the VE across regions. The study is not powered to demonstrate significance of VE in any of those regions using only the data of that region in isolation.

Sensitivity analysis of the overall VE after each multiple of 12 months following last vaccination will be provided in order to assess consistency of VE over time.

Secondary Inferential Analyses

The elapsed time following the HZ-case exclusion period after the second vaccination to the first HZ episode may be analyzed using Cox's proportional hazard regression stratified for age strata and region with vaccine groups as covariates. Wald test and CIs will be produced.

Ties will be handled using the Efron method. Cox adjusted survival curves will be produced for each combination of vaccine group and age category.

10.8.2.2. Reduction in overall PHN risk

The overall reduction in PHN risk will be evaluated similarly to the HZ risk using the exact inference on the relative risk stratified for age strata and regions conditionally to the total number of HZ cases observed and time at risk. Similarly to the HZ VE, a Poisson distribution for the number of PHN cases under placebo and vaccine groups is assumed. Since the incidence of PHN is approximately 10% to 25% of the incidence of HZ, the Poisson approximation of the overall number of PHN cases with regards to the mTVc is similarly valid. The inference of the PHN VE is partially confounded with the analysis of HZ risk as it includes the efficacy of the vaccine against HZ in all subjects randomized and the efficacy of the vaccine against PHN in those subjects that presented with HZ. However, the overall PHN analysis is deemed relevant for the following reasons:

1. An analysis performed on randomized cohort ensures comparability of the vaccine groups under evaluations. An analysis performed on the subset of subjects who

presented with HZ may be biased due to the selection of that subset due to the disease.

2. It matters to provide Health Authorities with overall benefit on PHN risk, whether the primary efficacy is against HZ or against PHN.

10.8.2.3. Reduction in Burden-of-Illness

The "Chop-lump" test [Follmann, 2009] for the overall reduction in Burden-of-Illness scores in all subjects between vaccine and placebo will be implemented and compared to the original analysis of the Burden-of-Illness proposed by Chang, 1994. That analysis is exploratory and will be described in the RAP. The purpose of this analysis is to compare with results published elsewhere [Oxman, 2005] and no further change to the methodology is this considered appropriate.

The HZ "Burden-Of-Illness (BOI) score" represents the average severity of illness among all subjects in the vaccine or placebo groups. It is calculated according to the "modified" scale described by Coplan [Coplan, 2004] as the sum of the HZ "severity-of-illness" scores of all members of the treatment group divided by the total number of subjects in the group.

The pain experienced by the subjects over the period that precedes a 24 hour window prior to the visit to the investigator will be captured in a single measure. VE with respect to the BOI due to HZ (VE BOI) is defined as the relative reduction in the BOI score in the vaccine group as compared with that in the placebo group and calculated as 1 - relative risk (i.e., 1- the HZ BOI score in the vaccine group divided by the HZ BOI score in the placebo group).

The same definition of clinically relevant improvement as given for HZ severity applies to BOI.

10.8.2.4. Reduction in HZ severity score

Based on Rowbotham [Rowbotham, 2001] and Farrar et al. [Farrar, 2001], a reduction of 1.74 units or 28% on pain score between baseline and endpoint were best associated with clinically relevant improvement, according to the Patient's Global Impression of Change (PGIC) category of "much improved" or better. The authors also concluded that, in studies with no minimum baseline requirement, the relationship between percentage changes and PGIC is more consistent than with the raw change. Dworkin et al, [Dworkin, 2008] reach a similar conclusion. Therefore, a percentage reduction in pain between vaccine and placebo of ~28% may be considered as clinically relevant in this study.

Additional implementation details will be provided in the RAP.

The statistical methodology for the analysis of HZ severity will be described in the RAP and is similar to the methodology described previously for BOI assessment in [Chang, 1994]. The method for accounting for the potential differential in use of antiviral treatment or pain medications between the vaccine and placebo groups will be pre-specified. Contrary to the BOI analysis, the HZ severity analysis only applies to subjects

with HZ (i.e., a score of zero is not assigned to subjects who do not present with HZ) and only includes the first 4 weeks following the HZ episode.

Additional analyses may be performed using partial AUC, calculated from 0 to specific elapsed time after HZ onset. That approach accounts partially for any difference in pain score profiles or pattern (e.g., long duration with low scores versus short score with high scores) even though subjects may have the same overall AUC.

10.8.2.5. Reduction in incidence of HZ associated complications

At the end of the trial, it is reasonable to assume that a final assessment of the presence or absence of HZ associated complication will be made for most patients with confirmed HZ. As a consequence, the number HZ associated complications in subjects with HZ under placebo or vaccine may be considered as a binomial distribution rather than a Poisson distribution.

The overall incidence of HZ associated complications, in subjects with an HZ episode, overall and by sub-categories will be presented and compared with placebo using asymptotic standardized unconditional binomial test [Miettinen, 1985]. The analysis will be stratified by age group and weights associated to each stratum will be pre-specified. The statistical methodology will be further described in the RAP.

10.8.2.6. Reduction of duration of severe 'worst' pain in subjects with an HZ episode

This analysis aims at demonstrating the effect of the vaccine on the reduction of the duration of pain, irrespective of whether the pain is acute or chronic. Similarly to the approach taken for the analysis of incidence of PHN, this analysis will involve any subject reporting ZBPI pain scores of 3 or more at any time during the study.

The time-to-cessation of severe 'worst' pain will be analyzed using a survival methodology. The primary analysis will consist in a Cox-proportional model to assess the hazard rate reduction in ZBPI worst pain duration due to the vaccine in those subjects that presented HZ.

A change-point piecewise exponential model [Arani, 2001; Desmond, 2002] may be used as sensitivity analysis to compare hazard rates related to acute (0-30 days), sub-acute (30-120 days) and chronic (120+ days) pain between vaccine group and placebo. The cut-off points 30 days and 120 days were suggested according to Desmond [Desmond, 2002]. Those cut-off points may additionally be estimated using the data. The comparisons across both sub-acute pain and chronic pain will be combined using a likelihood-ratio test.

Both methodologies will be further detailed in the RAP.

10.8.2.7. Reduction in PHN incidence in subjects with an HZ episode

At the end of the trial, it is reasonable to assume that a final assessment of the presence or absence of PHN will be made for most patients who experienced an HZ episode. As a consequence, the number of PHN cases in subjects with HZ under placebo and vaccine maybe considered as a binomial distribution rather than a Poisson distribution.

The incidence of PHN in subjects with an HZ episode, overall and by sub-categories will be presented and compared with placebo using asymptotic standardized unconditional binomial test [Miettinen, 1985]. The analysis will be stratified by age group and weights associated to each stratum will be pre-specified. The statistical methodology will be further described in the RAP.

10.8.2.8. Improvement of subject's quality of life by ZBPI

Descriptive statistics and inferential analysis of QoL subscale of ZBPI (item 9: questions A to G) total scores and scores per item over time will be provided overall and by age group.

10.8.3. Analysis of immunogenicity

The primary analysis will be based on the ATPc for analysis of immunogenicity (Section 10.5.5). If the percentage of enrolled subjects excluded from this ATPc is more than 5%, a second analysis based on the TVc will be performed to complement the ATP analysis.

10.8.3.1. Cell-mediated immune response

CMI response will only be assessed and analyzed in the CMI component of the Immunogenicity subset as defined in Section 4.1.

Descriptive statistics

For CMI response, the following parameters will be tabulated by treatment group, overall and by age group at Months 0, 3, 14, 26 and 38:

- descriptive statistics of the frequency of CD4 T cell secreting at least two different cytokines (IFN-γ, IL-2, TNF-α,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least IFN-γ and another cytokine (IL-2, TNF-α,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least IL-2 and another cytokine (IFN-γ, TNF-α,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least TNF-α and another cytokine (IFN-γ, IL-2,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least CD40L and another cytokine (IFN-γ, IL-2, TNF-α) to both VZV and gE antigens;
- proportion of responders with exact 95% CI.

Inferential Analyses

If the data allows, inferential analysis on the log-transformed frequency of CD4 T cells producing at least two different cytokines following induction with antigen will be performed overall and by age strata or sub-strata, in subjects infected with HZ and healthy subjects. Least-squares means and 95% CI are back-transformed to provide geometric means and ratios. Covariates will include the log-transformed pre-vaccination frequency following induction with the antigen and the non-specific background log-transformed frequency. Sensitivity analyses may include additional effects for appropriate interactions in the model in order to provide estimations and 95% CI by region.

10.8.3.2. Humoral immune response

Humoral immune response will be assessed and analyzed in the Humoral Immunogenicity subset as defined in Section 4.1.

Descriptive statistics

The following parameters will be tabulated by treatment group, overall and by age group at Month 0, Month 3, Month 14, Month 26 and Month 38:

- Geometric mean concentrations (GMCs) of anti-gE Ab with 95% CIs;
- Humoral seropositivity rates with exact 95% CIs;
- Vaccine response rates with 95% CIs;
- Tabulations will be presented overall and by region.

Inferential Analyses

If the data allows, inferential analysis on the log-transformed Ab concentrations will be performed overall and by age strata or sub-strata, in subjects infected with HZ and healthy subjects. Least-squares means and 95% CI are back-transformed to provide geometric means and ratios. Covariates will include the log-transformed pre-vaccination concentrations. Sensitivity analyses may include additional effects for regions and appropriate interactions in the model in order to provide estimations and 95% CI by region.

The analysis for immunogenicity will be performed on the pooled data of both ZOSTER-006 and ZOSTER-022 and the results will be provided in an annex report.

10.8.3.3. VZV neutralizing antibody response

Descriptive statistics

The following parameters will be tabulated by treatment group, overall and by age group at Month 0, Month 3, Month 14, Month 26 and Month 38:

- Geometric mean titres (GMTs) of anti-VZV neutralizing Abs with 95% CIs;
- Tabulations will be presented overall and by region.

10.8.3.4. Correlate of protection

An exploratory analysis will be implemented in an attempt to correlate humoral immune responses to vaccination and subsequent HZ risk [Dunning, 2006]. A specific RAP will describe the methodologies to be used for that purpose. The exploratory analyses may be initiated during the course of the trial by SDAC to support IDMC.

Serum blood samples will be collected from all subjects at Month 0 (pre-vaccination) and Month 3, and may be used for correlate of protection analysis. Additional subject samples may be retrieved and analyzed based on some demographics and baseline characteristics to match more exactly with characteristics of those who developed HZ.

The analysis for correlate of protection will be performed on the pooled data of both ZOSTER-006 and ZOSTER-022 and provided in an annex report.

10.8.4. Quality of life

10.8.4.1. SF-36 health survey

The methodology used for the analysis of the SF-36® questionnaire is detailed by Ware et al. [Ware, 2000]. Table 33 presents the SF-36® items that were to be taken into account for each score.

A Minimal Important Difference (MID) for EQ-5D is defined as a change of ~0.07 to ~0.08 [Walters, 2005]. However, when the ultimate objective is to influence resource allocation decisions, the difference in cost-effectiveness is more relevant and a difference of 0.03 is considered the minimum clinically important difference for QALY sample size calculations [Drummond, 2001].

10.8.5. Analysis of safety

The primary analysis for safety will be based on the TVc. A second analysis based on this ATPc will be performed to complement the TVc analysis.

When appropriate, tabulations will be presented overall and by time of occurrence relative to last vaccination (e.g., using windows such as Days 0 – 6, Days 0 – 29 and more than 30 days post-vaccination).

10.8.5.1. Within groups assessment

For each treatment group, the following results will be tabulated overall and by age strata.

- The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general adverse event (solicited and unsolicited) and with any AE during the solicited follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall.
- The percentage of doses followed by at least one local AE (solicited and unsolicited), by at least one general AE (solicited and unsolicited) and by any AE will be tabulated, overall vaccination course, with exact 95% CI.
- The percentage of subjects reporting each individual solicited local and general AE during the solicited 7-day (Days 0-6) follow-up period will be tabulated with exact 95% CI.
- The percentage of doses followed by each individual solicited local and general AE during the solicited 7 day (Days 0-6) follow-up period will be tabulated, overall vaccination course, with exact 95% CI.
- For all solicited symptoms, the same tabulation will be performed for grade 3 solicited AEs and for solicited general AEs with relationship to vaccination.
- Duration and prevalence of fever will be presented.
- The proportion of subjects with at least one report of unsolicited AE during the 30-day (Days 0 – 29) follow-up period after each vaccination classified according to the MedDRA System Organ Class and Preferred Terms will be tabulated, with exact 95% CI.
- The distribution of the number of unsolicited AEs per subject will be tabulated.
- The same tabulation will be performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination. The proportion of AEs resulting in a medically attended visit (other than routine health maintenance visits) will also be tabulated.

- Incidences of SAEs during the 30-day (Days 0 – 29) follow-up period after each vaccination, up to 8 months and during any time during the study classified according to the MedDRA System Organ Class and Preferred Terms will be tabulated, with exact 95% CI.
- A separate tabulation will report major categories of SAEs that occur with higher frequencies in elderly subjects including: cardiac, vascular, respiratory, neurological, congestive heart failure, myocardial infarction, varicella or HZ-like rash, cerebral or vascular events.
- Incidences of SAEs by major categories including: cardiac, vascular, respiratory, neurological, congestive heart failure, myocardial infarction, varicella or HZ-like rash, cerebral vascular. Listing will also be provided, sorted by patients and sorted by preferred term.
- Incidence of withdrawal due to AEs. Listing will also be provided, sorted by subjects and sorted by MedDRA Preferred Term.
- The proportion of subjects with at least one report of NOADs and other immune mediated inflammatory disorders during the entire study period will be tabulated overall and by time window. Listing will also be provided, sorted by subjects and sorted by MedDRA Preferred Term.
- The proportion of subjects with concomitant medication will be tabulated, until 30 days after each vaccine dose and overall, with exact 95% CI.
- Proportion and incidence rate of subjects with fatal outcome, HZ-related complications and overall and HZ-related hospitalizations, will be tabulated overall and by time window.
- Proportion of subjects experiencing an HZ episode using pain medications by type (opiods, non-narcotics, antidepressants, miscellaneous) will be tabulated.

10.8.5.2. Additional exploratory safety comparisons

The standardized asymptotic 95% CI for the difference between the two groups and the associated 2-sided p-value to detect group difference will be computed for the following endpoints.

- The proportion of subjects with at least one report of unsolicited AE classified by the MedDRA presented by System Organ Class and Preferred Term.
- Incidences of SAEs classified according to the MedDRA System Organ Class and Preferred Terms.

The objective of these analyses is to identify a safety signal as defined by the Council for the International Organization of Medical Sciences (CIOMS) VI working group, i.e., a report or reports of an event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continues surveillance. It is recognized that the use of any method to identify safety signals has the potential to identify a large number of events which may or may not have a causal relationship to drug treatment due to multiplicity of endpoints. In order to put any safety signal in perspective a permutation test will be conducted to quantify the probability to observe at least one false safety

signal according to the threshold p-value defining a signal. In addition, clinical significance and biological plausibility will need to be accounted before establishing causality.

Other exploratory safety analyses may be described in the RAP.

11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

11.1. Case Report Form/Remote Data Entry instructions

Remote Data Entry (RDE), a validated computer application, will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

11.2. Monitoring by GSK Biologicals

Monitoring visits by a GSK Site Monitor are for the purpose of confirming that GSK Biologicals' sponsored studies are being conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical practice (GCP) and the applicable regulatory requirement(s) (verifying continuing compliance with the protocol, amendment(s), reviewing the investigational product accountability records, verifying that the site staff and facilities continue to be adequate to conduct the study).

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a RDE review and a Source Document Verification (SDV). By SDV we understand verifying RDE entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the RDE. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the RDE will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For RDE, the monitor will mark completed and approved screens at each visit.

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF entries will serve as the source document.

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any amendments, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Archiving of data at study sites

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g. audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic for studies with an eCRF); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the

investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by ICH GCP, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

11.4. Audits

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.5. Posting of information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov before enrolment of subjects begins.

11.6. Ownership, confidentiality and publication

11.6.1. Ownership

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

11.6.2. Confidentiality

Documented evidence that a potential investigator is aware and agrees to the confidential nature of the information related to the study must be obtained by means of a confidentiality agreement.

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (i) information which becomes publicly available through no fault of the investigator or site staff; (ii) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (iii) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (iv) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

11.6.3. Publication

For multicentre studies, the first publication or disclosure of study results shall be a complete, joint multicentre publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a 'Publication'), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period to review the proposed Publication (at least twenty-one working days, or at least fifteen working days for abstracts/posters/presentations). Proposed Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

11.6.4. Provision of study results to investigators, posting to the clinical trials registers and publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to the GSK Clinical Study Register at the time of the first regulatory approval or within 12 months of any decision to terminate development. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 12 months of the first approval or within 12 months of any decision to terminate development. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

12. COUNTRY SPECIFIC REQUIREMENTS

12.1. Requirements for France

This section includes all the requirements of the French law (n° 2004-806 of 09 August 2004), and identifies, item per item, the mandatory modifications or additional information to the study protocol.

Concerning the « STUDY POPULATION»

- In line with the local regulatory requirements, the following text about «PAYMENT TO SUBJECTS » is added:

If the subjects will be paid for the inconvenience of participating in the study. The amount of payment is stated in the informed consent form. Subjects not completing the study for whatever reason could be paid at the discretion of the Investigator, generally on a pro rata basis.

- In line with the local regulatory requirements, the following text about **« NATIONAL FILE »** is added:

All subjects participating in studies could be identified and monitored under the « Fichier national ».

The following details will be described**:**

– first 3 letters of name and first 2 letters of surname,

– date of birth,

– reference of the study and dates of beginning and termination,

– exclusion period,

– the total amount of honorarium.

- In line with the local regulatory requirements, the following text in section «OTHER STUDY ELIGIBILITY CRITERIA CONSIDERATIONS » is added:

A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category.

It is the investigator's responsibility to ensure and to document (in source document - patient notes) that the patient is either affiliated to or beneficiary of a social security category.

Concerning the "DATA ANALYSIS AND STATISTICAL CONSIDERATIONS" and specially in the "SAMPLE SIZE ASSUMPTION"

- The expected number of patients to be recruited in France is declared to the French regulatory authority.

Concerning the "STUDY CONDUCT CONSIDERATIONS"

- In section "Regulatory and Ethical Considerations, Including the Informed Consent Process"

Concerning the process for informing the patient or his/her legally authorized representative, the following text is added:

- French Patient Informed Consent form is a document in triplicate which summarizes the main features of the study and allows collection of the patient's written consent. It also contains a reference to the authorisation of Afssaps and the approval from the French Ethics committee and the maintenance of confidentiality of the returned consent form by GSK France.

Concerning the process for obtaining subject informed consent:

- When **biomedical research is carried out on an adult in the care of a "tutelle" guardian**, consent is given by their legal representative and, if the committee mentioned in article L. 1123-1 considers that the research in question, because of the gravity of the restraints or the specificity of the medical acts involved, entails a serious risk of affecting their private life or the integrity of their body, by the family council if it has been instated, or by the judge of "tutelle" guardians.
- When biomedical research is carried out on an adult in the care of a "curatelle" guardian, consent is given by the subject assisted by his guardian.

However, if the adult in the care of a "curatelle" guardian is invited to participate in research which the committee mentioned in article L. 1123-1 considers, because of the gravity of the restraints or the specificity of the medical acts involved, to entail a serious risk of affecting their private life or the integrity of their body, the matter is submitted to the judge of guardians who decides whether the adult is capable of giving his consent. In the case of incapacity, the judge will decide whether or not to authorise the biomedical research.

- When biomedical research, which complies with the conditions laid down in article L. 1121-8, is considered for **an adult incapable** of expressing his consent and not under a legal protection order, consent is given by a person of confidance as defined in article L. 1111-6 and, failing this, by a person who maintains close and stable links with the subject. However, if the committee mentioned in article L. 1123-1 considers that the research in question, because

of the gravity of the restraints or the specificity of the medical acts involved, entails a serious risk of affecting their private life or the integrity of their body, consent is given by the judge of guardians.

Concerning the management of the Patient Informed Consent forms, the following text is added:

- The first copy of the Patient Informed Consent form is kept by the investigator. The second copy is kept by the Director of the Medical Department of GlaxoSmithKline France and the last copy is given to the patient or his/her legally authorized representative.
- The second copy of all the consent forms will be collected by the investigator at the end of the trial under the Clinical Research Assistant's (CRA's) control, and placed in a sealed envelope bearing only:

– the study number,

– the identification of the Centre : name of the principal investigator and number of centre),

– the number of informed consents,

– the date,

– and the principal investigator's signing.

Then, the CRA hands the sealed envelope over to the Director of the Medical Department, for confidential recording, under his responsibility.

In section concerning the " NOTIFICATION TO THE HOSPITAL DIRECTOR " the following text is added (if applicable)

- In accordance with Article L1123-13 of the Public Health Code, the Hospital Director is informed of the commitment to the trial in his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-63).

In section concerning the " INFORMATION TO THE HOSPITAL PHARMACIST " the following text is added (if applicable)

- In accordance with Article R.1123-64 of the Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in his establishment. The Pharmacist is supplied with a copy of the protocol (which allows him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the CIB), the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

In section " DATA MANAGEMENT " the following text is added

- " within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacist if applicable, involved in this clinical trial, and data regarding the patients recruited in this clinical trial (patient number, treatment number, patient status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by Laboratoire GlaxoSmithKline or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Act n° 78-17 of 6th January 1978 further modified, each of these people aforesaid has a right of access, correction and opposition on their own data through Laboratoire GlaxoSmithKline (Clinical Operations Department)."

12.2. Requirements for Germany

EXPLANATORY STATEMENT CONCERNING GENDER DISTRIBUTION (ARTICLE 7, PARAGRAPH 2 (12) OF THE GERMAN GCP ORDER)

- There is no intention to conduct specific analyses investigating the relationship between the gender of the subjects and the efficacy, immunogenicity or safety of the GSK Biologicals' gE/AS01$_B$ vaccine. The ratio of male to female subjects recruited into the study ZOSTER-006 is expected to be in line with the demographics of the population aged ≥ 50 YOA in the Member State.

12.3. Requirements for Japan

Regulatory and Ethical Considerations

The study will be conducted in accordance with Good Clinical Practice (GCP), Article 14-3 and 80-2 of the Pharmaceutical Affairs Law, all applicable subject privacy requirements, and the guiding principles of the declaration of Helsinki.

Clinical Trial Notification to Regulatory Authority

GSK will submit the CTN to the regulatory authorities in accordance with Article 80-2 of the Pharmaceutical Affairs Law before conclusion of any contract for the conduct of the study with study sites.

Informed Consent of Subjects

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

Informed Consent

Prior to the start of the study, the investigator (or subinvestigator) should fully inform the potential subject of the study including the written information given approval by the

IRB. The investigator (or subinvestigator) should provide the subject ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. After giving informed consent based on his/her free will, the subject should sign and personally date the consent form. If the subject wishes to consider the content of the written information at home, he/she may sign the consent form at home. The person who conducted the informed consent discussion should sign and personally date the consent form. If the subject is unable to read, an impartial witness should be present during the entire informed consent discussion, and the witness should sign and personally date the consent form. The investigator (or subinvestigator) should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the subject.

If information becomes available that may be relevant to the subject's willingness to continue participation in the study (revision of informed consent form and other written information)

If information becomes available that may be relevant to the subject's willingness to continue participation in the study, the investigator (or subinvestigator) should immediately inform the subject of it to confirm the willingness to continue participation in the study, and document the communication of this information (in medical records). If necessary, the investigator should revise the written information to be provided to subjects, promptly report it to the sponsor, and obtain approval from the IRB. The investigator should not enroll any new subject in the study before the IRB's approval. After the IRB approves the revision of the written information to be provided to subjects, the investigator (or subinvestigator) should inform each subject participating in the study of the revised written information, and obtain written informed consent.

Study Monitoring

By monitoring the parties involved in the study including medical institutions, investigators, subinvestigators, study collaborators, and storage managers, monitors will:

1. Oversee the process of obtaining written informed consent, the control of investigational products and the progress of the study (including withdrawals and adverse events, and ensure that the conduct of the study is in compliance with GCP, Revised GCP, this protocol, and any other written agreement between the sponsor and the investigator/institution.
2. Collect and provide information that is necessary to conduct the study properly (information on investigational products' safety, efficacy and quality).
3. Verify that the investigator/institution has adequate qualifications and resources and remain adequate throughout the study period, and that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the study and remain adequate throughout the study period.
4. Verify that source documents and other study records are accurate, complete, kept up-to-date and maintained.

5. Determine whether the person responsible for retaining records is maintaining the essential documents at each medical institution.
6. Check the accuracy and completeness of the CRF entries, source documents and other study-related records against each other.

The investigator and institution should agree to allow the monitor direct access to essential documents and other relevant documents.

Direct access to essential documents by monitors and the scope of those documents will be specified separately in the written procedures for monitoring prepared for this study.

The monitor will also review EQ-5D, SF-36 and ZBPI questionnaires for extraneous written comments that could indicate possible AEs. Information collected in the CRF, and in EQ-5D, SF-36 and ZBPI questionnaires will be handled as independent components of this study. Except for header section information (e.g., subject identification code (subject number), treatment number, visit date), neither the monitor nor the investigator (or subinvestigator) will attempt to reconcile responses to individual questions/items recorded on EQ-5D, SF-36 and ZBPI questionnaires or health outcomes portions of diary cards (if applicable) with other data recorded in the CRFs. EQ-5D, SF-36 and ZBPI questionnaires itself generally serve as the source document; therefore, unless otherwise specified elsewhere, no other source document is available for data validation.

Source Data Recorded Directly on CRF

The following data may be recorded directly on the CRFs and considered to be source data.

1. Assessment of causality between adverse events and the investigational product.

Deviations from and Changes of Protocol

Deviations from Protocol

The investigator (or subinvestigator) may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to subjects without agreement by the sponsor or prior IRB approval. As soon as possible, the implemented deviation or change and the reasons for it should be submitted to the head of the medical institution and the IRB for approval, and via the head of the medical institution to the sponsor for agreement.

The investigator (or subinvestigator) should document all deviations from the approved protocol. The investigator should document the reason only for the deviation from, or the change of, the protocol to eliminate an immediate hazard(s) to subjects, and submit it to the sponsor and the head of the medical institution, and retain its copy.

Changes of Protocol

1. If it becomes necessary to make any changes significantly affecting the conduct of the study, and/or increasing the risk to subjects, the sponsor should promptly

document the changes and reasons for them and amend the protocol after discussion with the [coordinating [investigator, committee members] and] investigators, and notify the heads of the medical institutions and investigators of the changes of the protocol [sample informed consent form and other written information, if necessary]. The investigator should not implement any significant changes without approval from the IRB.

2. For changes other than the above 1), the sponsor should document the changes and reasons for them and inform the heads of the medical institutions and investigators of the changes of the protocol. Such changes require prior approval from the IRB, except where necessary to eliminate an immediate hazard(s), or when the change(s) involves only logistical or administrative aspects of the study. The investigator should promptly report the changes implemented without prior approval to the IRB for approval.

Study Period

June, 2010 ~ August, 2014

13. REFERENCES

Araújo LQ, MacIntyre CR, Vujacich C. Epidemiology and burden of herpes zoster and post-herpetic neuralgia in Australia, Asia and South America. *Herpes* 2007;14(Suppl 2): 40A–44A.

Arani RB., Soong S-J, Weiss HL, et al. Phase specific analysis of herpes zoster associated pain data: a new statistical approach. *Statist., Med.* 2001;20:2429–2439.

Carter WP, Germann CA, Baumann MR. Ophthalmic diagnoses in the ED: herpes zoster ophthamicus. *Am. J. Ophthalmol.* 2008; 612– 617.

CDC. Prevention of herpes zoster. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2008;57:1–30.

Garcia Cenoz M, Castilla J, Montes Y, et al. Varicella and herpes zoster incidence prior to the introduction of systematic child vaccination in Navarre, 2005-2006. *An Sist Sanit Navar*. 2008;31:71-80.

Chan ISF, Wang WWB, Heyse J. Encyclopedia of Biopharmaceutical Statistics. *Vaccine Clinical Trials*. 2003;1005–1022.

Chang MN, Guess HA, Heyse JF. Reduction in burden of illness: a new efficacy measure for prevention trials. *Stat Med.*1994;13:1807–1814.

Cohen JI, Straus SE, Arvin AM. Varicella zoster virus and its replication. 2007; p. 2774-2818. In D. M. Knipe and P. M. Howley (ed.), *Fields virology*, 5th ed. Lippincott/The Williams & Wilkins Co., Philadelphia, PA.

Coplan PM, Schmader K, Nikas A, et al. Development of a measure of the burden of pain due to herpes zoster and postherpetic neuralgia for prevention trials: adaptation of the brief pain inventory. *J Pain*. 2004;5(6):344–356.

Dolan P, Gudex C, Kind P, Williams A; A social Tariff for EuroQoL: Results from a UK General Population Survey. The University of York, center for Health Economics. 1995.

Desmond Renee A, Weiss Heidi L, Arani Ramin B, Soong Seng-jaw, Wood Martin J, Fiddian Paul A, Gnann John W, Whitley Richard J. Clinical Applications for Change-Point Analysis of Herpes Zoster Pain. *Journal of Pain and Symptom Management.* 2002, 23:510–516.

Drummond MF. *Ann. Med.* 2001;33;344–349.

Dunning A. A model for immunological correlates of protection. *Statist. Med. 2006*, 25:1485–1497.

Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis.* 2007;44 Suppl 1:S1–26.

Dworkin et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. *The Journal of Pain*. 2008;9(2):105–121.

EMEA. Zostavax Summary of Product Characteristics. http://www.emea.europa.eu/humandocs/PDFs/EPAR/zostavax. Website accessed 24 March 2009.

Farrar JT, Young JP Jr, LaMoreau L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on a 11-point numerical pain rating scale. *Pain*. 2001;94:149–158.

FDA, U.S. Department of Health and Human Services, Center for Biologics Evaluation and Research. Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Version of September 2007.

Follmann DA, Fay MP, Proschan, MA. Chop-lump tests for Vaccine trials. *Biometrics.* 2009;65: 885–893.

Gilden D, Cohrs RJ, Mahalingam R, et al. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. *Lancet Neurology*. 2009;8(8):731–740.

Hanley and Lippman-Hand. If nothing goes wrong, is everything all right? Interpreting zero numerators. *JAMA.* 1983;249:1743–1745.

Heid CA, Stevens J, Livak KJ et al. Real time quantitative PCR. *Genome Res*. 1996;6(10):986–994.

Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika.* 1988;75:800–802.

Kang CI, Choi CM, Park TS, et al. Incidence of herpes zoster and seroprevalence of varicella-zoster virus in young adults of South Korea. *Int J Inf Dis.* 2008;12(3):245–247.

Levin MJ, Oxman MN, Zhang JH, et al; Veterans Affairs Cooperative Studies Program Shingles Prevention Study Investigators. Varicella-zoster virus-specific immune responses in elderly recipients of a herpes zoster vaccine. *J Infect Dis* 2008; 197:825–835.

Mallinckrodt C, Lane P, Schnell D, Peng Y, Mancuso J. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials, *DIJ.* 2008;42:303–319.

Miettinen OS, Nurminen M. Comparative analysis of two rates. *Statistics in Medicine*. 1985; 4:213–226.

Oxman MN, Levin MJ, Johnson GR, et al. Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352:2271–2284.

Proschan MA, Lan GKK, Turk Wittes J. Statistical Monitoring of Clinical Trials A Unified Approach; Springer-Verlag, 2006

Rowbotham MC. What is a "Clinically meaningful" reduction in pain? *Pain*. 2001;94:131–132.

Schmader K, Sloane R, Pieper C, et al. The impact of acute herpes zoster pain and discomfort on functional status and quality of life in older adults. *Clin J Pain*. 2007;23(6):490–496.

Schmader KE, Dworkin RH. Natural history and treatment of herpes zoster. *The Journal of pain*. 2008;9(1):S3–S9.

Scott F, Johnson R, Leedham-Green M, et al. The burden of herpes zoster: A prospective population based study. *Vaccine.* 2006; 24:1308–1314.

Sperber SJ, Smith BV, Hayden FG. Serologic response and reactogenicity to booster immunization of healthy seropositive adults with live or inactivated varicella vaccine. *Antiviral Res*. 1992;17:213–222.

TGA eBS Australian Register of Therapeutic Goods Medicines. Public summary ZOSTAVAX FROZEN zoster virus vaccine live min 19400 PFU/0.65mL powder for injection vial. https://www.ebs.tga.gov.au/ebs/ANZTPAR/PublicWeb.nsf/cuMedicines?OpenView. Website accessed 25 March 2009.

Toyama N, Shiraki K, and Members of the Society of the Miyazaki Prefecture Dermatologists. Epidemiology of herpes zoster and its relationship to varicella in Japan: A 10-year survey of 48,388 herpes zoster cases in Miyazaki prefecture. *J Med Virol.* 2009;81(12)2053–2058.

Walters S, Brazier J. *Quality of Life Research*. 2005 14:1523–1532.

Ware JE, Kosinski M, Dewey JE. How to score Version 2 of the SF-36® Health Survey. Lincoln, RI: Quality Metric Incorporated, 2000.

Appendix A LABORATORY ASSAYS

Specific Ab (anti-VZV and anti-gE) measurements

Anti-VZV ELISA: Anti-VZV Ab concentrations will be measured using a commercial ELISA kit (*Enzygnost*/Dade Behring), which is based on a single point quantification Ab method (sera tested at a 1:231 dilution). The assay cut-off is 25 milli-international units (mIU)/mL. The assay will be performed on human serum at GSK Biologicals' laboratory or another laboratory designated by GSK Biologicals.

Anti-gE ELISA: Anti-gE Ab concentrations will be measured using an anti-gE ELISA. Diluted blood serum samples of study subjects will be added to microtitre wells pre-coated with gE antigen. Secondary peroxidase-conjugated anti-human Abs will be added, which bind to the primary human anti-gE Abs. After incubation of the microtitre wells with a chromogen substrate solution, the enzymatic reaction will be stopped. Optical densities will be recorded and anti-gE Ab concentrations are calculated from a standard curve. The assay cut-off is 18 mIU/mL. The assay will be performed on human serum at GSK Biologicals' laboratory or another laboratory designated by GSK Biologicals.

Intracellular cytokine staining (ICS)

CMI responses will be performed by GSK Biologicals (or designated laboratory) on thawed Peripheral Blood Mononuclear Cells (PBMCs) by ICS. The assay will be performed on samples collected during the course of the study. This assay provides information on the frequency of CD4 T cells responding to culture medium or antigens (gE peptide pool or VZV lysate) by secreting cytokine molecules involved in immunity such as IFN-γ, IL-2, TNF-α, and CD40L.

Briefly, PBMC collected from the subjects are stimulated for two hours using culture medium (for evaluation of the non-specific response), a pool of overlapping peptides covering the entire sequence of the vaccine antigen gE or a VZV lysate. Then, an intracellular block (brefeldin A) is added to inhibit cytokine secretion for a subsequent overnight incubation. Cells are then harvested, stained for surface markers (CD3, CD4 and CD8) and fixed. The fixed cells are then permeabilised and stained with anti-cytokine Abs, washed and analyzed by cytofluorometry.

The results of ICS assays are expressed as the frequency of specific CD4 T cells per million total CD4 T cells.

Anti-VZV neutralizing antibody assay

Anti-VZV neutralizing Abs will be quantified using a plaque reduction neutralization test (PRNT). Briefly, two-fold serum serial dilutions are incubated with a fixed amount of VZV. The mixture is then added to a monolayer of Vero cells in a 96-well plate and incubated for 2 days. The cells are then fixed, and viral replication is detected using a mixture of murine anti-VZV monoclonal Abs and anti-mouse Abs conjugated to horseradish peroxidase (HRPO). The HRPO activity is detected using a precipitated peroxidase substrate resulting in a brown coloration of VZV-infected cells. The plaques, visualized as collections of stained cells, are counted, and the ratio of the number of

plaques for each serum dilution to the number of plaques when no serum is added (control wells) is calculated. The neutralizing Ab titre is reported as the reciprocal of the serum dilution that reduces the number of plaques by 50% (ED50).

PCR Assay for Confirmation of suspected case of HZ

HZ cases will be confirmed by a Polymerase Chain Reaction (PCR) based algorithm that assesses the presence of VZV DNA in samples, the adequacy of the samples (by assessing the presence of β-actin DNA) and, finally, the potential presence of Herpes Simplex Virus (HSV) -1 and -2 DNA.

VZV, HSV1/2 and β-actin DNA in HZ clinical specimens will be assessed using real-time PCR detection by the 5' nuclease assay based on the Taqman probe technology [Heid, 1996]. If the VZV PCR is negative, β-actin PCR will be performed to assess adequacy of the sample and if a specimen is found to be VZV–PCR negative and β-actin–PCR negative, it is considered to be inadequate. If VZV PCR is negative and β-actin PCR is positive, a generic PCR for HSV1/2 will be performed.

In the Taqman-based PCR experiments, the formation of a PCR product is monitored in real-time during amplification by means of fluorogenic probes that bind specifically to the amplified product. The reporter fluorophore is at the 5' end of the Taqman probe and the quencher is at the 3' end. As long as the probe is intact, no fluorescence is produced by the fluorophore. During the PCR polymerization step, the Taq DNA polymerase displaces the Taqman probe by 3-4 nucleotides, and the 5' nuclease activity of the DNA polymerase separates the fluorophore from the quencher, and a measurable fluorescent signal proportional to the DNA copy number is produced.

As mentioned above, the 5' nuclease-based PCR assay allows the determination of the DNA copy number within samples, but in the present study the VZV, HSV1/2 and β-actin DNA PCR data on samples from suspected HZ lesions (swabs of vesicles, papules and crusts, and crusts themselves) will be used qualitatively only according to the above mentioned algorithm.

Appendix B ASCERTAINMENT OF HZ CASES INCLUDING PCR TESTING ALGORITHM TO CLASSIFY HZ SUSPECTED CASES

A suspected case of HZ is defined as new unilateral rash accompanied by pain (broadly defined to include allodynia, pruritus or other sensations) and no alternative diagnosis. This suspected case will be documented by digital photography of the rash and by collecting any relevant information as described in the clinical protocol.

To classify the suspected case of HZ, the samples from the rash lesions will be collected for laboratory testing by PCR (minimum 3 samples, collected on the same day, per subject). Each rash lesion will be tested using standardized and validated molecular assays according to the PCR testing algorithm described below.

A hierarchical case definition algorithm, similar to the algorithm used by Merck in their Shingle Prevention Study (*Zostavax* efficacy study) [Oxman, 2005] will be used to classify each suspected case of HZ as a confirmed HZ case or not.

1. If at least 1 sample coming from a given subject is "VZV positive" by PCR, this "suspected HZ case" will be classified as a "confirmed case of HZ".
2. If all the samples coming from a given subject are "VZV negative" and "β-actin positive", this means that the sampling procedure is validated and that the "suspected HZ case" will be classified as "not a case of HZ". Regarding the testing algorithm, the HSV qPCR assay will assess if the rash lesions were due to HSV and not to VZV.
3. If all the PCR results for a particular subject could not confirm or exclude a "suspected HZ case" (i.e. samples coming from a given subject are considered as "inadequate" as both VZV and β-actin PCR results are negative, or the samples are missing), this case will be referred to the HZ Ascertainment Committee (HZAC) to be classified. The HZAC will consist of five physicians with HZ expertise. For every such case, each HZAC member will be asked to make a clinical determination of whether the case is HZ based on the review of the available clinical information. A "suspected HZ case" will be considered as a "confirmed HZ case" if at least 3 HZAC members concur (majority vote); otherwise, it will be classified as "not a case of HZ".

This algorithm includes the following steps (see Figure 1):

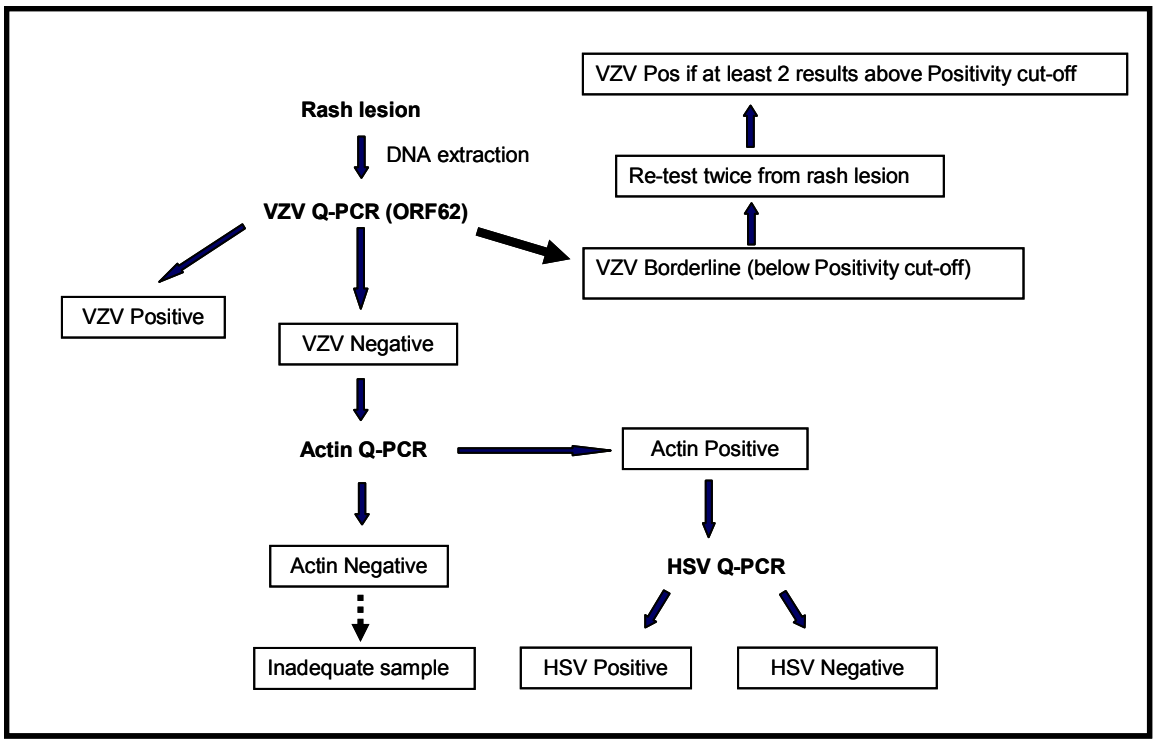
1. DNA extraction from the rash lesion.
2. VZV real-time PCR assay (qPCR) targeting the *orf62* gene is performed to detect VZV in the rash lesion:
    1. If the VZV qPCR signal is above the cut-off of positivity corresponding to the technical limit of detection of the assay, the sample will be considered as "VZV positive".
    2. If the VZV qPCR signal is included between 1 copy/qPCR and the cut-off of positivity, it will be considered as "VZV borderline" and will be re-tested twice in order to obtain 3 results per sample. The sample will be considered as "VZV

positive" if at least 2 results out of the three obtained are above the cut-off of positivity.

3. If the VZV qPCR signal is equal to 0 copies/PCR, the sample will be considered as "VZV negative" and the extracted DNA will be assessed for the presence of β-actin housekeeping gene to validate the rash lesion sampling procedure (see item 3).

1. As described here above, the β-actin qPCR will be performed only on "VZV negative" samples to validate the sampling procedure:
   1. If the β-actin qPCR signal is below the cut-off of positivity of this assay, the sample will be considered as "inadequate" as no DNA coming from human cells is detected within the rash lesion sample.
   2. If the β-actin qPCR signal is above the cut-off of positivity of this assay, the sample will be considered as "valid" but it does not contain any VZV DNA. According to the testing algorithm, the extracted DNA will be assessed for the presence of HSV-1/2 within the rash lesion (see item 4.).
2. As described here above the HSV qPCR assay will be performed on "VZV negative/ β-actin positive samples:
   1. If the HSV qPCR signal is below the cut-off of positivity of this assay, the sample will be considered as "HSV negative".
   2. If the HSV qPCR signal is above the cut-off of positivity of this assay, the sample will be considered as "HSV positive".

Figure 1 Algorithm for HZ case definition by PCR



VZV: Varicella Zoster Virus; Q-PCR: real-time (quantitative) PCR; HSV: Herpes Simplex Virus

Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals
Rue de l'Institut 89, 1330 Rixensart, Belgium

Primary Study vaccine	GlaxoSmithKline Biologicals' Lyophilized formulation of the Herpes Zoster (HZ) vaccine (GSK1437173A)
eTrack study number and Abbreviated Title	110390 (ZOSTER-006)
Investigational New Drug (IND) number	BB-IND 13857
EudraCT number	2008-000367-42
Date of protocol	Final: 07 April 2010
Date of administrative change	Administrative change 1 Final: 20 April 2010
Date of protocol amendment	Amendment 1 Final: 16 December 2010 Amendment 2 Final: 16 March 2012 Amendment 3 Final: 28 June 2012 Amendment 4 Final: 18 April 2014
Title	Efficacy, safety, and immunogenicity study of GSK Biologicals' Herpes Zoster vaccine GSK1437173A in adults aged ≥ 50 years.
Detailed Title	A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' gE/AS01$_B$ vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older.
Co-ordinating author	[redacted] Scientific Writer
Contributing authors (Amended 18 April 2014)	• [redacted] Director, Global Clinical Development, Vaccines • [redacted] ***Project Level Clinical Research & Development Lead,*** Director, Global Clinical Development , ***Vaccines*** • [redacted] ***, Clinical Research and Development Lead*** • [redacted] Biostatistician, ***Lead Statistician*** • [redacted] ***Global Vaccine Clinical Laboratories Project Manager*** • [redacted] ***Global Vaccine Clinical Laboratories Project Director*** • [redacted] ***Project Data Manager*** • [redacted] ***Global*** Regulatory Affairs • [redacted] ***Global Regulatory Affairs***

eTrack study number and Abbreviated Title	110390 (ZOSTER-006)
Investigational New Drug (IND) number	BB-IND 13857
EudraCT number	2008-000367-42
Title	Efficacy, safety, and immunogenicity study of GSK Biologicals' Herpes Zoster vaccine GSK1437173A in adults aged ≥ 50 years.
Detailed Title	A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' gE/AS01$_B$ vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older.
Contributing authors (Amended 18 April 2014) (continued)	• [redacted] ***Global Regulatory Affairs*** • [redacted] ***Global Regulatory Lead,*** Director • [redacted] ***Health Economics*** • [redacted] Safety Physician • [redacted] ***Study Delivery Lead***

GSK Biologicals' Protocol DS v 13.1.

Protocol Amendment 4 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	110390 (ZOSTER-006)
IND number	BB-IND 13857
EudraCT number	2008-000367-42
Date of amendment	Amendment 4 Final: 18 April 2014
Detailed Title	A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' gE/AS01$_B$ vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older.
Sponsor signatory **(Amended 18 April 2014)**	[redacted] ***Project Level Clinical Research & Development Lead, Director, Global Clinical Development, Vaccines***
Signature	_____
Date	_____

Protocol Amendment 4 Rationale

Amendment number: Amendment 4

Rationale/background for changes:

- It is predicted that study ZOSTER-006 will reach the conditions required for triggering final analysis of herpes zoster (HZ) primary endpoint about one year before those conditions being reached for study ZOSTER-022. Therefore GSK decided, as originally planned in these circumstances, to dissociate the two studies in terms of timing of the analysis of each study. Moreover, a two-step approach is allowed for the analysis of each study. Both studies will end concurrently . (Synopsis, Sections 3, 10.4.6)
- In study ZOSTER-022, postherpetic neuralgia (PHN) is demoted from co-primary endpoint to a descriptive secondary endpoint and the overall PHN co-primary endpoint in subjects ≥ 70 YOA for pooled analyses of ZOSTER 006 and ZOSTER-022 will be considered as primary analysis for PHN. Overall PHN in subjects ≥ 50 YOA has become a secondary endpoint for pooled analyses of ZOSTER-006 and ZOSTER-022. The applicable objectives and endpoints have been updated accordingly in the ZOSTER-022 protocol. Pooled analyses of ZOSTER-006 and ZOSTER-022 will only be conducted if the primary objective [HZ vaccine efficacy (VE)] is demonstrated in both ZOSTER-006 and ZOSTER-022 separately. The gatekeeping strategy has been updated accordingly and aligned with the objectives (Synopsis, Sections 1.2, 10.4.2, Table 19, 10.4.3, 10.4.4); the gatekeeping strategy diagram has been numbered (Fig. 1).
- The expected number of PHN cases is projected based on current accrual rates. The target number of PHN cases required to trigger pooled PHN analysis has been reduced, while maintaining statistical robustness. A total of at least 35 PHN cases in subjects ≥ 70YOA provides 90% power to demonstrate an overall PHN VE of at least 0% (previously a total of at least 88 PHN cases provided 93% power to demonstrate an overall PHN VE in subjects ≥ 50YOA of at least 25%). In the pooled analysis of studies ZOSTER-006 and ZOSTER-022 clinically meaningful overall PHN VE (PHN VE in ≥ 70 YOA randomized subjects) will be demonstrated if the lower limit of the 95% CI is above 0%. The sample size of the pooled studies ZOSTER-006 and ZOSTER-022 provides 10% chance (previously 22%) to demonstrate statistically significant PHN VE (LL above 0%) in those subjects presenting with a HZ episode. (Sections 10.4.5.1, Table 20, 21, 22, Section 10.4.5.2)
- The analysis steps, i.e. final HZ efficacy analysis (step 1) and end of study analysis (step 2) are defined. The conditions determining the cut-off dates of the 2 analysis steps are detailed.

The cut-off date for final HZ efficacy analysis will occur given the following conditions:

- at least 196 confirmed HZ cases are accrued in the primary cohort for analysis of efficacy;
- approximately 60 HZ cases in subjects 50-59 YOA and approximately 60 HZ cases in subjects 60-69 YOA are accrued in the mTVc;
- approximately 75% of subjects in each stratum have completed at least 36 months follow-up after Dose 2, and the remaining subjects have completed at least 30 months follow-up after Dose 2.

The cut-off date for end of study analysis will occur given the following:

- all previous conditions are met for final HZ analyses in study ZOSTER-022;
- at least 35 PHN cases in subjects $\geq$70YOA are accrued in the in the primary cohort for analysis of efficacy when pooling the studies ZOSTER-006 and ZOSTER-022.

The end of study analysis cannot be performed before the final HZ efficacy analysis. Details regarding study duration are described.
(Synopsis, Sections 3, 10.4.5.1, 10.4.6)

- An overview of the analyses performed at each analysis step is given. Step 1 will include analyses of the following objectives of ZOSTER-006: all HZ VE objectives and all reactogenicity/safety and immunogenicity objectives. At step 2, all objectives of study ZOSTER-006 will be analyzed. Objectives already analyzed at step 1 will be re-analyzed (confirmatory descriptive in case of inferential analysis at step 1 or descriptive analysis otherwise). At step 2, pooled analyses of studies ZOSTER-006 and ZOSTER-022 are planned; overall PHN VE in subjects ≥ 70 YOA, and other pre-specified endpoints will be analyzed. (Synopsis, Sections 3, 10.4.9, Table 33)
- Each inferential objective in study ZOSTER-006 will be assessed only one time, therefore no alpha adjustment will be applied. For all inferential objectives assessed at first step analysis, a second descriptive analysis will be performed at the end of each study and will serve as confirmatory analysis (Sections 10.4.4, 10.4.7).
- It has been detailed that depending on the further evolution of the case accrual rate, the generated data may be presented in one or more study reports per study (ZOSTER-006 and ZOSTER-022). The final study report for each study will be a comprehensive report containing the results of the two analysis steps (Sections 10.7.4, 10.8.3.2). Wording in Section 10.8.3.4 has been aligned with Section 10.7.4.
- The same blinding level (i.e. observer-blind) remains to be kept throughout the study. Measures taken to ensure the blinding, including the installation of a firewall, are described in a separate charter. Pending the outcome of the final HZ efficacy analysis of studies ZOSTER-006 and ZOSTER-022, a long-term follow-up study might be planned enrolling subjects who participated in the primary studies ZOSTER-006 and ZOSTER-022 and are willing to participate in the follow-up study. The design of the follow-up study remains to be confirmed. (Sections 5.4, 10.4.6, 10.4.8, 10.7.3)

- Given the two-step analyses, in accordance with GSK procedures, in the List of study procedures the final HZ efficacy analysis trigger has been specified, with transcription in the eCRF of the date of the last visit or contact with the subject and addition of the investigator signature (Section 5.6, Table 2). This has also been detailed in a new Section 5.7.3.15; the numbering of subsequent sections has been updated accordingly (i.e., Sections 5.7.3.16 and 5.7.3.17).
- It is anticipated that all subjects will have completed Visit 6 at the time of study conclusion; updates have been made accordingly (Sections 3 and 5.6, Table 2 and Table 4).
- Given the two-step analyses, reference is made to the cut-off date for end of study analysis (instead of cut-off date for final analysis) when describing follow-up of HZ up to or close to study end (Sections 5.5.1, 5.5.2.2, 5.5.2.4, 5.6 Table 3, 5.7.3.11, 5.7.3.17, 7, 10.7.3).
- The description of the process for follow up of HZ has been aligned throughout the Table 3 footnotes (Section 5.6) reflecting that if HZ-associated pain ceases (defined as a 28-day [or 4-week] pain free period) and the HZ rash resolves, subsequent HZ follow-up visits or contacts will be cancelled.
- Given the two-step analyses, reference is made to 'final HZ efficacy analysis' instead of 'final analysis', when applicable (Sections 10.4.5.3, 10.7.1 and 10.7.2, Table 23 and Table 24).
- It has been detailed that in case of unblinding upon the subject's request to allow the subject to decide if he/ she will consider immunization with a licensed HZ vaccine, the subject will be withdrawn from the study (Sections 5.7.3, 9.2.1)
- The cut-off of the gE-specific ELISA assay has been changed from 18 to 97 mIU/mL. Background signal has been measured with the anti-gE ELISA on samples from Varicella Zoster Virus (VZV) naïve paediatric subjects. This observation of background signal on VZV naïve samples was not part of the original validation of the assay and establishment of the assay cut-off. Background signal measured with the anti-gE ELISA has no impact on Zoster project clinical conclusions as the vast majority of the samples (at all timepoints) have high titers well above the unspecific response level measured on VZV naïve samples from Measles, Mumps, Rubella and Varicella (MMRV) studies and Zoster vaccine responses are very robust. However this finding triggered re-evaluation of the assay cut-off. Based on complementary validation experiments performed in line with Clinical and Laboratory Standards Institute (CLSI) guidelines and taking into account internal company guidelines the technical and seropositivity cut-off has been set at 97mIU/mL. (Section 5.8.3, Table 7, Appendix A)
- Regarding the reporting of SAEs that are related to study participation (e.g. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine or any fatal SAE, it has been clarified that this includes SAEs that are considered by the investigator to be related to the investigational vaccine and are to be reported until study end (Section 8.3.1; Table 14).

- The section on derived and transformed data for cell-mediated immunogenicity vaccine responses (gE- and VZV-specific) including the definition of vaccine response has been updated in alignment with the harmonised definitions within the ZOSTER project (Section 10.6.4).
- For clarity, the total number of subjects included in the Immunogenicity subset and the CMI subset has been detailed (Section 10.4.5.6.4, Table 30; Section 10.4.5.7.2, Table 32).
- A process related to review of immunogenicity data as described in the protocol is not applicable for the study, therefore any related wording has been removed (Section 10.7.3).
- In accordance with current GSK procedures, where applicable the name of the plan previously referred to as 'reporting analysis plan' has been updated to 'statistical analysis plan' (List of abbreviations, Sections 10.5.3, 10.7.3, 10.8.2, 10.8.2.3, 10.8.2.4, 10.8.2.5, 10.8.2.6, 10.8.2.7, 10.8.3.4, 10.8.4.1, 10.8.4.2, 10.8.5.2).
- For clarity, it has been detailed that the subject will be reminded that the current study has yearly follow-up visits planned until Month 38 (Visit 6) (Section 5.7.3.14).
- The estimated study period has been updated in the section with country specific requirements for Japan (Section 12.3).
- A reference has been further detailed and references which are not applicable anymore have been removed (Section 13).
- The list of contributing authors and the sponsor signatory have been updated (cover page, sponsor signatory approval page).

Protocol Amendment 4 Investigator Agreement

I agree:

To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals (GSK Biologicals).

- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational product(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorised representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	110390 (ZOSTER-006)
IND number	BB-IND 13857
EudraCT number	2008-000367-42
Date of amendment	Amendment 4 Final: 18 April 2014
Detailed Title	A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' gE/AS01$_B$ vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older.
Investigator name	
Signature	
Date	
Leiter der klinischen Prüfung' (LKP) name Signature	
Date	
Study Representative (Japan)	
Signature	
Date	

SYNOPSIS

Detailed Title	A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' gE/AS01$_B$ vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older.
Indication	Primary immunization of subjects ≥ 50 years of age (YOA) against Herpes Zoster (HZ). The study population includes males and females without severely immunocompromising conditions in the age ranges 50-59 YOA, 60-69 YOA, 70-79 YOA and ≥ 80 YOA. The 70-79 YOA and ≥ 80 YOA strata will be combined for primary analyses.
Rationale for the study and study design	Two studies (ZOSTER-006 enrolling subjects ≥ 50 YOA and ZOSTER-022 enrolling subjects ≥ 70 YOA) will be conducted concurrently to evaluate efficacy of GlaxoSmithKline (GSK) Biologicals' gE/AS01$_B$ vaccine. Study ZOSTER-006 will provide pivotal data on the overall efficacy in prevention of HZ in subjects ≥ 50 YOA. The primary endpoint of this study will be overall HZ vaccine efficacy (VE) across all age cohorts. To this end, ZOSTER-006 will evaluate VE of the gE/AS01$_B$ vaccine compared to placebo in reducing the risk of developing HZ in subjects ≥ 50 YOA. This study will enrol subjects in the age ranges 50-59 YOA, 60-69 YOA, 70-79 YOA and ≥ 80 YOA in approximately an 8:5:3:1 ratio to achieve comparable numbers of HZ in the 3 main age strata (50-59 YOA, 60-69 YOA and ≥ 70 YOA) so that a balanced estimate of the overall VE in persons ≥ 50 YOA can be determined. Apportionment of approximately 20-25% of the ≥ 70 YOA cohort to persons ≥ 80 YOA in both ZOSTER-006 and ZOSTER-022 ensures that this particularly vulnerable population is adequately represented. Assessment of Postherpetic Neuralgia (PHN) VE would require a large sample size of subjects ≥ 70 YOA due to a relatively lower incidence of PHN in younger adults. This cannot be achieved in study ZOSTER-006 without impacting the intent of the study, since a large overrepresentation of subjects ≥ 70 YOA in the ZOSTER-006 study would not allow an accurate assessment of HZ VE across the entire ≥ 50 YOA age range enrolled in the trial and may potentially underestimate overall efficacy of the gE/AS01$_B$ vaccine, since

HZ VE may diminish with age.

Study ZOSTER-022 will address VE against ***HZ*** in subjects ≥ 70 YOA. ***At the end of studies ZOSTER-006 and ZOSTER-022***, a pooled analysis of HZ and PHN data from both studies combined is planned and will be described prospectively. ***The analysis of pooled data from both studies for overall PHN in subjects ≥ 70 YOA is positioned as primary analysis for PHN.*** **(Amended 18 April 2014)**

A saline solution is included as a negative control (placebo) in this study to evaluate the efficacy and safety profile of the candidate HZ vaccine. Use of the placebo control and the observer-blind, randomized study design, will allow to control for potential biases in the conduct of the study.

Objectives

Primary

- To evaluate VE in the prevention of HZ compared to placebo in adults ≥ 50 YOA, as measured by the reduction in HZ risk.

Secondary

- To evaluate VE in the prevention of HZ compared to placebo in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, as measured by the reduction in HZ risk;
- To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;
- To evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate VE in the reduction of overall and HZ-related mortality and hospitalizations compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;
- To evaluate VE in the reduction in incidence of HZ-associated complications compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;

- To evaluate VE in the reduction in use of pain medications compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate vaccine safety and reactogenicity.

Exploratory objectives

- To evaluate VE in reducing the severity of acute HZ-associated pain compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate VE in improving Quality of Life (QoL) compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate VE in the mitigation of Burden-Of-Illness (BOI) caused by HZ compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;
- To evaluate vaccine induced cell mediated and humoral immune responses and the persistence of each type of response after two injections of study vaccine in subjects ≥ 50 YOA, and by age strata;
- To evaluate anti-varicella-zoster virus (VZV) neutralizing antibody (Ab) titres in a subset of subjects at Month 0 (pre-vaccination), and at Months 3, 14, 26 and 38, in subjects ≥ 50 YOA, and by age strata.

Study design

- Experimental design: multicentre, parallel group
- Control: placebo (NaCl solution)
- Vaccination schedule: 0, 2 months
- Treatment groups: 2 groups of subjects
  - Vaccine group (gE/AS01$_B$ vaccine)
  - Placebo group (NaCl solution as control)
- Study allocation: Eligible subjects 70-79 YOA and ≥ 80 YOA will be randomly assigned to ZOSTER-006 or ZOSTER-022 at Visit 1.
- Treatment allocation: Eligible subjects will be randomized to investigational vaccine/placebo according to a 1:1 ratio (vaccine:placebo). Subjects will be stratified

by age: 50-59 YOA; 60-69 YOA; 70-79 YOA and ≥ 80 YOA in approximately an 8:5:3:1 ratio. The 70-79 YOA and ≥ 80 YOA strata will be combined for primary analyses.

- Blinding: observer-blind
- Biological samples to be collected:
  - Blood samples will be collected from all subjects at Visit 1 and 3 to contribute to the correlate of protection assessment should the subject experience a HZ episode or be selected as a case control.
  - Blood samples will be collected from a subset of subjects at Visit 4, 5 and 6 to assess persistence of humoral immune response. In these subjects, the blood samples from Visit 1 and 3 will also be assessed for humoral immune response.
  - Blood samples will be collected from a subset of subjects at Visit 1, 3, 4, 5 and 6 to assess cell-mediated immunogenicity (CMI) response.
  - Clinical specimens of HZ lesions will be collected from subjects clinically diagnosed as having a suspected case of HZ.
- Type of study: Self-contained, and will be combined with study ZOSTER-022 for some analyses.
- Data collection: Remote Data Entry (RDE) on electronic Case Report Form (eCRF).
- ***Planned analysis steps:***

  It is predicted that study ZOSTER-006 will reach the conditions required for triggering final analysis of HZ primary endpoint about one year before those conditions being reached for study ZOSTER-022. Therefore GSK decided, as originally planned in these circumstances, to dissociate the two studies in terms of timing of the analysis of each study. Moreover, a two-step approach is allowed for the analysis of each study. Both studies will end concurrently.

In study ZOSTER-006, the planned analysis steps are the following:

1. ***Final HZ efficacy analysis (step 1). Final analysis of HZ primary endpoint:***

The cut-off date for final HZ efficacy analysis will occur when the following conditions are met:

- ***at least 196 confirmed HZ cases are accrued in the modified Total Vaccinated cohort (mTVc)[1];***
- ***approximately 60 HZ cases in subjects 50-59 YOA and approximately 60 HZ cases in subjects 60-69 YOA are accrued in the mTVc;***
- ***approximately 75% of subjects in each stratum have completed at least 36 months follow-up after Dose 2, and the remaining subjects have completed at least 30 months follow-up after Dose 2.***

Step 1 will include analyses of the following objectives:

- ***all HZ VE objectives;***
- ***all reactogenicity/safety and immunogenicity objectives.***

2. ***End of study analysis (step 2).***

The cut-off date for end of study analysis will occur given the following:

- ***all conditions (as detailed in ZOSTER-022 protocol) are met for final HZ efficacy analysis in study ZOSTER-022;***
- ***at least 35 PHN cases in subjects ≥ 70YOA are accrued in the mTVc when pooling the studies ZOSTER-006 and ZOSTER-022.***

The end of study analysis (step 2) cannot be performed before the final HZ efficacy analysis (step 1).

At step 2 all objectives of study ZOSTER-006 will be analyzed. Objectives already analyzed at step 1 will be re-analyzed (confirmatory descriptive in case of inferential analysis at step 1 or descriptive analysis otherwise).

Pooled analyses of studies ZOSTER-006 and ZOSTER-

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[1] ***The modified Total Vaccinated cohort (mTVc) is the primary cohort for analysis of efficacy which excludes subjects in the TVc for efficacy analysis who were not administered with the second vaccination or who develop a confirmed case of HZ prior to 1 month after the second vaccination.***

022 are planned if the primary objective of study ZOSTER-006 and the primary objective of study ZOSTER-022 are demonstrated. Overall PHN VE in subjects ≥ 70 YOA, and other pre-specified endpoints will be analyzed in the pooled analyses, as specified in ZOSTER-022 protocol.

(Amended 18 April 2014)

- Duration of the study: Each subject will be followed for at least 30 months after Dose 2.

  All subjects will continue in the study at least until the cut-off date for ***end of study*** analysis regardless of their date of enrolment. Study end will take place when ***the*** conditions for ***end of study*** analysis are met and a minimum 90 days follow-up is completed for each HZ case that occurs up to the cut-off date for ***end of study*** analysis.

  The exact duration of the study for individual subjects will vary. The maximum total study duration for each subject is expected to be ***approximately*** 4 to 5 years.

  (Amended 18 April 2014)

Number of subjects

Target enrolment will be 15,980 eligible subjects (7,990 in the vaccine group and 7,990 in the placebo group).

Endpoints

Primary

- Confirmed HZ cases.
  - Confirmed HZ cases during the study in the mTVc.

Secondary

- Occurrence of overall PHN
  - Incidence of PHN calculated using the mTVc;
- Duration of severe 'worst' HZ-associated pain
  - Duration of severe 'worst' HZ-associated pain following the onset of a confirmed HZ rash over the entire pain reporting period as measured by the Zoster Brief Pain Inventory (ZBPI) in subjects with confirmed HZ;
- Incidence of overall and HZ-related mortality
  - Incidence of overall and HZ-related mortality during the study;
- Incidence of HZ complications
  - Incidence of HZ complications during the study in

subjects with confirmed HZ;

- Incidence of overall and HZ-related hospitalizations
  - Incidence of overall and HZ-related hospitalizations during the study;
- Duration of pain medication administered for HZ
  - Duration of pain medication administered for HZ during the study in subjects with confirmed HZ;
- Solicited local and general symptoms in a subset of subjects
  - Occurrence, intensity of each solicited local symptom within 7 days (Days 0-6) after each vaccination, in subjects included in the 7-day diary card subset;
  - Occurrence, intensity and relationship to vaccination of each solicited general symptom within 7 days (Days 0-6) after each vaccination, in subjects included in the 7-day diary card subset;
- Unsolicited adverse events (AEs)
  - Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days (Days 0 – 29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification in all subjects;
- Serious Adverse Events (SAEs)
  - Occurrence and relationship to vaccination of all SAEs from Month 0 to Month 14 in all subjects;
  - Occurrence of SAEs related to study participation or to a concurrent GSK medication/vaccine during the entire study period in all subjects;
  - Occurrence of any fatal SAEs during the entire study period in all subjects;
- Occurrence of pre-defined AEs
  - Occurrence and relationship to vaccination of any potential immune-mediated diseases (pIMDs)[2] during the entire study period in all subjects;

[2] Formerly referred to as new onset of autoimmune diseases (NOADs) and other immune mediated inflammatory disorders.

- Occurrence of medically attended visits
  - Occurrence and relationship to vaccination of medically attended visits (defined as hospitalizations, emergency room visits or visits to or from medical personnel), other than routine health care visits, from Month 0 to Month 8 in all subjects.

Exploratory endpoints

- Acute HZ severity
  - Acute HZ severity as determined by the mean Area Under Curve (AUC) of the severity-by-duration of HZ-associated pain as measured by the ZBPI during a 4-week period following the onset of confirmed HZ in subjects with confirmed HZ;
- Interference of HZ with QoL
  - Interference of HZ with QoL as measured by ZBPI in subjects with confirmed HZ;
  - Interference of HZ with QoL as measured by EQ-5D in subjects with confirmed HZ;
  - Interference of HZ with QoL as measured by SF-36 in subjects with confirmed HZ;
- HZ BOI
  - HZ BOI as determined by the mean AUC of the severity-by-duration HZ-associated pain during a 26 week period following the onset of the HZ rash in the mTVc;
- CMI in terms of frequencies of antigen-specific CD4 T cells at Months 0, 3, 14, 26 and 38
  - Frequencies of CD4 T cells with antigen-specific Interferon gamma (IFN-γ) and/or Interleukin-2 (IL-2) and/or Tumour Necrosis Factor alpha (TNF-α) and/or CD40 Ligand (CD40L) secretion/expression to glycoprotein E (gE) and VZV as determined by intracellular cytokine staining (ICS) in a subset of subjects at Months 0, 3, 14, 26 and 38;
- Antigen-specific Ab concentrations at Months 0, 3, 14, 26 and 38
  - Anti-gE and anti-VZV Ab concentrations as determined by Enzyme-linked Immunosorbent Assay (ELISA), in a subset of subjects at Months 0, 3, 14, 26 and 38;

- Anti-VZV neutralizing Ab titres at Months 0, 3, 14, 26 and 38
  - Anti-VZV neutralizing Ab titres as determined by the neutralization assay in a subset of subjects at Months 0, 3, 14, 26 and 38.

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LIST OF ABBREVIATIONS

Ab	Antibody
AE	Adverse Event
$AS01_B$	MPL, QS21, liposome based Adjuvant System (50 µg MPL and 50 µg QS21)
$AS01_E$	MPL, QS21, liposome based Adjuvant System (25 µg MPL and 25 µg QS21)
ATPc	According To Protocol cohort
AUC	Area Under Curve
BOI	Burden-Of-Illness
CD40 L	CD40 Ligand
CI	Confidence Interval
CMI	Cell-Mediated Immunogenicity/immunity
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked Immunosorbent Assay
FDA	Food and Drug Administration, United States
GCP	Good Clinical Practice
gE	Glycoprotein E
GMC/T	Geometric Mean Concentration/Titres
GM	Geometric Mean
GSK	GlaxoSmithKline
HRPO	Horseradish Peroxidase
HSV	Herpes Simplex Virus
HZ	Herpes Zoster
HZAC	HZ Ascertainment Committee
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Intracellular Cytokine Staining
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	Interferon Gamma
IL-2	Interleukin-2

IM	Intramuscular/Intramuscularly
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine System
LOD	Limit Of Detection
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimal Important Difference
mIU	Milli-International Unit
MPL	3-*O*-desacyl-4'-Monophosphoryl Lipid A
mTVc	Modified Total Vaccinated Cohort
NOAD	New Onset of Autoimmune Disease
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PHN	Postherpetic Neuralgia
PIMD	Potential Immune-Mediated Disease
PRNT	Plaque Reduction Neutralization Test
QALY	Quality Adjusted Life Years
QoL	Quality of Life
QS21	*Quillaja saponaria* Molina, fraction 21 (Antigenics, New York, NY, US)
RAP	Reporting and Analysis Plan
RDE	Remote Data Entry
SAE	Serious Adverse event
SAP	***Statistical Analysis Plan*** **(Amended 18 April 2014)**
SAS	Statistical Analysis System
SBIR	Simply Better Internet Randomisation
SD	Standard Deviation
SDAC	Statistical Data Analysis Centre
SDRRA	Study Determination (Recruitment/Randomisation) Agreement
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPM	Study Procedures Manual

TNF-α	Tumour Necrosis Factor Alpha
TVc	Total Vaccinated Cohort
US	United States
VAS	Visual Analog Scale
VE	Vaccine Efficacy
VZV	Varicella-Zoster Virus
YOA	Years Of Age
ZBPI	Zoster Brief Pain Inventory

GLOSSARY OF TERMS

Adequate contraception: Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly (when applicable, as mentioned in the product label) for example abstinence, combined or progestogen oral contraceptives, injectable progestogen, implants of levonorgestrel, oestrogenic vaginal ring, percutaneous contraceptive patches or intrauterine device (IUD) or intrauterine system (IUS), vasectomy with documented azoospermia of the sole male partner or male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository) or male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

For azoospermia, 'documented' refers to the laboratory report of azoospermia, required for acceptable documentation of successful vasectomy in the subject's male partner.

Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Blinding: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an observer-blind study, the subject and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment allocation (see Section 5.4 for details on observer-blinded studies).

Burden-of-illness score:	The HZ "Burden-Of-Illness (BOI) score" represents the average severity of illness among all subjects in the vaccine or placebo groups. It is calculated according to the "modified" scale described by Coplan [Coplan, 2004] as the sum of the HZ "severity-of-illness" scores of all members of the treatment group divided by the total number of subjects in the group.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 6.6.1 and 10.5 for details on criteria for evaluability).
Investigational vaccine/product: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. A NaCl solution, also referred to as saline is used as placebo in this study.
Menopause:	Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.
Protocol amendment:	ICH defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. NB Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.

Quality of Life	Quality of Life is measured, using three questionnaires (ZBPI, EQ-5D and SF-36) to be completed by the subject. ZBPI specifically assesses HZ-associated pain and discomfort during an HZ episode. EQ-5D and SF-36 provide multi-dimensional evaluation of the health status.
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	Adverse events (AEs) to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Study determination number:	A unique number that assigns subjects aged 70 years and older to either study ZOSTER-006 or ZOSTER-022.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the product(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.
Treatment number:	A number identifying a treatment to a subject, according to the study randomisation or treatment allocation.
Unsolicited adverse event:	Any adverse event (AE) reported in addition to those solicited during the clinical study. Also any ‘solicited’ symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

TRADEMARKS

The following trademarks are used in the present protocol.

Note: In the body of the Protocol (including the synopsis), the names of the vaccines/products and/or medications will be written in italic font and without the subscript symbol ™ or ®.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Varilrix™	Varicella vaccine consisting of live attenuated Varicella-zoster virus (Oka strain)

Trademarks not owned by the GlaxoSmithKline group of companies	Generic descriptions
Varivax® (Merck & Co)	Varicella vaccine consisting of live attenuated varicella-zoster virus (Oka strain)
Zostavax® (Merck & Co)	Herpes zoster vaccine consisting of high-titre live attenuated Varicella-zoster virus (Oka strain)
Enzygnost® (Dade Behring)	ELISA kit

1. INTRODUCTION

1.1. Background

Varicella-zoster Virus (VZV) causes two distinct diseases. Varicella (chickenpox) shortly occurs after primary VZV infection and is characterised by systemic illness and a widely disseminated rash. Herpes zoster (shingles) occurs when VZV reactivates from latency and typically manifests as a localised, dermatomal rash.

The typical herpes zoster (HZ) rash usually lasts 2 to 4 weeks and is usually accompanied by pain that is often described as burning, shooting, or stabbing. In some patients, even touching the affected area lightly may cause pain, a phenomenon known as allodynia. This HZ-associated pain may be severe, and pruritus, which can also be severe, may be as common as pain.

The most common complication of HZ is postherpetic neuralgia (PHN). PHN is defined as pain that persists after the resolution of the HZ rash. Affected patients typically report constant burning, throbbing, intermittent sharp or electric shock-like pain, or allodynia. Older age is a clear risk factor for PHN. Other risk factors may include a severe HZ rash and a painful HZ prodrome. PHN tends to improve over a period of months. About 70-80% of cases resolve within 1 year, however, in some persons PHN persists for many years [Dworkin, 2007].

Other complications of HZ include ophthalmologic, neurological, cutaneous and visceral disease, which can result in severe disability. The most common ocular complications of HZ are keratitis and uveitis; other ophthalmologic complications include ptosis, episcleritis/scleritis, retinitis, secondary glaucoma and cataract [Schmader, 2008; Carter, 2008]. Neurologic complications associated with HZ include myelitis, motor neuropathy, ischaemic infarction of the brain and spinal cord, aneurysm, and subarachnoid and cerebral haemorrhage [Gilden, 2009; Schmader, 2008].

Age is the most common risk factor for developing HZ. The incidence of HZ is relatively constant at 2-3 cases per 1000 persons per year until age 40, and then increases progressively with age: At 50-59 years of age (YOA) the incidence is about 5 cases per 1000 persons per year, and it increases to 10 cases per 1000 persons per year in people ≥ 60 YOA [CDC, 2008; Oxman, 2005]. While most HZ incidence data come from the United States (US) and Europe, available data indicate similar incidences of HZ in other parts of the world including Japan, Korea, Australia and Latin America [Araújo, 2007; Garcia Cenoz, 2008; Kang, 2008; Toyama, 2009].

Half of all HZ cases occur in patients over the age of 60, and individuals who reach 85 years old have a 50% chance of having HZ during their lifetime [Oxman, 2005]. The risk for PHN is also highest in older people with HZ, occurring in 18-50% of those aged 70 years and older [Oxman, 2005; Scott, 2006]. Patients with impaired cell-mediated immunity (CMI) due to disease, drug treatment, medical interventions or advanced age are at increased risk for the development of HZ [Cohen, 2007]. Since the loss of VZV-specific T cell responses as a result of aging or immunosuppression leads to heightened

susceptibility to HZ, vaccination is considered as a means to reduce the risk of HZ in older adults and immunocompromised persons [Oxman, 2005; Sperber, 1992].

The potential of vaccination to protect against HZ was evaluated in a large efficacy study in which *Zostavax* (a live attenuated HZ vaccine that is a high titre preparation of the varicella vaccine, *Varivax* [both manufactured by Merck & Co]) partially protected immunocompetent older adults against HZ [Oxman, 2005]. In the overall population (≥ 60 YOA), *Zostavax* reduced the incidence of HZ by 51.3% (p-value < 0.001), although its effectiveness decreased with the age of the vaccinee. In particular, vaccine efficacy (VE) diminished to 37.6% among persons in older age groups (≥ 70 years of age) [Oxman, 2005]. Based on the data from this study, *Zostavax* was licensed in the US and other countries. In the US, *Zostavax* is indicated for prevention of HZ in individuals ≥ 50 YOA and older [Zostavax Prescribing information, 2011]. In Australia, *Zostavax* is indicated for the prevention of HZ, PHN and for reduction of acute and chronic HZ-associated pain in individuals ≥ 60 YOA, and for the prevention of HZ in individuals 50-59 YOA [TGA, 2009]. In Europe, *Zostavax* is indicated for prevention of HZ and PHN in individuals ≥ 50 YOA [EMEA, 2009]. *Zostavax* is contraindicated in persons with immunodeficiency due to malignancy, human immunodeficiency virus (HIV) infection or immunosuppressive medical therapy.

Although no immunological correlate for protection against HZ has been identified, current knowledge suggests that VZV-specific CMI is of primary importance in preventing HZ [CDC, 2008]. The role of humoral immune responses in preventing HZ is less clear. However, VZV-specific antibodies (Abs) may help control viral dissemination in immunocompromised persons and may thereby help limiting the severity of HZ. Furthermore, a correlation between post-vaccination anti-VZV Ab concentrations and protection against HZ was observed in the *Zostavax* efficacy study [Levin, 2008]. While VZV-specific Abs may not be directly protective against HZ, they may represent a "downstream" measure of the CMI response to vaccination.

GlaxoSmithKline (GSK) Biologicals is developing a candidate HZ vaccine consisting of VZV glycoprotein E (gE) and an adjuvant. The VZV gE was chosen as the subunit vaccine antigen because of both its prominence as a target for host immune responses [Cohen, 2007] and its functional significance during viral infection. Since the vaccine does not contain live virus, it is expected that this vaccine will prove safe in all populations including highly immunocompromised persons. Adjuvant System $AS01_B$ used in combination with the gE antigen was developed at GSK Biologicals, and contains the immunostimulants MPL (3-O-desacyl-4'-monophosphoryl lipid A) and QS21 (*Quillaja saponaria* Molina, fraction 21; Antigenics, New York, NY, US) formulated in combination with liposomes. MPL is a chemically detoxified form of the parent lipopolysaccharide from the gram negative bacterium *Salmonella minnesota*. QS21 is a natural saponin molecule (triterpene glycoside) obtained from the tree bark of *Quillaja saponaria* Molina.

Three recently completed trials in healthy older adults have provided clinical evidence for the immunogenicity and tolerability of GSK Biologicals' candidate HZ vaccine, $gE/AS01_B$.

In a phase I/II exploratory trial (Explo CRD-004), 155 subjects received two doses of either gE/AS01$_B$, gE/AS01$_B$ and *Varilrix* (a live attenuated varicella vaccine similar to *Zostavax*), or *Varilrix* alone. Of the 110 subjects who received gE/AS01$_B$, 90 were 50-70 YOA (the other 20 subjects were 18-30 YOA). Subjects in the gE/AS01$_B$ groups developed significantly higher CD4 T cell responses to gE and VZV than those in the *Varilrix* alone group. Immune responses persisted up to 40 months after administration of the second vaccination in older adults receiving gE/AS01$_B$ alone (the latest timepoint evaluated). Reactogenicity was higher in the gE/AS01$_B$ groups than in the group that received *Varilrix* alone; however, the incidences of grade 3 local and general symptoms were low. Based on the results of this study, gE/AS01$_B$, without *Varilrix*, was selected for further clinical evaluation.

In a phase II dose finding trial (ZOSTER-003), gE/AS01$_B$ was administered to 714 adults ≥ 60 YOA. Subjects received either 2 doses of either 25 μg, 50 μg or 100 μg gE adjuvanted with AS01$_B$, one dose of 100 μg gE adjuvanted with AS01$_B$ and one of NaCl solution [Saline], or 2 doses of 100 μg gE/Saline (no adjuvant). Subjects in all gE/AS01$_B$ dose groups (660 total) developed significantly higher CD4 T cell and humoral immune responses to gE than did those who received unadjuvanted gE. Also, 2 vaccinations with any of the gE/AS01$_B$ vaccine formulations elicited higher immunological responses than a single dose. Comparison between the 25 μg, 50 μg and 100 μg gE/AS01$_B$ vaccine formulations administered in a 2 dose schedule demonstrated that humoral immune responses to 50 μg gE/AS01$_B$ were significantly greater than those induced by 25 μg gE/AS01$_B$, whereas 100 μg gE/AS01$_B$ was not superior to 50 μg gE/AS01$_B$. In addition, cellular immune responses to gE/AS01$_B$ vaccines exhibited slight dose dependence in favour of higher gE doses. Reactogenicity was similar for 25 μg, 50 μg, and 100 μg gE/AS01$_B$ formulations, but greater than that induced by 100 μg gE/Saline. Overall, vaccine safety and tolerability were acceptable in all gE/AS01$_B$ vaccine groups. Based on these data, the antigen dose of 50 μg gE combined with AS01$_B$ and administered as two doses was selected for use in future trials.

In a phase II adjuvant dose comparison trial (ZOSTER-010), 410 adults ≥ 50 YOA received two doses of 50 μg gE adjuvanted with AS01$_B$, AS01$_E$ (½ dose of AS01$_B$) or no adjuvant (gE/Saline), or saline alone, administered on a 2-dose schedule at months 0 and 2. The objective of this study was to compare the immunogenicity and safety of gE/AS01$_B$ and gE/AS01$_E$ groups. Analysis of data obtained up to Month 14 is currently available for this study. Subjects in the gE/AS01$_B$ group had 30% superior cellular immune responses and 40% superior antigen-specific humoral immune responses compared to the gE/AS01$_E$ group, which were both statistically significant differences. Local and general reactogenicity were common in both the gE/AS01$_B$ and gE/AS01$_E$ groups; however, approximately 11% more doses of gE/AS01$_B$ were associated with local or general reactogenicity than gE/AS01$_E$ doses. The overall incidence of grade 3 local and general reactions was low for both vaccines, and similar between the gE/AS01$_B$ and gE/AS01$_E$ groups. No related serious adverse events (SAEs) were reported in either the gE/AS01$_B$ or gE/AS01$_E$ groups. Based on these results, AS01$_B$ was chosen for the final vaccine formulation, in combination with 50 μg gE, to be used in future studies.

Please refer to the current Investigator Brochure (IB) for a review of the pre-clinical and clinical studies, and the potential risks and benefits of GSK Biologicals' candidate HZ vaccine.

1.2. Rationale for the study and study design

Two studies (ZOSTER-006 enrolling subjects ≥ 50 YOA and ZOSTER-022 enrolling subjects ≥ 70 YOA) will be conducted concurrently to evaluate efficacy of GSK Biologicals' gE/AS01$_B$ vaccine.

Study ZOSTER-006 will provide pivotal data on the overall HZ VE. The primary endpoint of this study will be overall HZ VE across all age cohorts. To this end, ZOSTER-006 will evaluate VE of the gE/AS01$_B$ vaccine compared to placebo in reducing the risk of developing HZ in subjects ≥ 50 YOA. This study will enrol subjects in the age ranges 50-59 YOA, 60-69 YOA, 70-79 YOA and ≥ 80 YOA in approximately an 8:5:3:1 ratio to achieve comparable numbers of HZ cases in the 3 main age strata (50-59 YOA, 60-69 YOA and ≥ 70 YOA; the 70-79 YOA and ≥ 80 YOA strata will be combined for primary analyses) so that a balanced estimate of the overall VE in persons ≥ 50 YOA can be determined. Apportionment of approximately 20-25% of the ≥ 70 YOA cohort to persons ≥ 80 YOA ensures that this particularly vulnerable population is adequately represented.

Assessment of PHN VE would require a large sample size of subjects ≥ 70 YOA due to a relatively lower incidence of PHN in younger adults. This cannot be achieved in ZOSTER-006 without impacting the intent of the study, since a large overrepresentation of subjects ≥ 70 YOA in the ZOSTER-006 study would not allow an accurate assessment of HZ VE across the entire ≥ 50 YOA age range enrolled in the trial and may potentially underestimate overall efficacy of the gE/AS01$_B$ vaccine, since HZ VE may diminish with age. Study ZOSTER-022 will address VE against ***HZ*** in subjects ≥ 70 YOA. ***At the end of studies ZOSTER-006 and ZOSTER-022***, a pooled analysis of HZ and PHN data from both studies combined is planned and will be described prospectively. ***The analysis of pooled data from both studies for overall PHN in subjects ≥ 70 YOA is positioned as primary analysis for PHN.*** **(Amended 18 April 2014)** Detailed information regarding study ZOSTER-022 and the pooled analysis of data of both studies combined will be included in the protocol of study ZOSTER-022.

A saline solution is included as a negative control (placebo) in this study and provides an objective baseline for the evaluation of the efficacy and safety profile of the candidate HZ vaccine. Use of the placebo control and the observer-blind, randomized study design, will allow to control for potential biases in the conduct of the study.

2. OBJECTIVES

2.1. Primary objective

- To evaluate VE in the prevention of HZ compared to placebo in adults ≥ 50 YOA, as measured by the reduction in HZ risk.

Refer to Section 10.1 for the definition of the primary endpoint.

2.2. Secondary objectives

- To evaluate VE in the prevention of HZ compared to placebo in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, as measured by the reduction in HZ risk;
- To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;
- To evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate VE in the reduction of overall and HZ-related mortality and hospitalizations compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;
- To evaluate VE in the reduction in incidence of HZ-associated complications compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate VE in the reduction in use of pain medications compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate vaccine safety and reactogenicity.

Refer to Section 10.2 for the definition of the secondary endpoints.

2.3. Exploratory objectives

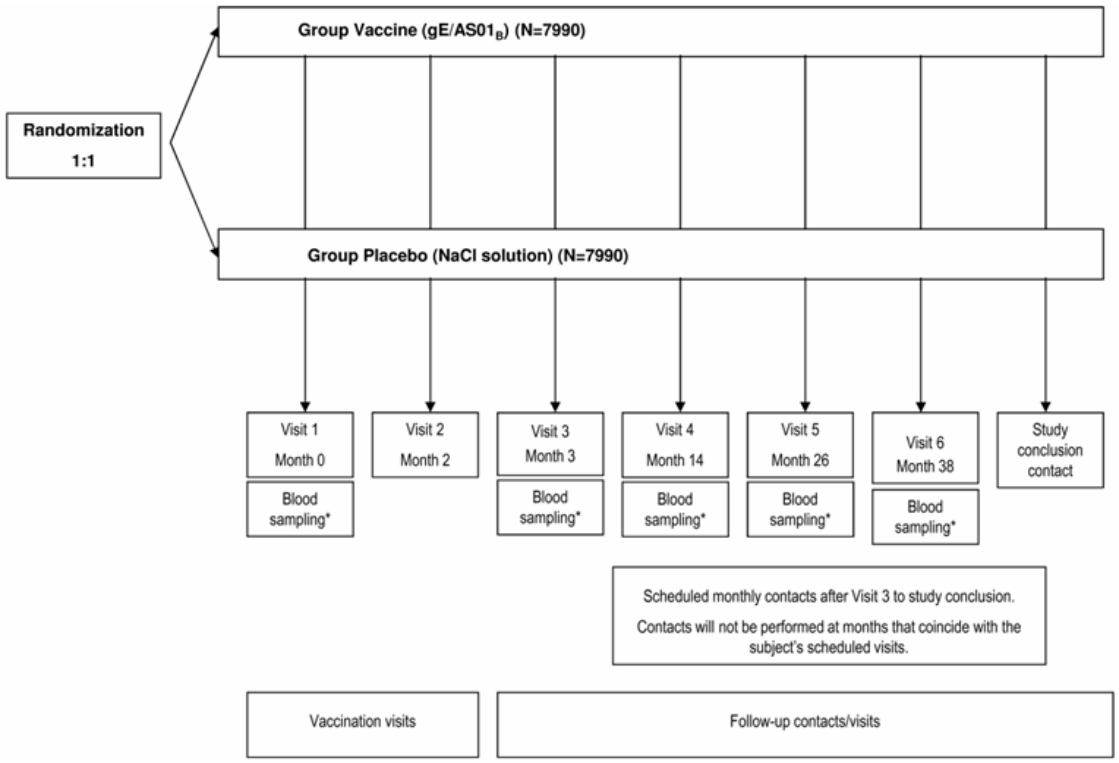
- To evaluate VE in reducing the severity of acute HZ-associated pain compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate VE in improving Quality of Life (QoL) compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
- To evaluate VE in the mitigation of Burden-Of-Illness (BOI) caused by HZ compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;
- To evaluate vaccine induced cell mediated and humoral immune responses and the persistence of each type of response after two injections of study vaccine in subjects ≥ 50 YOA, and by age strata;

- To evaluate anti-VZV neutralizing Ab titres in a subset of subjects at Month 0 (pre-vaccination), and at Months 3, 14, 26 and 38, in subjects ≥ 50 YOA, and by age strata.

Refer to Section 10.3 for the definition of the exploratory endpoints.

3. STUDY DESIGN OVERVIEW

(Amended 18 April 2014)



* Blood samples will be collected from all subjects at Visit 1 and Visit 3, and from subsets of subjects additionally at the other visits to assess immune responses.
(Amended 18 April 2014)
Note: In case of suspected HZ, the subject will have additional visits and contacts for follow-up of HZ (see Table 3).

- Experimental design: multicentre, parallel group
- Control: placebo (NaCl solution)
- Vaccination schedule: 0, 2 months
- Treatment groups: Treatment groups: 2 groups of subjects
  - Vaccine group (gE/AS01$_B$ vaccine)
  - Placebo group (NaCl solution as control)
- Study allocation: Eligible subjects 70-79 YOA and ≥ 80 YOA will be randomly assigned to ZOSTER-006 or ZOSTER-022 at Visit 1.

- Treatment allocation: Eligible subjects will be randomized to investigational vaccine/placebo according to a 1:1 ratio (vaccine:placebo). Subjects will be stratified by age: 50-59 YOA; 60-69 YOA; 70-79 YOA and ≥ 80 YOA in approximately an 8:5:3:1 ratio. The 70-79 YOA and ≥ 80 YOA strata will be combined for primary analyses.
- Blinding: observer-blind
- Biological samples to be collected:
  - Blood samples will be collected from all subjects at Visit 1 and 3 to contribute to the correlate of protection assessment should the subject experience a HZ episode or be selected as a case control.
  - Blood samples will be collected from a subset of subjects at Visit 4, 5 and 6 to assess persistence of humoral immune response. In these subjects, the blood samples from Visit 1 and 3 will also be assessed for humoral immune response.
  - Blood samples will be collected from a subset of subjects at Visit 1, 3, 4, 5 and 6 to assess CMI response.
  - Clinical specimens of HZ lesions will be collected from subjects clinically diagnosed as having a suspected case of HZ.
- Type of study: Self-contained, and will be combined with study ZOSTER-022 for some analyses.
- Data collection: Remote Data Entry (RDE) on electronic Case Report Form (eCRF).
- ***Planned analysis steps :***

  It is predicted that study ZOSTER-006 will reach the conditions required for triggering final analysis of HZ primary endpoint about one year before those conditions being reached for study ZOSTER-022. Therefore GSK decided, as originally planned in these circumstances, to dissociate the two studies in terms of timing of the analysis of each study. Moreover, a two-step approach is allowed for the analysis of each study. Both studies will end concurrently.

  In study ZOSTER-006, the planned analysis steps are the following:

  1. ***Final HZ efficacy analysis (step 1). Final analysis of HZ primary endpoint:***

     The cut-off date for final HZ efficacy analysis will occur when the following conditions are met:

     - ***at least 196 confirmed HZ cases are accrued in the modified Total Vaccinated cohort (mTVc)[3];***
     - ***approximately 60 HZ cases in subjects 50-59 YOA and approximately 60 HZ cases in subjects 60-69 YOA are accrued in the mTVc;***

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[3] ***The modified Total Vaccinated cohort (mTVc) is the primary cohort for analysis of efficacy which excludes subjects in the TVc for efficacy analysis who were not administered with the second vaccination or who develop a confirmed case of HZ prior to 1 month after the second vaccination.***

– ***approximately 75% of subjects in each stratum have completed at least 36 months follow-up after Dose 2, and the remaining subjects have completed at least 30 months follow-up after Dose 2.***

Step 1 will include analyses of the following objectives:

– ***all HZ VE objectives;***

– ***all reactogenicity/safety and immunogenicity objectives.***

2. End of study analysis (step 2).

The cut-off date for end of study analysis will occur given the following:

– ***all conditions (as detailed in ZOSTER-022 protocol) are met for final HZ efficacy analysis in study ZOSTER-022;***

– ***at least 35 PHN cases in subjects ≥ 70 YOA are accrued in the mTVc when pooling the studies ZOSTER-006 and ZOSTER-022.***

The end of study analysis (step 2) cannot be performed before the final HZ efficacy analysis (step 1).

At step 2 all objectives of study ZOSTER-006 will be analyzed. Objectives already analyzed at step 1 will be re-analyzed (confirmatory descriptive in case of inferential analysis at step 1 or descriptive analysis otherwise).

Pooled analyses of studies ZOSTER-006 and ZOSTER-022 are planned if the primary objective of study ZOSTER-006 and the primary objective of study ZOSTER-022 are demonstrated. Overall PHN VE in subjects ≥ 70 YOA, and other pre-specified endpoints will be analyzed in the pooled analyses, as specified in ZOSTER-022 protocol.

(Amended 18 April 2014)

- Duration of the study: Each subject will be followed for at least 30 months after Dose 2.

  All subjects will continue in the study at least until the cut-off date for ***end of study*** analysis regardless of their date of enrolment. Study end will take place when ***the*** conditions for ***end of study*** analysis are met and a minimum 90 days follow-up is completed for each HZ case that occurs up to the cut-off date for ***end of study*** analysis.

  The exact duration of the study for individual subjects will vary. The maximum total study duration for each subject is expected to be ***approximately*** 4 to 5 years.

  (Amended 18 April 2014)

Throughout the protocol, visit numbers are referred to interchangeably with their month designations (Month 0 refers to Visit 1, Month 2 refers to Visit 2, etc).

4. STUDY COHORT

4.1. Number of subjects/centres

Study ZOSTER-006 will be an international multicentre trial.

Target enrolment is approximately 15,980 eligible subjects using a 1:1 randomization ratio (vaccine:placebo).

Refer to Section 10.4 for a detailed description of the criteria used in the estimation of sample size.

The following subsets of subjects will be included in this study (see Table 1). Details regarding the number of subjects included in each of the subsets are described in Sections 10.4.5.5 and 10.4.5.6. The randomization of subjects to subsets is described in Section 5.3.4.

Table 1 Subsets in study ZOSTER-006

Subset name	Description
7-day diary card	Diary card completion for recording of solicited adverse events (AEs) (from Day 0 to Day 6 after each vaccination)
Immunogenicity	Blood samples (approximately 10 mL) collected at Visit 1, 3, 4, 5 and 6 will be analyzed to assess humoral immune response
CMI component of the Immunogenicity subset	Blood samples (approximately 20 mL) collected at Visit 1, 3, 4, 5 and 6 will be analyzed to assess CMI response

Note: Blood samples (approximately 10 mL) will be collected from all subjects at Visits 1 and 3, and will be used to assess correlate of protection.

Overview of the recruitment plan

Study ZOSTER-006 is planned to be conducted at sites in multiple countries in North America, Europe, Latin America and Australasia.

The recruitment rate will be monitored using a study specific central randomization system on internet (SBIR). Prior to randomization within each study, a SBIR distribution application will be used to assign subjects 70-79 YOA and ≥ 80 YOA to either ZOSTER-006 or ZOSTER-022.

Transfer of supplies will be tracked by the central randomization system. Monitoring visits frequency will be adapted to the pace of enrolment. Enrolment is estimated to last for approximately 12 months.

Vaccine doses will be distributed to each study site respecting the randomization block size. In addition, SBIR will account for the number of subjects in each age stratum (Section 5.3.3.2).

In case any countries would fall behind in subject recruitment (in a specific age group or overall), a redistribution of the enrolment target per country may be made to allow other participating countries to enrol additional subjects in an effort to ensure full and timely enrolment of the overall targeted number of subjects specified in this protocol. Furthermore, enrolment target numbers per region (see Section 10.4.5.4) are approximate and may change depending on the enrolment.

4.2. Inclusion criteria for enrolment

All subjects must satisfy ALL the following criteria at study entry:

- Subjects who the investigator believes will comply with the requirements of the protocol (e.g. completion of the diary cards/questionnaires, return for follow-up visits, have regular contact to allow evaluation during the study);
- Written informed consent obtained from the subject;
- A male or female aged 50 years or older at the time of the first vaccination;
- Female subjects of non-childbearing potential may be enrolled in the study;

  For this study population, non-childbearing potential is defined as current tubal ligation, hysterectomy, ovariectomy or post-menopause.

Please refer to the glossary of terms for the definition of menopause.

OR

Female subjects of childbearing potential may be enrolled in the study, if the subject has practiced adequate contraception for 30 days prior to vaccination, and has a negative urine pregnancy test on the day of vaccination, and has agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the vaccination series.

Please refer to the glossary of terms for the definition of adequate contraception.

4.3. Exclusion criteria for enrolment

The following criteria should be checked at the time of study entry. If **ANY** exclusion criterion applies, the subject must not be included in the study:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine, or planned use during the study period;
- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational product (pharmaceutical product or device);
- Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., malignancy, HIV infection) or immunosuppressive/cytotoxic therapy (e.g., medications used during cancer chemotherapy, organ transplantation or to treat autoimmune disorders);
- History of HZ;
- Previous vaccination against varicella or HZ (either registered product or participation in a previous vaccine study, and including previous vaccination with childhood varicella vaccine);
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine. Additionally, consider allergic reactions to other material or equipment

related to study participation (such as materials that may possibly contain latex - gloves, syringes, etc). Please note, the vaccine and vials in this study do not contain latex;

- Significant underlying illness that in the opinion of the investigator would be expected to prevent completion of the study (e.g., life-threatening disease likely to limit survival to less than 4 years);
- Receipt of immunoglobulins and/or any blood products within the 90 days preceding the first dose of study vaccine or planned administration during the study period;
- Administration or planned administration of any other immunizations within 30 days before the first or second study vaccination or scheduled within 30 days after study vaccination. However, licensed non-replicating vaccines (i.e., inactivated and subunit vaccines, including inactivated and subunit influenza vaccines for seasonal or pandemic flu, with or without adjuvant) may be administered up to 8 days prior to each dose and/or at least 14 days after any dose of study vaccine;
- Any other condition (e.g., extensive psoriasis, chronic pain syndrome, cognitive impairment, severe hearing loss) that, in the opinion of the investigator, might interfere with the evaluations required by the study;
- Acute disease and/or fever at the time of enrolment;
  - Fever is defined as temperature ≥ 37.5°C (99.5°F) on oral, axillary or tympanic setting, or ≥ 38.0°C (100.4°F) on rectal setting. The preferred route for recording temperature in this study will be oral.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.
- Chronic administration (defined as > 15 consecutive days) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose. For corticosteroids, this will mean prednisone < 20 mg/day, or equivalent, is allowed**.** Inhaled and topical steroids are allowed.
- Pregnant or lactating female;
- Female planning to become pregnant or planning to discontinue contraceptive precautions (if of childbearing potential);

A list of criteria that will eliminate subjects from According To Protocol (ATP) analyses can be found in Section 6.6.1, Section 6.7 and Section 10.5.

5. CONDUCT OF THE STUDY

5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will also be conducted in accordance with the International conference on harmonisation (ICH) Guideline for Good Clinical Practice (GCP), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written (or witnessed thumb printed consent in case of an illiterate subject) informed consent must be obtained from each subject prior to participation in the study.

GSK Biologicals will prepare a model ICF which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

5.2. Study Determination (Recruitment/Randomisation) Agreement

Eligible subjects 70-79 YOA and ≥ 80 YOA will be randomly assigned to ZOSTER-006 or ZOSTER-022 at Visit 1. Prior to study assignment, these subjects must sign a Study

Determination (Recruitment/Randomisation) Agreement (SDRRA). The signing of the SDRRA is not a consent or confirmation of the subject's participation in either study. The SDRRA allows the sponsor/study staff to collect limited personal information about a subject who has been contacted to participate in a clinical study. By signing the SDRRA, the subject enables the study staff to input age information into the SBIR system. The SBIR system will review current enrolment in the two age strata in both ZOSTER-006 and ZOSTER-022 and determine the study assignment for the subject. The subject will then be provided with the study specific informed consent to review and determine if they wish to participate in the assigned study. The first study related activity/procedure other than the study determination randomisation procedure may only be carried out after the subject has confirmed willingness to participate in the assigned study and signed an informed consent form.

5.3. Subject identification and randomization of treatment

All subjects 50-69 YOA will be randomized to vaccine or placebo in ZOSTER-006. Subjects 70-79 YOA and ≥ 80 YOA will be randomized to either ZOSTER-006 or ZOSTER-022, and then randomized to vaccine or placebo. This procedure ensures the compatibility of the ≥ 70 YOA subjects between the two studies and facilitates the pooled evaluation of both studies for HZ and PHN episodes. All subjects in ZOSTER-006 will be randomly assigned to two treatment groups in a 1: 1 ratio.

5.3.1. Study identification

ZOSTER-006 and ZOSTER-022 are similar studies, differing essentially in the age strata recruited. A SBIR study determination application will use a study determination number to assign subjects 70-79 YOA and ≥ 80 YOA to either ZOSTER-006 or ZOSTER-022. Subjects 50-69 YOA can only be assigned to ZOSTER-006.

5.3.2. Subject identification

Subject numbers will be assigned sequentially to subjects consenting to participate in the study, according to the range of subject numbers allocated to each study centre.

5.3.3. Randomization of treatment

5.3.3.1. Randomization of supplies

The randomisation will be performed at GSK Biologicals, Belgium, using MATEX, a program developed for use in SAS® (Cary, NC, US) by GSK Biologicals.

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centres in this multicentre study, and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.

The vaccine doses will be distributed to each study centre, respecting the randomization block size.

5.3.3.2. Treatment allocation to the subject

The treatment allocation at the investigator site will be performed using a central randomization system on the internet (SBIR). The treatment numbers will be allocated by kit. Within ZOSTER-006, the randomization algorithm will use stratification (preventing further randomization when a stratum is complete) and weighted minimization techniques for each parameter, below:

- By region: Stratification
- By age cohort within each region: Stratification
- By country within each region: Minimization
- By site within each country: Minimization

Note that as soon as the target number of subjects in a specific stratification group has been reached the recruitment will be frozen for that age group.

When SBIR is not available, please refer to SBIR user guide or Study Procedures Manual (SPM) for specific instructions.

After having checked the eligibility of the subject and obtaining the signed ICF, the site staff in charge of the vaccination will access SBIR.

Upon providing the subject identification number, the randomization system will use stratification and minimization algorithms to determine the treatment number to be used for the subject. The treatment number must be recorded in the eCRF on the Vaccine Administration screen (Randomization/Treatment Allocation Section).

5.3.4. Randomization of subjects to assay subsets

Subjects from 50-59 YOA and 60-69 YOA strata will be randomly allocated to be part of the 7-day diary card subset (note: all subjects from ≥ 70 YOA strata will be included in the 7-day diary card subset) according to criteria defined in Section 10.4.5.5. Subjects will be randomly allocated to be part of the Immunogenicity subset according to criteria defined in Section 10.4.5.6. For operational reasons, the same subjects may be randomized to the various subsets.

The CMI analyses will be performed in the randomly selected Immunogenicity subset in three countries (Czech Republic, Japan and United States) at designated sites that have access to a Peripheral Blood Mononuclear Cells (PBMC) processing facility within the acceptable time window from sample collection to PBMC processing.

5.4. Method of blinding

Because the reconstituted gE/AS01$_B$ study vaccine differs in appearance from the NaCl solution placebo, the study will be conducted in an observer-blind manner.

Data will be collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccine/placebo recipient and those responsible for the

evaluation of any study endpoint (e.g., safety, reactogenicity, and efficacy) will all be unaware of which vaccine/placebo was administered. To do so, vaccine/placebo preparation and administration will be done by authorised medical personnel who will not participate in the clinical evaluation of the subjects. Immunological data, which could lead to the unblinding of the treatment groups, will not be available during the course of the trial to any investigator or any person involved in the clinical conduct of the study (including data cleaning). **(Amended 18 April 2014)** Immunological data may however be available to the Statistical Data Analysis Centre (SDAC) and Independent Data Monitoring Committee (IDMC) in order to answer potential questions related to safety, efficacy or presence of correlate of protection during the interim analysis.

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

Refer to Section 10.4.8 for more details regarding aspects of blinding in the study. **(Amended 18 April 2014)**

5.5. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

5.5.1. Data collection

After Visit 3 monthly contacts between the subjects and the investigator and/or his delegate will take place to collect information on any event of interest that may have occurred [see Table 2 and Section 5.7.3.14 for details]. The contacts will not take place at months that coincide with the subject's scheduled study visits. Also, subjects with suspected HZ will be contacted periodically as outlined in Table 3. The contacts will take place using the most convenient method suited for the sites (e.g., telephone calls by site staff or designee, or SMS text messages through a call centre, or visit by the study staff to the subject's home). A guidance document outlining the information that needs to be collected at each contact will be provided to each country, and will serve as a guidance to develop the local script. The logistic details on the set-up of the contacts will be documented by each site/country. At each contact, the subjects will respond to a standard set of questions in a language that is understandable to them. The investigator and/or his delegate will transcribe the relevant information on any event of interest in the appropriate section of the subject's eCRF, in English. In case of ongoing HZ, subjects will also be reminded to complete Zoster Brief Pain Inventory (ZBPI), EQ-5D and SF-36 questionnaires.

The diary cards and/or questionnaires to be completed will be distributed and explained by the investigator or his/her delegate. Any supplied diary cards or questionnaires should be preferably completed by the subject themselves. In case of difficulty in self-completion of the diary cards or questionnaires, an aide (such as a family member or care provider who is not involved in the study) may provide assistance with reading the

questions (verbatim) and/or transcribing the subject's responses on the questionnaires and/or diary cards. When the completed diary cards and/or questionnaires are returned to the study staff, the study staff will ask the subject (at the time of return or at subsequent contact) if he/she received any assistance in completing diary cards or questionnaires. If the subject had assistance completing the diary card and/or questionnaires, it should be noted in the eCRF. In case questionnaires are completed at the study site, study staff can assist in reading the questions (verbatim).

For all subjects:

- **30-day diary cards:** To be completed by all subjects for unsolicited AEs (from Day 0 to Day 29 after each vaccination) and any concomitant medication and vaccination taken from Day 0 to Day 29 after each vaccination.
- **EQ-5D and SF-36 questionnaires:** To be completed by all subjects at study entry. Also, to be completed by all subjects at Visits 4, 5 and 6 (subjects with an ongoing suspected HZ episode will follow a weekly schedule and do not need to additionally complete the questionnaires at these visits).

EQ-5D and SF-36 will remain as source documents. The information from these questionnaires will only be transcribed into the eCRF for subjects who have suspected HZ during the study.

For subjects in the 7-day diary card subset (in addition to the above):

- **7-day diary card:** To be completed by subjects to record solicited AEs (from Day 0 to Day 6 after each vaccination).

For all subjects in case of a suspected or confirmed case of HZ:

- **HZ-specific diary card:** To be completed by subjects who develop symptoms suggestive of HZ beginning immediately upon development of these symptoms and prior to visiting the study site for evaluation of the suspected HZ.
- **Zoster Brief Pain Inventory (ZBPI) questionnaire**: To be completed by subjects with suspected HZ on Day HZ-0 (Visit HZ-1) and daily from Day HZ-1 (day after the Visit HZ-1) up to Day HZ-28, and weekly from Day HZ-29 onwards until a 4-week pain-free period is documented OR until the cut-off date for ***end of study*** analysis. For all subjects with ongoing HZ-associated pain-at the time of cut-off date for ***end of study*** analysis, ZBPI data will be collected until a 4-week pain-free period is documented OR until at least Day HZ-90 (Refer to Section 5.5.2.2 for more details)**. (Amended 18 April 2014)**
- **EQ-5D and SF-36 questionnaires**: To be completed weekly by the subjects with suspected HZ from Day HZ-0 onwards until a 4-week pain-free period is documented OR until the cut-off date for ***end of study*** analysis. For all subjects with ongoing HZ-associated pain at the time of the cut-off date for ***end of study*** analysis, EQ-5D and SF-36 data will be collected until a 4-week pain-free period is documented OR until at least Day HZ-90 (Refer to Section 5.5.2.2 for more details). **(Amended 18 April 2014)**

5.5.2. Evaluation and confirmation of suspected HZ cases

5.5.2.1. Definitions

A suspected case of HZ is defined as new unilateral rash accompanied by pain (broadly defined to include allodynia, pruritus or other sensations) and no alternative diagnosis.

Subjects clinically diagnosed as having a suspected case of HZ by the investigator will be referred to as a case of 'suspected HZ', and followed up. If a case is not clinically diagnosed as suspected HZ, the investigator should not progress further with evaluation of the case. Also refer to Section 5.5.2.2.

Determination of confirmed cases of HZ for efficacy analyses is provided in Section 5.5.2.3.

The HZ onset date is the earlier of the following two events: 1) the HZ rash start date; or 2) the date on which pain at the site of a subsequent HZ rash is first noted.

The end date of a HZ episode is defined as the first time at which a subject had no rash (papules, vesicles, ulcers or crusts) present. This end date will be recorded in the eCRF.

PHN is defined by the presence of HZ-associated severe 'worst' pain persisting or appearing more than 90 days after onset of the HZ rash. Severe 'worst' pain is defined as HZ-associated pain rated as 3 or greater on the "worst pain" ZBPI question. Alternative definitions of PHN, based on duration of pain of 30, 60, 120 and 180 days will also be used for reporting purposes.

Cessation of pain to assess duration of HZ-associated pain: A 28-day pain-free period is used to confirm cessation of HZ-associated pain. If that pain-free period is not achieved or if pain did not cease, the time-to-event will be censored at the last day of HZ-associated pain.

Acute pain is defined as pain measured during the 4-week period following the onset of confirmed HZ.

5.5.2.2. Evaluation of suspected case of HZ

All HZ cases that occur during the study period up to the cut-off date for ***end of study*** analysis will be followed and evaluated. Please refer to the SPM for information about recording HZ cases that occur after the cut-off date for ***end of study*** analysis. Such cases will be referred to the local physician for follow-up. **(Amended 18 April 2014)**

Any symptom/sign suggestive of HZ must be evaluated. At Visit 1, all subjects will be educated with regard to the signs and symptoms of HZ. The subjects are also given a HZ-specific diary card that they would complete with the date that rash and/or pain began. Subjects will be instructed to contact their study site immediately, and start completing the HZ-specific diary card if he/she develops any symptoms suggestive of HZ. The subjects will be asked to visit the study site (within 48 hours if possible) for evaluation of the "suspected case of HZ". The subject will be asked to bring the completed HZ-specific diary card when he/she visits the study site for evaluation of the suspected HZ. The

investigator will perform a clinical examination when the subject visits the study site for the first evaluation of the suspected case of HZ [Visit HZ-1 at Day HZ-0]. If not considered a suspected HZ diagnosis, the investigator should not progress further with evaluation of this event as a HZ case for the purpose of this study. However, if meeting the definition of an AE/SAE (Section 8.1), the case should be handled as applicable (Section 8.3).

The schedule of visits/contacts that will take place for follow-up of suspected HZ cases is presented in Table 3.

For clinically diagnosed suspected HZ cases, the following will take place at Visit HZ-1:

- The investigator or his delegate will verify the completed HZ-specific diary card returned by the subject. The information from the diary card will be transcribed into the eCRF. The investigator or his delegate will record relevant information regarding the HZ episode in the eCRF (such as date of onset of pain and rash, date of clinical diagnosis of HZ, location and nature of HZ lesions, HZ-related complications if any);
- The study staff/investigator will ask the subject to complete a ZBPI questionnaire at Visit HZ-1 to rate HZ-associated pain within the last 24 hours. If the time between the HZ onset and clinical evaluation at Visit HZ-1 is greater than 24 hours, the subject will be asked to complete a second ZBPI also for the elapsed time between the HZ onset and 24 hours before Visit HZ-1;
- The rash will be documented by digital photography;
- The study staff/investigator will record concomitant medication/vaccination, including concomitant medication for HZ treatment or any HZ-related complications (Section 6.6), and record intercurrent medical conditions (Section 6.7). If antiviral therapy is needed, it is recommended to use valacyclovir, acyclovir or famciclovir. Concomitant medication the subject has already received and/or will receive for HZ treatment will be recorded in the eCRF. The study staff/investigator will check if the subject received any medical attention [hospitalization, emergency room visit, or a visit to or from medical personnel (medical doctor)] for HZ or any HZ-related complication.
- Rash lesion samples (three replicate samples on the same day) will be collected from subjects clinically diagnosed as having a suspected case of HZ (Section 5.7.3.11);
- The subject will be given a supply of ZBPI, EQ-5D and SF-36 questionnaires. The ZBPI questionnaires will be used to collect information on the severity of HZ-associated pain, the duration of HZ-associated pain, and the impact of the HZ episode on the subject's QoL. The impact of HZ on subject's QoL will also be measured using the EQ-5D and SF-36 questionnaires (Section 7). The study staff/investigator will provide instructions to the subjects for completing the ZBPI, EQ-5D and SF-36 questionnaires and explain the importance of completing and returning the questionnaires to the site in order to provide more information on HZ.

- The subject will be asked to complete the ZBPI questionnaires daily from Day HZ-1 (day after the Visit HZ-1) up to Day 28 (ZBPI must be completed to Day HZ-28 at minimum) and weekly from Day HZ-29 onwards until:
  - 28 days after HZ-associated pain ceases. The subject should continue to complete the ZBPI questionnaires weekly until a 28-day (or 4-week) pain free period is documented (a 'No' answer to the ZBPI question: 'Have you had any pain caused by your shingles in the last 24 hours' (item 1) at each assessment during that entire period); OR
  - The cut-off date for ***end of study*** analysis. **(Amended 18 April 2014)**

    For all subjects with ongoing HZ-associated pain at the time of cut-off date for ***end of study*** analysis, completion of ZBPI questionnaires will continue until a 4-week pain-free period is documented OR until at least Day HZ-90. **(Amended 18 April 2014)**
- The subjects will be asked to complete the EQ-5D and SF-36 questionnaires from Day HZ-0 and continued weekly during the entire period that the ZBPI questionnaires are completed. Therefore, these questionnaires should be completed until Day HZ-28 at minimum.

After Visit HZ-1 until Visit HZ-7, visits/contacts will take place for follow-up of the HZ episode according to the schedule presented in Table 3. Follow-up of HZ-associated pain and complications will continue irrespective of whether the rash has ended in some cases. Follow-up of HZ-associated pain persisting beyond Visit HZ-7 or other complications will be done at monthly contacts between the subjects and the investigator and/or his delegate that are planned after Visit 3. When a case initially clinically diagnosed as suspected HZ is subsequently not considered anymore by the investigator as suspected HZ, this will be noted in the eCRF. However study procedures to be performed during the follow-up period for a suspected HZ case (see Table 3) should be continued.

If HZ-associated pain ceases (defined as a 28-day [or 4-week] pain free period), the study staff/investigator will inform the subjects to stop completing the ZBPI, EQ-5D and SF-36 questionnaires and will provide instructions for the subject to return the completed questionnaires to the study site. If a 4-week pain-free period is achieved and the HZ rash resolves, subsequent follow-up visits or contacts related to this case of HZ will be cancelled. Collection of subsequent HZ episode-related information will be stopped and no further information on that suspected HZ episode will be encoded in the clinical database.

The following will take place at each visit or contact that occurs after Visit HZ-1:

- The study staff/investigator will: 1) record relevant information regarding the suspected HZ case (such as the location and nature of HZ lesions, the end date of the rash, HZ-related complications, if any); 2) record concomitant medications/vaccinations, including concomitant medication the subject has already received and/or will receive for HZ treatment or treatment of any HZ-related complications (Section 6.6); 3) record intercurrent medical conditions (Section 6.7); and 4) check if the subject received any medical attention [hospitalization,

emergency room visit, or a visit to or from medical personnel (medical doctor)] for HZ or any HZ-related complication.

- Additional photographs of HZ lesions may be taken after Visit HZ-1 to help note the progression of the rash.
- If the investigator determines that adequate rash samples are not present at Visit HZ-1 (i.e., <3 lesions present or only papules present), the investigator has the option of collecting three additional samples prior to or at Visit HZ-2 (see Section 5.7.3.11).
- The study staff/investigator will remind subjects to complete the ZBPI, EQ-5D and SF-36 questionnaires, and return the completed ZBPI, EQ-5D and SF-36 questionnaires to the study site according to the instructions given by the study staff/investigator. Once the completed ZBPI, EQ-5D and SF-36 questionnaires are available, the investigator will transcribe the information into the subject's eCRF. A new supply of ZBPI, EQ-5D and SF-36 questionnaires will be provided to the subjects as necessary.

5.5.2.3. Confirmation of a suspected case of HZ

A suspected case of HZ can be confirmed in two ways:

- By Polymerase Chain Reaction (PCR):

  Rash lesion samples will be collected from subjects clinically diagnosed as having a suspected case of HZ. The samples will be transferred to GSK Biologicals or a validated laboratory designated by GSK Biologicals using standardised and validated procedures for laboratory diagnosis of HZ by PCR. Refer to Appendix A for details of PCR assay to be performed on HZ lesion samples. Refer to Appendix B for details of the PCR testing algorithm to classify suspected cases of HZ.

  In addition, if based on qPCR test results the diagnosis of HZ can be excluded, Herpes Simplex Virus (HSV) qPCR may be performed to assess if the rash lesions are due to HSV (1 or 2). This exploratory testing is not part of the process for HZ case confirmation (see Appendix A and Appendix B). This exploratory testing is optional and requires specific consent from the individual subjects.

- By the HZ Ascertainment Committee:

  All suspected HZ cases will be referred to the HZ Ascertainment Committee (HZAC). The HZAC will classify all referred cases as either "HZ" or "not HZ". However, the HZAC classification will serve as the final case definition only when the case cannot be confirmed or excluded by PCR, e.g., when all samples from a given subject are inadequate (as when both VZV and β-actin PCR results are negative), or when no samples are available for a given subject. Therefore, definitive PCR results, when available, will determine the final HZ case assignment. In such cases, the HZAC classification will not contribute to HZ case determination decision.

  The HZAC will consist of three to five physicians with HZ expertise. HZAC members, participating as investigator in this study, will not evaluate cases from their own study site. HZAC members will be blinded to treatment assignments. For every such case, each reviewing HZAC member will be asked to make a clinical determination of whether the case is HZ based on review of the available clinical

information (e.g., summary of the rash and pain evaluations, digital photographs of the subject's rash, and clinical progress notes). A suspected case of HZ will be considered as "HZ" if the HZAC members concur unanimously; otherwise, it will be classified as "not HZ". As described above, the HZAC case assignment will only be considered as the final case assignment if definitive PCR results are not available. Further details will be provided in the HZAC charter.

5.5.2.4. Evaluation of severity of HZ-associated pain using the Zoster Brief Pain Inventory

The ZBPI is an assessment tool in the form of a questionnaire completed by the subject that is specifically designed to assess HZ-associated pain and discomfort during an HZ episode. The ZBPI also takes into account the effect of HZ treatment on subject's pain and the interference of HZ-associated pain with subject's QoL, and general health status. Previous studies have been shown that increasing HZ-associated pain scores are highly correlated with worsening of subject's QoL [Coplan, 2004; Schmader, 2007].

In each case of suspected HZ, the subjects will be asked to assess their HZ-associated pain and interference of HZ with their QoL by completing the ZBPI questionnaire either themselves or assisted, by an aide (Section 5.5.1) until HZ-associated pain ceases (defined as a 28-day [or 4-week] pain free period) or until the cut-off date for ***end of study*** analysis (see further details in Section 5.5.2.2). **(Amended 18 April 2014)**

Information on HZ-associated pain is derived from the ZBPI question: "Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours" (item 3), so called "worst pain" in this protocol.

The following outputs will be derived from the data recorded in the ZBPI: HZ Burden-Of-Illness (BOI) score and HZ severity score (Section 10.6.2).

5.5.2.5. HZ complications

The presence of HZ complications listed below will be documented in the eCRF, independently from the AE reporting of those HZ complications (see Section 8.3.1 and refer to the SPM for details). Any HZ complications, according to the definitions below, will be recorded by the investigator. If a recorded complication is associated with a case of suspected HZ, and that case is finally not considered to be a confirmed case, the associated complication will not be considered a complication of HZ.

HZ vasculitis	Vasculopathy or vasculitis (based on clinical, laboratory or radiologic findings) that is temporally associated with an episode of HZ and, in the opinion of the investigator, was caused directly by the VZV infection arising from the HZ episode.
Disseminated disease	Defined as ≥ 6 HZ lesions outside the primary dermatome as per the investigator's judgment.
Ophthalmic disease	Defined as HZ affecting any eye structure as per investigator's judgment.

Neurologic disease	Defined as cranial or peripheral nerve palsies, myelitis, meningoencephalitis, stroke, etc. that is temporally associated with an episode of HZ and, in the opinion of the investigator, was caused directly by VZV infection arising from the HZ episode.
Visceral disease	Defined as an abnormality of one or more internal organs (e.g., hepatitis, pneumonitis, gastroenteritis, etc.) that is temporally associated with an episode of HZ and, in the opinion of the investigator, was caused directly by VZV infection arising from the HZ episode.
Stroke	A diagnosis of stroke requires that criteria 1, 2 and 3 are fulfilled or criteria 1 and 4 and in the opinion of the investigator is temporally associated with an episode of HZ Criterion 1: Rapid onset of localising neurological deficit and/or change in level of consciousness; Criterion 2: Localising neurological deficit or change in level of consciousness that lasts greater than 24 hours; Criterion 3: No other cerebral process, peripheral lesion, or other disorder is the cause of the localising neurological deficit or change in level of consciousness; Criterion 4: CT scan or MRI scan evidence of an acute thrombotic or hemorrhagic lesion.

5.5.3. Independent Data Monitoring Committee

In order to ensure the safety of the subjects during the entire study period, an IDMC will be appointed to 1) monitor and follow-up the safety and tolerability of the subjects enrolled in the trial and 2) make recommendations to the sponsors concerning the continuation, modification, or termination of the trial.

An independent statistical team (i.e., not GSK employees), appointed by GSK Biologicals and not involved in the study management, will be unblinded to treatment assignment and provide all necessary tables, listings, figures and individual subject data to the IDMC. The IDMC will consist of four to six clinical experts, who are not participating in the study and an independent statistician.

The role of the IDMC will be to review the progress of the trial and the accumulating data to detect evidence of safety issues for the subjects while the trial is ongoing. The IDMC will be held to evaluate the safety assessments (e.g., AEs, SAEs, fatal events and withdrawals due to AEs) during the trial and make recommendations regarding continuation, modification or discontinuation of the study to the sponsor following each meeting.

The frequency of IDMC sessions and other operational details are described in the IDMC charter. The IDMC meetings will consist of an open session in which the conduct, recruitment and general baseline characteristics of the trial are presented, and a closed session in which the safety assessments by treatment group will be presented. One or more members of the Zoster vaccine program will attend the IDMC meeting open sessions to immediately reply to any questions from the IDMC members. No GSK staff will participate in the closed sessions.

The IDMC may be also involved in evaluation of VE for futility analyses and prevent the continuation of a clinical study that already showed its inability to demonstrate the primary and main secondary endpoints.

Vaccine efficacy for futility analysis, and other analyses described in the protocol to be done in preparation of IDMC review, will be further detailed in the Reporting and Analysis Plan (RAP)**.**

The IDMC will review all safety parameters and efficacy data together before making a final recommendation. In case of a serious safety issue during the study, the sponsor will inform the IDMC expeditiously.

5.6. Outline of study procedures

Table 2 summarises the list of study procedures to be followed during the study visits and at the study conclusion contact. Table 3 summarises study procedures to be performed for the follow-up of each suspected HZ case.

Table 2 List of study procedures (Amended 18 April 2014)

Type of contact/***trigger*** (Amended 18 April 2014)	VISIT 1	VISIT 2	VISIT 3	Monthly contacts[e]	VISIT 4	Monthly contacts[e]	VISIT 5	Monthly contacts[e]	VISIT 6	Monthly contacts[e]	***Final HZ efficacy analysis trigger*** (Amended 18 April 2014)	Study conclusion contact
Timepoints	Day 0*/ Month0	Month 2	Month 3		Month 14		Month 26		Month 38			
Sampling timepoints	Pre-Vacc	Post-Vacc 1	Post-Vacc 2		Post-Vacc 2		Post-Vacc 2		Post-Vacc 2			
SDRRA[a]	●											
Informed consent	●											
Check inclusion criteria	●											
Check exclusion criteria	●											
Check contraindications	●	●										
Medical history	●											
Physical examination	○											
Record demographic data	●											
Training on self-reporting by subjects[b]	○	○	○		○		○		○			
Urine pregnancy test[c]	●	●										
Pre-vaccination body temperature	●	●										
Blood sampling (approximately 10 mL) for Ab determination in all subjects	●		●									
Blood sampling (approximately 10 mL) for Ab determination in Immunogenicity subset subjects only					●		●		●			
Blood sampling (approximately 20 mL) for CMI response in CMI subset subjects only	●		●		●		●		●			
Randomization	○											

Type of contact/***trigger*** (Amended 18 April 2014)	VISIT 1	VISIT 2	VISIT 3	Monthly contacts[e]	VISIT 4	Monthly contacts[e]	VISIT 5	Monthly contacts[e]	VISIT 6	Monthly contacts[e]	***Final HZ efficacy analysis trigger*** (Amended 18 April 2014)	Study conclusion contact
Timepoints	Day 0*/ Month0	Month 2	Month 3		Month 14		Month 26		Month 38			
Sampling timepoints	Pre-Vacc	Post-Vacc 1	Post-Vacc 2		Post-Vacc 2		Post-Vacc 2		Post-Vacc 2			
Recording of treatment number	●	●										
Vaccination	●	●										
Dispensing of HZ-specific diary cards to all subjects	○											
Recording of intercurrent medical conditions according to guidelines in Section 6.7	●[d]	●	●	●	●	●	●	●	●	●		●
Reporting of all SAEs until Month 14	●[d]	●	●	●	●							
Reporting of SAEs related to study participation or to a concurrent GSK medication/vaccine, or any fatal SAE, after Month 14 until study conclusion						●	●	●	●	●		●
Reporting of potential immune-mediated diseases (pIMDs) † according to guidelines In Section 8.3.2.5.	●[d]	●	●	●	●	●	●	●	●	●		●
Follow-up of HZ	●[d]	●	●	●	●	●	●	●	●	●		●
Reporting of medically attended visits until Month 8	●[d]	●	●	●								
Recording of concomitant medication/vaccination by study staff/investigator according to guidelines in Section 6.6	●	●	●	●	●	●	●	●	●	●		●

Type of contact/***trigger*** (Amended 18 April 2014)	VISIT 1	VISIT 2	VISIT 3	Monthly contacts[e]	VISIT 4	Monthly contacts[e]	VISIT 5	Monthly contacts[e]	VISIT 6	Monthly contacts[e]	***Final HZ efficacy analysis trigger*** (Amended 18 April 2014)	Study conclusion contact
Timepoints	Day 0*/ Month0	Month 2	Month 3		Month 14		Month 26		Month 38			
Sampling timepoints	Pre-Vacc	Post-Vacc 1	Post-Vacc 2		Post-Vacc 2		Post-Vacc 2		Post-Vacc 2			
Reporting of pregnancy	● [d]	●	●	●	●	●	●	●	●	●		●
Completion of EQ-5D and SF-36 questionnaires -by all subjects (subjects with an ongoing HZ episode will follow the weekly schedule and do not need to additionally complete the questionnaires at these visits)	○				○		○		○			
Transcription [f] by study staff/investigator of EQ-5D and SF-36 questionnaires completed	●				●		●		●			
Dispensing of 7-day diary cards for solicited AEs to the 7-day diary card subset only and 30-day diary cards for unsolicited AEs and concomitant medication/vaccination to all subjects	○	○										
Daily post-vaccination recording by subjects of solicited symptoms (Days 0 – 6 after each vaccination) on the 7-day diary card by the 7-day diary card subset subjects	○	○										

Type of contact/***trigger*** (Amended 18 April 2014)	VISIT 1	VISIT 2	VISIT 3	Monthly contacts[e]	VISIT 4	Monthly contacts[e]	VISIT 5	Monthly contacts[e]	VISIT 6	Monthly contacts[e]	***Final HZ efficacy analysis trigger*** (Amended 18 April 2014)	Study conclusion contact
Timepoints	Day 0*/ Month0	Month 2	Month 3		Month 14		Month 26		Month 38			
Sampling timepoints	Pre-Vacc	Post-Vacc 1	Post-Vacc 2		Post-Vacc 2		Post-Vacc 2		Post-Vacc 2			
Daily post-vaccination recording by subjects of unsolicited symptoms (Days 0 – 29 after each vaccination), and concomitant medication/ vaccination (Days 0 – 29 after each vaccination) on 30-day diary card by all subjects	○	○										
Returning by subjects of 7-day diary cards diary cards for solicited symptoms and 30-day diary cards for unsolicited AEs and concomitant medication and vaccination		○	○									
Transcription of 7-day diary cards for solicited symptoms and 30-day dairy cards for unsolicited AEs and concomitant medication and vaccination by study staff/investigator		●	●									
Transcription in eCRF of date of last visit or contact with subject (Amended 18 April 2014)											●	
Investigator signature in eCRF (Amended 18 April 2014)											●	

Type of contact/***trigger*** (Amended 18 April 2014)	VISIT 1	VISIT 2	VISIT 3	Monthly contacts[e]	VISIT 4	Monthly contacts[e]	VISIT 5	Monthly contacts[e]	VISIT 6	Monthly contacts[e]	***Final HZ efficacy analysis trigger*** (Amended 18 April 2014)	Study conclusion contact
Timepoints	Day 0*/ Month0	Month 2	Month 3		Month 14		Month 26		Month 38			
Sampling timepoints	Pre-Vacc	Post-Vacc 1	Post-Vacc 2		Post-Vacc 2		Post-Vacc 2		Post-Vacc 2			
Study Conclusion												●

Note: After Visit 3, monthly contacts between the subjects and the investigator and/or his delegate will be scheduled for the subject to respond to a standard set of questions, in a language that is understandable to the subject, to collect information on safety and the occurrence of HZ, and to follow-up ongoing HZ cases (Section 5.5.1).

Note: Futility analysis may occur (Section 10.4.5.3)

Note: The double-line border indicates the analyses which will be performed on data (i.e., data that are as clean as possible) obtained at the cut-off date for final HZ efficacy analysis. The possibility of data changes after the final HZ efficacy analysis exists because data collection and data entry may continue until study end. Indicated by the dotted line, pending subjects' advancement in the study, the cut-off date for final HZ efficacy analysis may occur at Visit 6 or some time prior or after this visit.
(Amended 18 April 2014)

* Day of first vaccination

† formerly referred to as new onset of autoimmune diseases (NOADs) and other immune mediated inflammatory disorders

● is used to indicate a study procedure that requires documentation in the individual eCRF.

O is used to indicate a study procedure that does not require documentation in the individual eCRF.

[a] Subjects 70-79 YOA and ≥ 80 YOA will be randomly assigned to ZOSTER-006 or ZOSTER-022 at Visit 1. These subjects must sign a Study Determination (Recruitment/Randomization) Agreement (SDRRA) prior to study assignment, and will receive a study determination number to be recorded in the eCRF. Study assignment can be done prior to Visit 1 if needed.

[b] Subjects will be instructed to contact their study site immediately if he/she develops any symptoms suggestive of HZ, if he/she manifests any symptoms he/she perceive as serious and, in case of pregnancy for women of childbearing potential.

[c] Only for women of child-bearing potential.

[d] Study procedure to be assessed only after administration of vaccine at Visit 1.

[e] Monthly contact after Visit 3 until study conclusion, except at months that coincide with the subject's scheduled visits
(Amended 18 April 2014)

[f] EQ-5D and SF-36 will remain as source documents. The information from these questionnaires will only be transcribed in the eCRF for subjects who have a suspected HZ event during the study.

Table 3 Study procedures to be performed during the follow-up period for each suspected HZ case

	VISITS/CONTACTS IN CASE OF HZ						
Type of contact Timepoints	Visit HZ-1 Day HZ-0	Visit HZ-2 Day HZ-7	Contact HZ-3 Day HZ-14	Contact HZ-4 Day HZ-21	Visit HZ-5 Day HZ-28	Contact HZ-6 Day HZ-56	Visit HZ-7 Day HZ-91
Perform clinical examination	○						
Return HZ-specific diary cards to study staff/investigator	○						
Transcription of the HZ-specific diary card by study staff/investigator	●						
Take digital photographs of HZ rash $^{\alpha}$	●						
Recording of the HZ onset date by study staff/investigator	●						
Collect HZ lesion samples (3 replicate samples) for confirmation by PCR of a case of clinically diagnosed suspected HZ as specified in Section 5.7.3.11*, and for exploratory HSV qPCR**	●						
Record relevant information regarding HZ in eCRF by study staff/investigator	●	●	●	●	●	●	●
Record concomitant medication/vaccination according to guidelines in Section 6.6	●	●	●	●	●	●	●
Record intercurrent medical conditions according to guidelines in Section 6.7	●	●	●	●	●	●	●
Record any medical attention received for HZ or any HZ-related complication	●	●	●	●	●	●	●
Dispense ZBPI questionnaires to subjects	○						
Completion† of ZBPI questionnaires by the subjects until pain ceases or the cut-off date for ***end of study*** analysis (ZBPI pain data will be collected until at least Day HZ-90) (Amended 18 April 2014)	○	○	○	○	○	○	○
Return completed ZBPI questionnaires to study staff/investigator according to instructions provided by the investigator/study staff to subjects		○	○	○	○	○	○
Transcription of ZBPI questionnaires by study staff/investigator	●	●	●	●	●	●	●
Dispense EQ-5D and SF-36 questionnaires to subjects	○						

	VISITS/CONTACTS IN CASE OF HZ						
Type of contact Timepoints	Visit HZ-1 Day HZ-0	Visit HZ-2 Day HZ-7	Contact HZ-3 Day HZ-14	Contact HZ-4 Day HZ-21	Visit HZ-5 Day HZ-28	Contact HZ-6 Day HZ-56	Visit HZ-7 Day HZ-91
Completion‡ of EQ-5D and SF-36 questionnaires by the subjects until pain ceases or the cut-off date for ***end of study*** analysis (EQ-5D and SF-36 data will be collected until at least Day HZ-90) (Amended 18 April 2014)	○	○	○	○	○	○	○
Return completed EQ-5D and SF-36 questionnaires to study staff/investigator according to instructions provided by the investigator/study staff to subjects		○	○	○	○	○	○
Transcription of EQ-5D and SF-36 questionnaires by study staff/investigator	●	●	●	●	●	●	●

Note: If HZ-associated pain ceases (defined as a 28-day [or 4-week] pain free period) and the HZ rash resolves, subsequent HZ follow-up visits or contacts will be cancelled. If pain reappears in the same area after a 4-week pain-free period and is not accompanied by a new HZ rash, it will be assigned to the previous HZ-episode. Visits/contacts will restart with Day HZ-0 defined as the first visit of the assigned episode, prior to the pain free period.

$^{\alpha}$ Additional photographs of HZ lesions may be taken after Visit HZ-1 to help note the progression of the rash

* If during clinical evaluation at Visit HZ-1, the investigator determines that adequate rash samples are not present at Visit HZ-1 (i.e., <3 lesions present or only papules present), the investigator has the option of collecting three additional samples prior to or at Visit HZ-2. See the SPM for further details on PCR sample collection. ** If based on qPCR test results the diagnosis of HZ can be excluded, Herpes Simplex Virus (HSV) qPCR may be performed to assess if the rash lesions are due to HSV (1 or 2). This exploratory testing is not part of the decision making process for HZ case confirmation (see Appendix A and Appendix B). This testing is optional and requires specific consent from the individual subjects.

† Subjects with suspected HZ will be asked to complete the ZBPI questionnaire at Day HZ-0 (Visit HZ-1) to rate HZ-associated pain within the last 24 hours (If the time between the HZ onset and clinical evaluation at Visit HZ-1 is greater than 24 hours, the subject will be asked to complete a second ZBPI also for the elapsed time between the HZ onset and 24 hours before Visit HZ-1); daily from Day HZ- 1 to Day HZ-28, and weekly from Day HZ-29 onwards until a 4-week pain-free period is documented or until the cut-off date for ***end of study*** analysis. (Amended 18 April 2014) If pain reappears in the same area after a 4-week pain-free period and is not accompanied by a new HZ rash, it will be assigned to the previous HZ-episode. The completion of ZBPI questionnaires will resume based upon the weekly schedule established at the start of the assigned episode. For all subjects with ongoing HZ-associated pain at the time of cut-off date for ***end of study*** analysis, ZBPI data will be collected until a 4-week pain-free period is documented OR until at least Day HZ-90 (See Section 5.5.2.2). (Amended 18 April 2014)

‡Subjects with suspected HZ will be asked to complete the EQ-5D and SF-36 questionnaire weekly from Day HZ-0 to Day HZ-28, and weekly onwards until a 4-week pain-free period is documented or until the cut-off date for ***end of study*** analysis. (Amended 18 April 2014) If pain reappears in the same area after a 4-week pain-free period and is not accompanied by a new HZ rash, it will be assigned to the previous HZ-episode. The completion of EQ-5D and SF-36 questionnaires will resume based upon the weekly schedule established at the start of the assigned episode. For all subjects with ongoing HZ-associated pain at the time of cut-off date for ***end of study*** analysis, EQ-5D and SF-36 data will be collected until a 4-week pain-free period is documented OR until at least Day HZ-90. Each suspected HZ that occurs up to the cut-off date for ***end of study*** analysis will be followed at least until Visit HZ-7 (the study visit at Day HZ-91) ***(or sooner if the subject has no HZ-associated pain for 4 consecutive weeks and the HZ rash resolves)***. (Amended 18 April 2014) Follow-up of HZ-associated pain and complications will continue irrespective of whether the rash has ended in some cases. (See Section 5.5.2.2).

The study staff/investigator will dispense additional questionnaires and provide instructions for the subject to return the completed questionnaires to the study site. The subjects will be given a new supply of questionnaires as necessary. Follow-up of HZ-associated pain persisting beyond Visit HZ-7 (Day HZ-91) or other complications will be done at monthly contacts that are planned after Visit 3 between the subjects and the investigator and/or his delegate.

It is the investigator's responsibility to ensure that the intervals between study visits/contacts are strictly followed. These intervals determine each subject's evaluability in the ATP analyses.

Time intervals between study visits/contacts related to study procedures performed in subjects participating in the study are presented in Table 4. In addition; after Visit 3, monthly contacts between the subjects and the investigator and/or his delegate will be scheduled.

Follow-up for the occurrence of any SAEs will begin at Day 0 and continue until Month 14. Follow-up for the occurrence of SAEs related to an HZ complication as defined in Section 5.5.2.5, related to study participation, related to a concurrent GSK medication/vaccine or any fatal SAE will continue until study conclusion. Follow-up for the occurrence of potential immune-mediated diseases (pIMDs), formerly referred to as new onset of autoimmune diseases and other immune mediated inflammatory disorders, will begin at Day 0 and continue until study conclusion.

Table 4 Intervals between study visits/contacts (Amended 18 April 2014)

Interval	Length of interval	Range (days)
Visit 1 → Visit 2	2 months	49-83
Visit 2 → Visit 3	1 month	30-48
Visit 2 → Visit 4	12 months	335-395
Visit 2 → Visit 5	24 months	700-760
Visit 2 → Visit 6	36 months	1065-1125
Visit 2 → Study conclusion contact	Not fixed	Not fixed

Note: The date of Dose 1 (Visit 1) or Dose 2 (Visit 2), respectively, is used as reference date to define the interval between study visits/contacts.
(Amended 18 April 2014)

Time intervals between study visits/contacts to be performed for follow-up of HZ are presented in Table 5. Refer to the SPM for further guidance on data collection during follow-up of HZ.

Table 5 Intervals between contacts with subjects in case of suspected HZ

Interval between visits/contacts	Length of interval	Optimal Timing of contact (range of days)
Visit HZ-1 (Day HZ-0) → Visit HZ-2 (Day HZ-7)	7 days	Day HZ-7 (+/- 3 days)*
Visit HZ-2 (Day HZ-7) → Contact HZ-3 (Day HZ-14)	7 days	Day HZ--14 (+/- 3 days)*
Contact HZ-3 (Day HZ-14) → Contact HZ-4 (Day HZ-21)	7 days	Day HZ-21 (+/- 3 days)*
Contact HZ-4 (Day HZ-21) → Visit HZ-5 (Day HZ-28)	7 days	Day HZ-28 (+/- 3 days)*
Visit HZ-5 (Day HZ-28) → Contact HZ-6 (Day HZ-56)	28 days	Day HZ-56 (+/- 7 days)*
Visit HZ-1 (Day HZ-0) → Visit HZ-7 (Day HZ-91)	91 days	Day HZ-91 (+ 7 days)

Note: The date of the previous visit/contact is used as reference date to define the interval between the subsequent study visits/contacts

Note: If HZ-associated pain ceases (i.e., after a 4-week pain-free period is documented) and the HZ rash resolves, subsequent follow-up HZ visits or contacts will be cancelled (see Section 5.5.2.2). Follow-up of HZ-associated pain persisting beyond Visit HZ-7 (Day HZ-91) or other complications will be done at monthly contacts between the subjects and the investigator and/or his delegate that are planned after Visit 3

* If contacted early in the window, then remaining days in the interval will need to be captured with the next contact.

5.7. Detailed description of study procedures

5.7.1. Procedures prior to study participation

5.7.1.1. Study Determination (Recruitment/Randomization) Agreement

Eligible subjects 70-79 YOA and ≥ 80 YOA will be randomly assigned to ZOSTER-006 or ZOSTER-022 at Visit 1. Prior to study assignment, subjects need to provide their signature/thumb print on the Study Determination (Recruitment/Randomisation) Agreement. Subjects will receive a study determination number to be recorded in the eCRF. Study assignment can be done prior to Visit 1 if needed.

5.7.1.2. Informed consent

Before performing any other study procedure, subjects need to provide their signature/thumb print on the study specific informed consent. Refer to Section 5.1 for the requirements on how to obtain informed consent, as appropriate.

5.7.2. Procedures prior to the first vaccination

5.7.2.1. Check inclusion and exclusion criteria

Check all applicable inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

If a subject is enrolled while not meeting all inclusion criteria or while meeting any of the exclusion criteria, this must be reported in the eCRF.

5.7.2.2. Collect demographic data

Record demographic data such as information regarding date of birth, gender, geographic ancestry and ethnicity in the subject's eCRF.

5.7.2.3. Medical history

Review and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study in the eCRF.
Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

5.7.2.4. Physical examination

A history-directed physical examination according to local practice should be performed to ensure the subject is in good physical condition.

5.7.2.5. Urine pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test prior to any study vaccine administration. The study vaccine/placebo may only be administered if the pregnancy test is negative.

5.7.3. Procedures during the study

Note that the urine pregnancy test is performed prior to vaccination and is described in Section 5.7.2.

Note that subjects may decide at any time to end their participation in the study or request unblinding of the treatment received. In case of non-emergency unblinding, e.g., to receive a licensed HZ vaccine, subjects will be withdrawn from the study. An internal operating procedure that describes the process for non-emergency unblinding will be followed. **(Amended 18 April 2014)**

5.7.3.1. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant medication/vaccination must be recorded in the eCRF as described in Section 6.6. Refer to Section 6.6 for details on the medications/vaccinations that are forbidden or allowed during the study.

At each study visit or contact subsequent to the first vaccination, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition listed in Section 6.7. If it is the case, the condition(s) must be recorded in the eCRF.

Intercurrent medical conditions except HZ prior to one month after the second vaccination should be reported in the AE section of the eCRF.

Any subject with a clinically diagnosed suspected HZ episode between Visit 1 and Visit 2 should not receive the second vaccination.

Antiviral and/or pain medications administered to subjects with a suspected or confirmed case of HZ for the purpose of treating the HZ or the associated pain will be recorded in order to establish the link between the medications and the indication.

In addition, any medication/vaccination taken from Day 0 to Day 29 after each vaccination will be recorded by the subjects on a 30-day diary card (Section 5.7.3.8).

5.7.3.2. Check contraindications to vaccination

Contraindications to vaccination are to be checked at the beginning of each vaccination visit. Refer to Section 6.5.

See Section 5.7.3.7 for additional criteria to be checked prior to administration of the second vaccination dose.

5.7.3.3. Assess pre-vaccination body temperature

The axillary, rectal, oral or tympanic body temperature of all subjects will be measured prior to any study vaccine administration. The preferred route for recording temperature in this study will be oral. All vaccines may be administered to persons with low-grade fevers, i.e., oral, tympanic on oral setting, or axillary temperature < 37.5°C/99.5°F, or < 38.0°C (100.4°F) on rectal setting (Section 4.3). If a subject has an axillary/oral/tympanic on oral setting temperature ≥ 37.5°C/99.5°F, or ≥ 38.0°C (100.4°F) on rectal setting, it will constitute a contraindication to administration of vaccine or placebo at that point in time (Section 6.5).

5.7.3.4. Randomization

At the first vaccination visit, randomization will occur as explained in Section 5.3.

5.7.3.5. Blood sampling for safety or immune response assessments

As specified in Table 2, blood samples will be taken during certain study visits. Refer to the Module on Biospecimen Management in the SPM for general handling of blood samples.

- A volume of approximately 10 mL of whole blood should be drawn from all subjects at Visits 1 and 3, and, from all subjects included in the Immunogenicity subset, at Visits 4, 5 and 6**.**
- An additional volume of approximately 20 mL of whole blood should be drawn from all subjects included in the CMI component of the Immunogenicity subset at Visits 1, 3, 4, 5 and 6**.**

5.7.3.6. Treatment number assignment

At the first vaccination visit, the subject will be assigned a treatment number defining the treatment he/she will be receiving. The treatment number must be recorded in the eCRF at each vaccination visit**.**

If there is a need for a site to use a replacement vaccine, then that treatment number needs to be transcribed into the eCRF (see Section 6.4).

5.7.3.7. Vaccination

- After completing the prerequisite procedures prior to each vaccination, one dose of study vaccine/placebo will be administered intramuscularly (IM) in the deltoid of the non-dominant arm (refer to Section 6.3 for detailed description of the vaccine administration procedure). If the Investigator or delegate determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled within the interval for this visit.
- The vaccinees will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of anaphylaxis following the administration of vaccine.
- Any subject with clinically diagnosed suspected HZ episode between Visit 1 and Visit 2 should not receive the second dose.
- Any subject with an SAE related to the first dose of vaccine (as judged by the investigator) should not receive the second dose (Section 6.5).

5.7.3.8. Recording of non-serious AEs and SAEs

Refer to Section 8.3 for procedures for the Investigator to record AEs and SAEs and to Section 8.4 for guidelines on how to report these AEs/SAEs to GSK Biologicals.

- The subjects will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious or in case of pregnancy for women of childbearing potential.
- After each vaccination, 30-day diary cards will be provided to all subjects by study staff/investigator for daily recording by the subjects of:
  - unsolicited symptoms from Days 0 to 29 after each vaccination
  - any medication/vaccination taken from Days 0 to 29 after each vaccination.
- After each vaccination, 7-day diary cards will be provided to subjects who are part of the 7-day diary card subset by study staff/investigator for daily recording by the subjects of solicited symptoms from Days 0 to 6 after each vaccination
- The subjects will be instructed to return the completed diary cards to the investigator at Visit 2 and Visit 3, respectively.
- Collection and verification of completed diary cards will occur during discussion with the subject at Visit 2 and Visit 3. The investigator will transcribe the collected information into the eCRF in English.

5.7.3.9. Recording of potential immune-mediated diseases (pIMDs)

As specified in the List of Study Procedures (Table 2, Section 5.6), potential immune-mediated diseases (pIMDs), formerly referred to as NOADs and other immune mediated inflammatory disorders, occurring from administration of the first dose of vaccine/placebo onwards until end of the trial will be recorded.

Refer to Section 8.3.2.5 for information on recording of pIMDs.

5.7.3.10. Recording of data from completed EQ-5D and SF-36 questionnaires

EQ-5D and SF-36 questionnaires will be completed by all subjects at Visit 1.

- **EQ-5D and SF-36 questionnaires:** To be completed by all subjects at study entry. Also, to be completed by all subjects at Visits 4, 5 and 6 (subjects with an ongoing suspected HZ episode will follow a weekly schedule and do not need to additionally complete the questionnaires at these visits).

EQ-5D and SF-36 will remain as source documents. The information from these questionnaires will only be transcribed into the eCRF for subjects who have suspected HZ during the study.

5.7.3.11. Follow up of suspected HZ cases and HZ-associated pain

Data will be collected on all suspected HZ cases that occur from administration of the first dose of vaccine/placebo until the cut-off date for ***end of study*** analysis (Section 5.7.3.17). **(Amended 18 April 2014)** For each suspected case of HZ that the investigator concludes is clinically consistent with HZ, data on HZ-associated pain (using ZBPI questionnaires completed by the subject) will be collected until Day-HZ-28, and from Day HZ-29 until:1) the subject has no HZ-associated pain for 4 consecutive weeks; or, 2) the cut-off date for ***end of study*** analysis. For all subjects with ongoing HZ-associated pain at the time of cut-off date for ***end of study*** analysis, ZBPI data will be collected until a 4-week pain-free period is documented OR until at least Day HZ-90. **(Amended 18 April 2014)** In addition, subjects with suspected HZ will be asked to complete EQ-5D and SF-36 questionnaires weekly. If pain reappears in the same area after a 4-week pain-free period and is not accompanied by a new HZ rash, it will be assigned to the previous HZ-episode. The completion of ZBPI, EQ-5D and SF-36 questionnaires will resume based upon the weekly schedule established at the start of the assigned episode. Visits/contacts will also restart according to the schedule in Table 3 with Day HZ-0 defined as the first visit of the assigned episode, prior to the pain free period. Refer to Section 5.5.2.2 for more details.

At the first HZ evaluation visit (Visit HZ-1 at Day HZ-0 – The visit at which the suspected case of HZ is first evaluated by the investigator), rash lesion samples will be collected from the subject if the investigator considers the symptoms/signs to be consistent with HZ. Three replicate rash lesion samples (see Table 6) should be collected on the same day. If during clinical evaluation at Visit HZ-1, the investigator determines that adequate rash lesion samples cannot be collected (i.e., less than three lesions present, or if only papules are present), the subject should be asked to return to the study site for collection of additional samples prior to or at the Visit HZ-2 if there is rash progression (i.e., appearance of new/additional lesions if originally less than three lesions present, or appearance of vesicles if originally only papules present). When the subject returns for repeat sample collection, three samples from separate lesions should be collected. See the SPM for further details on sample collection.

At Visit HZ-1, the rash will be documented by digital photography. Additional photographs of HZ lesions may be taken after Visit HZ-1 to help note the progression of the rash.

Refer to Section 5.5.2 for details on follow-up of HZ cases and HZ-associated pain.

5.7.3.12. Recording of medically attended visits

Refer to Section 8.3.2.4 for detailed information on recording of medically attended visits occurring up until Month 8.

5.7.3.13. Reminder for self-reporting by subjects

Subjects will be instructed at Visit 1 (and will be reminded at each subsequent visit) to contact their study site immediately

- should the subject develop any symptoms suggestive of HZ, and to start completion of the HZ-specific diary card immediately upon development of these symptoms prior to visiting the study site for evaluation of the suspected HZ;
- should the subject manifest any signs or symptoms he/she perceive as serious;
- should the subject become pregnant (for women of childbearing potential).

5.7.3.14. Reminder for monthly follow-up contacts/yearly follow-up visits

The subject will be reminded that, after Visit 3, monthly contacts between the subjects and the investigator and/or his delegate will take place (except at months that coincide with the subject's scheduled visits) in order to collect all relevant information on any event of interest that may have occurred [including SAEs (Section 8.3), pIMDs (Section 8.3.2.5), occurrence or follow up of a suspected episode of HZ (Section 5.5.2), intercurrent medical conditions (Section 6.7), medically attended visits (up to Month 8 only, Section 8.3.2.4), the use of concomitant medications and/or vaccinations (Section 6.6) or pregnancy (Section 8.3)], and that information will be recorded in the appropriate section of the subject's eCRF.

The subject will be reminded that the current study still has yearly follow-up visits planned ***until Month 38 (Visit 6).*** **(Amended 18 April 2014)**

5.7.3.15. Final HZ efficacy analysis trigger (Amended 18 April 2014)

When the cut-off date for final HZ efficacy analysis has been reached and communicated to the sites, the following actions need to take place:

- ***Transcription in eCRF of date of last visit or contact with the subject***
- ***Addition of Investigator signature in eCRF (signing of data)***

(Amended 18 April 2014)

5.7.3.16. Invitation for a planned follow-up study

If study ZOSTER-006 is extended to include an additional long-term follow-up period beyond that currently mandated by the protocol**,** the investigator/study staff will ask all or a subset of subjects at the study conclusion contact if the subject would be willing to participate to a long-term follow-up study. If a subject declines to participate in a long-term follow-up study, refusal will be documented in the individual eCRF.

5.7.3.17. Study conclusion

Study end will take place when ***the*** conditions for ***end of study*** analysis are met and a minimum 90 days follow-up is completed for each case of suspected HZ that occurs prior to the cut-off date for ***end of study*** analysis. **(Amended 18 April 2014)**

Refer to Section 3 for more details regarding end of study analysis **(Amended 18 April 2014)**

When the cut-off date for ***end of study*** analysis is established, the study sites will contact the subjects for the study conclusion contact as soon as possible. If a subject with suspected HZ has not completed follow-up until at least Day HZ-90 at the cut-off date for ***end of study*** analysis, follow-up for such a subject will continue until Day HZ-90 (or sooner if the subject has no HZ-associated pain for 4 consecutive weeks and the HZ rash resolves). **(Amended 18 April 2014)** The study conclusion contact for such a subject will thus occur after he/she completes follow-up as described above.

At the study conclusion contact, the study sites will provide instructions to the subjects for returning any outstanding ZBPI questionnaires.

At the study conclusion contact, the following procedures will take place:

- Follow-up of any cases of suspected HZ and HZ-associated pain (Sections 5.5.2 and 5.7.3.10)
- Recording of any SAEs related to study participation or to a concurrent GSK medication/vaccine, or any fatal SAE (Section 5.7.3.8);
- Recording of pIMDs (Section 5.7.3.9);
- Check and record specific concomitant medication/vaccination and intercurrent medical conditions (Section 5.7.3.1);
- Study conclusion will be recorded in the eCRF.

After study conclusion, if the study vaccine demonstrates sufficient evidence of efficacy and safety such that a clinically important benefit may be reasonably expected, placebo recipients may be offered cross-over immunization with the study vaccine.

5.8. Biological sample handling and analysis

Please refer to the SPM for details of biospecimen management (handling, storage and shipment).

Samples will not be labelled with information that directly identifies the subjects but will be coded with the identification number for the subject (subject number).

Collected samples may be used in other assays, for test improvement or test development of analytical methods related to the study vaccine and its constituents or the disease under study to allow to achieve a more reliable measurement of the vaccine response. Under these circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject.

Herpes Simplex Virus (HSV) qPCR (see Section 5.8.2) may be performed on Varicella Zoster Virus (VZV) negative β-actin positive samples for exploratory purpose to assess if the rash lesions are due to HSV (1 or 2) and not to VZV; it is not part of the decision making process for HZ case confirmation. This testing is optional and requires specific consent from the individual subjects (see Appendix A and Appendix B).

Any human pharmacogenetic testing will require specific consent from the individual subjects and the ethics committee approval. Any anti-HIV testing will also require specific consent and ethics committee approval.

Refer also to the Investigator Agreement, where it is noted that the Investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking given in Section 5.8.4 may be changed.

Collected samples will be stored for up to 15 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.8.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (see Section 10.5 for the definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used. Refer to the Module on Clinical Trial Supplies in the SPM.

5.8.2. Biological samples

The different biological samples collected in the study, the quantities needed, the units and the timepoints are described in Table 6.

Table 6 Biological samples

Sample type	Quantity (approximate volume)	Unit	Timepoint	Subset Name*
Blood (Cell-mediated immunology)	20	mL	Visit 1, 3, 4, 5, 6	CMI component of Immunogenicity subset
Blood (Humoral immunology)	10	mL	Visit 1, 3	All subjects
	10	mL	Visit 4, 5, 6	Immunogenicity subset
Clinical specimens of HZ lesions	3 replicate samples, taken on the same day, of the highest priority lesion type available (1) vesicle fluid; 2) crust; 3) crust swab; 4) papule swab)†	NA	Scheduled in case of suspected HZ for diagnosis	Subjects clinically diagnosed as having a suspected case of HZ

* Refer to Section 4.1 for description of the subsets
†If during clinical evaluation at Visit HZ-1, the investigator determines that adequate rash samples are not present at Visit HZ-1 (i.e., <3 lesions present or only papules present), the investigator has the option of collecting three additional samples prior to or at Visit HZ-2. See the SPM for further details on sample collection.

5.8.3. Laboratory assays

Please refer to Appendix A for a detailed description of the assays performed in the study.

Laboratory assays, which will be used in this study, are summarised in respectively Table 7 (Humoral Immunity), Table 8 (CMI) and Table 9 (Molecular Biology).

Table 7 Humoral Immunity (Antibody determination) (Amended 18 April 2014)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off	Laboratory
Serum	Varicella Zoster Virus Ab.IgG	ELISA	Enzygnost Dade Behring	mIU/mL	25	GSK Biologicals*
Serum	gE Ab.IgG	ELISA	NA	mIU/mL	***97***	GSK Biologicals*
Serum	Varicella Zoster Virus Neutralizing Ab.IgG	PRNT	NA	ED50	TBD	GSK Biologicals*

*GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals.
ELISA = Enzyme-linked Immunosorbent Assay; PRNT = Plaque Reduction Neutralization Test
mIU = milli international unit; ED50 = endpoint dilution 50%
NA = Not applicable; TBD = to be determined; Ab = antibody

Table 8 Cell-Mediated Immunity (CMI)

System	Component	Challenge	Method	Unit	Laboratory
Peripheral Blood Mononuclear Cells	Cells CD4.All double CD40 Ligand or Interleukin-2 or Tumor Necrosis Factor alpha or Interferon gamma	gE	ICS	Events/10E6	GSK Biologicals*
Peripheral Blood Mononuclear Cells	Cells CD4.All double CD40 Ligand or Interleukin-2 or Tumor Necrosis Factor alpha or Interferon gamma	VZV	ICS	Events/10E6	GSK Biologicals*

*GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals.
ICS = Intracellular cytokine staining

Table 9 Molecular Biology (PCR tests)

System	Component	Method	Unit	Laboratory
HZ lesion sample	Varicella Zoster Virus.DNA	QPCR	No unit	GSK Biologicals*
HZ lesion sample	Herpes Simplex Virus.DNA**	QPCR	No unit	GSK Biologicals*
HZ lesion sample	Actin Gene.DNA	QPCR	No unit	GSK Biologicals*

*GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals.
** Herpes Simplex Virus (HSV) qPCR may be performed on VZV negative/β-actin positive samples for exploratory purpose to assess if the rash lesions are due to HSV (1 or 2) and not to VZV; it is not part of the decion making process for HZ case confirmation (see Appendix A and Appendix B). This exploratory testing is optional and requires specific consent from the individual subjects.

Collected samples will be used for purposes related to the quality assurance of data generated within the scope of this protocol, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

5.8.4. Biological samples evaluation

5.8.4.1. Immunological read-outs

The plan for immunogenicity testing on samples obtained is shown in Table 10. In case of insufficient blood sample volume to perform the assays, the samples will be analysed according to priority ranking provided in Table 10.

- For subjects included in the Immunogenicity subset (humoral immunity), anti-gE and anti-VZV Abs will be measured at specified timepoints. An anti-VZV neutralizing Ab assay may also be performed on the serum blood samples from a subgroup of subjects of the Immunogenicity subset.
- For a subgroup of subjects included in the CMI component of the Immunogenicity subset, gE and VZV specific CMI response will be measured at specified timepoints.
- For the correlates of protection analysis, analysis of the humoral immune responses at prevaccination and Month 3 will be performed on samples collected from vaccinated subjects who develop confirmed HZ and compared with the humoral immune responses at prevaccination and Month 3 from matched subjects that did not develop HZ. Additional blood samples may be analysed from other subjects to match more exactly with characteristics of those that developed HZ.

Table 10 Immunological read-outs

Blood sampling timepoint			Subset* Name	Marker	Components priority rank
Visit no	Timing	Month			
Visit 1	Pre-Vacc 1	0	Immunogenicity subset Immunogenicity subset Immunogenicity subset**	Ab gE ELISA Ab VZV ELISA anti-VZV neutralizing Ab	1 2 3
			CMI component of Immunogenicity subset CMI component of Immunogenicity subset	ICS gE ICS VZV	1 2
			Correlate of protection analysis‡ Correlate of protection analysis‡	Ab gE ELISA Ab VZV ELISA	1 2
Visit 3	Post-Vacc 2	3	Immunogenicity subset Immunogenicity subset Immunogenicity subset**	Ab gE ELISA Ab VZV ELISA anti-VZV neutralizing Ab	1 2 3
			CMI component of Immunogenicity subset CMI component of Immunogenicity subset	ICS gE ICS VZV	1 2
			Correlate of protection analysis‡ Correlate of protection analysis‡	Ab gE ELISA Ab VZV ELISA	1 2
Visit 4	Post-Vacc 2	14	Immunogenicity subset Immunogenicity subset Immunogenicity subset**	Ab gE ELISA Ab VZV ELISA anti-VZV neutralizing Ab	1 2 3
			CMI component of Immunogenicity subset CMI component of Immunogenicity subset	ICS gE ICS VZV	1 2
Visit 5	Post-Vacc 2	26	Immunogenicity subset Immunogenicity subset Immunogenicity subset**	Ab gE ELISA Ab VZV ELISA anti-VZV neutralizing Ab	1 2 3
			CMI component of Immunogenicity subset CMI component of Immunogenicity subset	ICS gE ICS VZV	1 2
Visit 6	Post-Vacc 2	38	Immunogenicity subset Immunogenicity subset Immunogenicity subset**	Ab gE ELISA Ab VZV ELISA anti-VZV neutralizing Ab	1 2 3
			CMI component of Immunogenicity subset CMI component of Immunogenicity subset	ICS gE ICS VZV	1 2

* Refer to Section 4.1 for description of subsets.

** Anti-VZV neutralizing Ab assay may be performed in a subgroup of the Immunogenicity subset.

‡ Refer also to Section 10.8.3.4 for details regarding correlate of protection analysis

Note: Test results obtained for the anti-gE and anti-VZV Ab ELISA assays will be used for correlate of protection analysis, if applicable.

Additional testing may be performed if deemed appropriate by GSK Biologicals should any findings in the present study, or in other studies, indicate that further investigation of the immunogenicity of the vaccine is warranted. In this case, the rankings above may also change.

5.8.4.2. Test for laboratory diagnosis of HZ

In case of a suspected HZ case diagnosis in any of the subjects, clinical specimens from HZ lesions will be collected to confirm the diagnosis of HZ by PCR. Please refer to Appendix A for or a detailed description of the PCR.

5.8.5. Immunological correlates of protection

No correlate of protection has been demonstrated so far for the antigen used as part of the candidate vaccine.

Study ZOSTER-006 will attempt to correlate humoral immune responses at Month 3 with protection. Additional evaluations to add precision to this assessment may be performed (see Section 10.8.3.4).

6. STUDY VACCINE AND ADMINISTRATION

6.1. Description of study vaccine

The Quality Control Standards and Requirements for the candidate vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccine is labelled and packed according to applicable regulatory requirements.

The study vaccine will be supplied in 2 vials, one containing the VZV gE antigen, and the other containing Adjuvant System $AS01_B$.

- The VZV gE antigen is provided in a lyophilized form in monodose vials. Each vial contains 62.5 μg of recombinant purified gE and formulation excipients. Therefore, when the 62.5 μg of VZV gE in each vial is reconstituted with the full volume of adjuvant, each vaccine dose will contain 50 μg of the VZV gE antigen per 0.5 mL of reconstituted vaccine.
- The $AS01_B$ Adjuvant System is provided as a liquid formulation in monodose vials, each vial containing at least 0.5 mL of adjuvant. One 0.5 mL dose of $AS01_B$ formulation contains 50 μg of MPL and 50 μg of QS21 mixed with liposomes.

When the VZV gE antigen is reconstituted in $AS01_B$ it appears as an opalescent, colourless liquid, free from visible particles.

After reconstitution, each 0.5 mL dose of study vaccine contains 50 μg of gE recombinant protein, 50 μg of MPL, 50 μg of QS21, and liposomes.

The NaCl solution is provided in monodose vials (0.5 mL/dose) containing 150 mM NaCl per 0.5 mL dose. The NaCl solution used as the placebo appears clear and colourless and is free from visible particles.

The method of preparation of the gE/AS01$_B$ study vaccine (reconstitution required) differs from that of the placebo (no reconstitution required for the NaCl solution placebo). The reconstituted gE/AS01$_B$ study vaccine differs in appearance from the NaCl solution placebo. To conduct the study in an observer-blind manner, the gE/AS01$_B$ vaccine and NaCl solution placebo doses will be prepared and administered by study staff not involved in the clinical evaluation of the subjects. In this way, neither the subject nor the investigator (or other study personnel) will know which treatment was administered. The method of blinding and the responsibilities of the study personnel in this regard will be documented by the investigator at each study site.

The SPM will include details of vaccine supplies.

6.2. Storage and handling of study vaccine

All study vaccines to be administered to the subjects must be stored in a safe and locked place with no access by unauthorised personnel.

The study vaccines must be stored at the defined temperature range (i.e. +2 to +8°C/36°F to 46°F) and must not be frozen. Please refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccine. The storage temperature of the vaccine will be monitored daily with temperature monitoring device(s) (at the minimum calibrated) and will be recorded as specified in the SPM.

The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact.

Any temperature deviation outside the range 0°C to +8°C/32°F to 46°F, must be reported to the sponsor as soon as detected. Following an exposure to such a temperature deviation, vaccines will not be used until approval has been given by the Sponsor.

In case of temperature deviation between 0 and +2°C/32 and 36°F, the impacted study vaccine can still be administered, but the site must take adequate actions to go back to the defined range +2 to +8°C/36 to 46°F and avoid re-occurrence of such a temperature deviation.

Please refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the Temperature deviation process, packaging and accountability of the study vaccine.

6.3. Dosage and administration of study vaccine

The vaccine should be reconstituted shortly after the vials are taken out of the refrigerator. The reconstituted vaccine is stable for up to two hours when kept at a temperature range of +2°C (36°F) to 30°C (86°F). Therefore, reconstituted vaccines should be administered within a maximum of two hours after reconstitution.

To reconstitute gE/AS01$_B$ study vaccine, the entire content of one diluent vial (i.e. AS01$_B$) is aspirated into a syringe and injected into one vial of lyophilized gE antigen. The pellet is dissolved by gentle shaking of the vial (for a few seconds) until complete dissolution of the lyophilized cake.

Table 11 summarises how vaccine will be administered.

The entire volume of the reconstituted vaccine should be withdrawn, the needle can be replaced, and any solution in excess of 0.5mL should be expelled. The reconstituted vaccine or a 0.5mL dose of the NaCl solution placebo should be administered by IM injection into the deltoid muscle using a standard aseptic technique, preferably in the non-dominant arm. In rare situations when there is no other alternative, the injection may be given in the dominant arm.

Table 11 Dosage and administration

Group	Visit	Vaccination	Treatment	Route	Site	Side
Vaccine	1, 2	1, 2	gE/AS01$_B$	IM	D	Non-dominant arm
Placebo	1, 2	1, 2	NaCl solution placebo	IM	D	Non-dominant arm

gE/AS01$_B$: lyophilized gE reconstituted in liquid AS01$_B$ Adjuvant System
Intramuscular (IM)
Deltoid (D) muscle of non-dominant arm

6.4. Replacement of unusable vaccine

Additional vaccine doses will be provided to replace those that are unusable (see the Module on Clinical Trial Supplies in the SPM for details).

In addition to the vaccine doses provided for the planned number of subjects (including over-randomization when applicable), at least 5% additional doses will be supplied to replace those that are unusable.

The investigator will use the central randomization system (SBIR) to obtain the replacement vial number. The system will ensure, in a blinded manner, that the replacement vial is of the same formulation as the randomized vaccine.

6.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of gE/AS01$_B$. If any of these events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 8.4.4).

- Anaphylaxis following the administration of vaccine(s);
- Pregnancy (Section 8.2.2);
- If the subject experiences an SAE judged to be vaccine-related by the investigator (Sections 8.1.2 and 8.3.2.2.2);
- Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., malignancy, HIV infection) or

immunosuppressive/cytotoxic therapy (e.g., medications used during cancer chemotherapy, organ transplantation or to treat autoimmune disorders). However subjects who have received less than 15 days of immunosuppressants or other immune modifying drugs should not be contraindicated from receiving subsequent vaccinations. Also, for corticosteroids, prednisone < 20 mg/day, or equivalent, is allowed. Inhaled and topical steroids are allowed.

The following events constitute contraindications to administration of the gE/AS01$_B$ HZ vaccine at that point in time; if any one of these events occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (Section 5.6), or withdrawn at the discretion of the investigator (Section 8.4.4).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 37.5°C (99.5°F) on oral, axillary or tympanic setting, or ≥ 38.0°C (100.4°F) on rectal setting. The preferred route for recording temperature in this study will be oral.

  Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines.

See Section 5.7.3.7 for an additional criterion to be checked prior to administration of the second vaccination dose.

6.6. Concomitant medication/vaccination

At each study visit/contact, the investigator should question the subject about any medication taken and vaccination received by the subject.

Concomitant medication administered for the treatment of pIMDs at any time during the study must be recorded in the eCRF. Refer to Section 8.3.2.5 for information regarding pIMDs.

Any concomitant medication administered for the treatment of confirmed or suspected HZ or any HZ-related complications (including pain) at any time during the study must be recorded in the eCRF and coded as ‘Treatment for HZ’.

Administration of any medications/vaccinations/products listed in Section 6.6.1 must be recorded in the eCRF respecting the time window as detailed in Section 6.6.2.

All concomitant medications, with the exception of vitamins and/or dietary supplements, administered at ANY time during the 30 days (Days 0 -29) after each vaccination are to be recorded in the eCRF. This also applies to concomitant medication administered prophylactically in anticipation of reaction to the vaccination and any medication intended to treat an AE.

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [oral/tympanic on oral

setting/axillary temperature < 37.5°C (99.5°F), or < 38.0°C (100.4°F) on rectal setting] and any other symptom, to prevent fever from occurring).

Similarly, concomitant medication administered for the treatment of a SAE must be recorded on the SAE screens in the eCRF, as applicable. Refer to Section 8.1.2 for the definition of a SAE and Section 8.3.1 for SAE reporting periods.

6.6.1. Medications/products that may lead to the elimination of a subject from ATP analyses

The following criteria should be checked at each visit subsequent to the first vaccination. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP analysis. See Section 10.5 for definition of study cohorts to be evaluated.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the study period;
- Administration of a vaccine not foreseen by the study protocol **within** 30 days prior to dose 2 of vaccine and/**or within** 30 days after any dose. However, licensed non-replicating vaccines (i.e., inactivated and subunit vaccines, including inactivated and subunit influenza vaccines, with or without adjuvant for seasonal or pandemic flu) may be administered up to 8 days prior to dose 2 and/or at least 14 days after any dose of study vaccine;
- Receipt of a vaccine against HZ other than the study vaccine during the study period;
- Prolonged use (> 14 consecutive days) of oral and/or parenteral antiviral agents that are active against VZV (acyclovir, valacyclovir, famciclovir etc.) during the study period for an indication other than to treat suspected or confirmed HZ or an HZ-related complication (topical use of these antiviral agents is allowed);
- Receipt of immunoglobulins and/or any blood products during the study period;
- Chronic administration (defined as > 15 consecutive days) of immunosuppressants or other immune-modifying drugs during the study period. For corticosteroids, this will mean prednisone < 20 mg/day, or equivalent, is allowed. Inhaled and topical steroids are allowed.

A detailed, comprehensive list of reasons for elimination from ATP analyses will be established at the time of data cleaning.

6.6.2. Time window for recording concomitant medication/vaccination in the eCRF

All concomitant medications administered for the treatment of all SAEs from Day 0 until Month 14, are to be recorded in the eCRF.

Concomitant medication, administered for the treatment of SAEs related to study participation or to a concurrent GSK medication/vaccine or any fatal SAE, from Day 0 until Study conclusion contact, must be recorded in the eCRF.

Concomitant medication, administered for the treatment of HZ or any related HZ-complications, or for the treatment of pIMDs, from Day 0 until Study conclusion contact, must be recorded in the eCRF.

Oral and/or parenteral antiviral agents that are active against VZV (acyclovir, valacyclovir, famciclovir etc.) administered for > 14 consecutive days for an indication other than to treat suspected or confirmed HZ or an HZ-related complication from Day 0 until Study conclusion contact, are to be recorded in the eCRF.

Any vaccine not foreseen in the study protocol, administered from Day 0 until Month 3, is to be recorded in the eCRF.

Any investigational medication or investigational vaccine, administered from Day 0 through Study conclusion contact, must be recorded in the eCRF.

Any vaccine against HZ other than the study vaccine, administered from Day 0 until Study conclusion contact, is to be recorded in the eCRF.

Immunoglobulins and/or any blood products, administered from Day 0 until Study conclusion contact, are to be recorded in the eCRF.

Immunosuppressants or other immune-modifying drugs administered during the study period for > 15 consecutive days, are to be recorded in the eCRF. For corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent.

All concomitant medications, with the exception of vitamins and/or dietary supplements, administered at ANY time during the 30 days (Days 0 -29) after each vaccination are to be recorded in the eCRF.

6.7. Intercurrent medical conditions that may lead to elimination from an ATP cohort

Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition that has the capability of confounding their immune response to the study vaccine (i.e. a confirmed case of HZ prior to one month after the second vaccination); or they have any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g. malignancy, HIV infection). Intercurrent conditions except HZ prior to one month after the second vaccination should be reported in the AE section of the eCRF.

7. HEALTH ECONOMICS

The following questionnaires will be administered to the subjects:

- **EQ-5D questionnaire**

  The EQ-5D is a generic multi-attribute health classification system. The EQ-5D uses a 5-dimension (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) descriptive system, with each consisting of 3 response options

(no problems, moderate problems or extreme problems). The EQ-5D also includes a Visual Analogue Scale (VAS) ranging from 0 to 100, with 100 representing the best imaginable health state and 0 representing the worst imaginable health state.

- **SF-36 health survey**

  The SF-36® is a multi-purpose health survey with 36 questions. It yields an 8-scale profile of scores (physical functioning, role physical, bodily pain, general health perceptions, vitality, social functioning, role emotional, and mental health) as well as a reported health transition score.

Both the EQ-5D and SF-36 questionnaires are international standards and have been extensively validated. They will generate Quality-Adjusted Life Years (QALY) weights in order to estimate the cost-effectiveness of an HZ vaccination strategy.

A standard algorithm has been developed for processing subjects' answers and producing QALY weights. These QALY weights will be generated for each age group: 50-59 YOA, 60-69 YOA and ≥ 70 YOA.

EQ-5D and SF-36 will be completed at Visit 1 for all subjects in order to generate a baseline measurement.

For subjects with suspected HZ, both questionnaires will be completed weekly from Day HZ-0 onwards until a 4-week pain-free period is documented OR until the cut-off date for ***end of study*** analysis. For all subjects with ongoing HZ-associated pain at the time of the cut-off date for ***end of study*** analysis, EQ-5D and SF-36 data will be collected until a 4-week pain-free period is documented OR until at least Day HZ-90. **(Amended 18 April 2014)** Refer to Section 5.5.2.2 for more details. For all subjects, the EQ-5D and SF-36 questionnaires will be completed at Visits 4, 5 and 6 (subjects with an ongoing HZ episode will follow the weekly schedule and do not need to additionally complete the questionnaires at these visits).

QALY weights measured for HZ cases in vaccine and placebo recipients will be compared and adjusted for their respective baseline values.

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator or site staff is/are responsible during the study for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol.

Each subject will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.

8.1. Safety definitions

8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

NB: AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs. (For subjects not included in the 7-day diary card subset, all AEs will be recorded as UNSOLICITED AEs.)

Example of events to be recorded in the medical history section of the eCRF:

- Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. prior to the first study vaccination).

The occurrence of HZ or PHN will not constitute an AE or SAE. However, HZ complications other than PHN (see Section 5.5.2.5) will be considered as AEs or SAEs.

8.1.2. Definition of a serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that:

a. Results in death.

b. Is life-threatening.

NB: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation.

NB: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition (known/diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, or

NB: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

8.1.3. Solicited adverse events

Subjects in the 7-day diary card subset will be asked to report daily, from Day 0 to Day 6 (7-day follow-up period) after each dose, the occurrence of local or general solicited

adverse experiences on a safety diary card provided by the sponsor. All clinical signs and symptoms will be recorded by the investigator on the appropriate section of the eCRF.

The following local (injection-site) AEs will be solicited (Table 12):

Table 12 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

The following general AEs will be solicited (Table 13):

General AEs are any experiences, which do not occur at the site of injection of a vaccine. They will be recorded as 'general' and include those events.

Table 13 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms †
Headache
Myalgia
Shivering

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain

NB: Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the eCRF.

8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

Safety laboratories are not collected in this study. Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments that come to the attention of, and are judged by, the investigator to be clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 8.1.1 or of a SAE, as defined in Section 8.1.2. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.2. Events or outcomes not qualifying as adverse events or serious adverse events

8.2.1. Disease-related events or outcomes not qualifying as serious adverse events

The occurrence of HZ or PHN will not constitute an AE or SAE. However, HZ complications other than PHN (see Section 5.5.2.5) will be considered as AEs or SAEs.

8.2.2. Pregnancy

Any female subjects that are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccine/placebo but may continue other study procedures at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE, as described in Section 8.1.1 and 8.1.2, and will be followed as described in Section 8.4.4.

A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 8.4. Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related in time to the receipt of the investigational product will be reported to GSK Biologicals as described in Section 8.4. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

Information on pregnancies identified during screening/prior to vaccine administration is not required to be collected and communicated to safety.

8.3. Detecting and recording adverse events, serious adverse events and pregnancies

8.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies

Solicited AEs will be evaluated only in subjects who are part of the 7-day diary card subset. Unsolicited AEs will be evaluated in all subjects from Day 0 to Day 29 after each vaccination.

All AEs occurring from Day 0 to Day 29 after each vaccination must be recorded into the Adverse Event screen in the subject's eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

SAEs will be evaluated in all subjects. The standard time period for collecting and recording SAEs will begin at Day 0 and continue until Month 14 for each subject. See Section 8.4 for instructions on reporting and recording SAEs.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (e.g. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine or any fatal SAE will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged. ***This is including SAEs that are considered by the investigator to be related to the investigational vaccine and are to be collected and recorded from the time of the first receipt of study vaccine/placebo until the subject is discharged from the study*.(Amended 18 April 2014)**

pIMDs will be evaluated in all subjects during the entire study period (Section 8.3.2.5)

Medically attended visits will be evaluated in all subjects from Day 0 until Month 8 (Section 8.3.2.4)**.**

Intercurrent medical conditions (Section 6.7) will be recorded in all subjects throughout the entire study period.

All HZ complications as defined in Section 5.5.2.5 (including AE/SAE information) will be reported throughout the entire study period.

An overview of the protocol-required reporting periods for AEs and SAEs, pIMDs, medically attended visits, pregnancies, intercurrent medical conditions and HZ complications in study ZOSTER-006 is shown in Table 14.

Table 14 Reporting periods for AEs, SAEs, pIMDs, medically attended visits, pregnancies, intercurrent medical conditions and HZ complications in study ZOSTER-006 (Amended 18 April 2014)

									CONTACT (monthly after Visit 3 until study conclusion, except at months that coincide with the subject's scheduled visits)				
Study activity	VISIT 1 DOSE 1				VISIT 2 DOSE 2			VISIT 3	CONTACT	VISIT 4	VISIT 5	VISIT 6	Study conclusion contact
Timing of reporting	Day 0/ Month 0	Day 6 post Dose 1	Day 29 post Dose 1		Day 0/ Month 2	Day 6 post Dose 2	Day 29 post Dose 2	Month 3	Month 8	Month 14	Month 26	Month 38	
Reporting of solicited AEs (only in 7-day diary card subset)													
Reporting of unsolicited AEs													
Reporting of all SAEs until Month 14													
Reporting of SAEs related to study participation or GSK concomitant medication/vaccine or any fatal SAE, ***including SAEs that are considered by the investigator to be related to the investigational vaccine,*** after Month 14 until study conclusion (Amended 18 April 2014)													
Reporting of pIMDs													
Reporting of medically attended visits until Month 8													

									CONTACT (monthly after Visit 3 until study conclusion, except at months that coincide with the subject's scheduled visits)				
Study activity	VISIT 1 DOSE 1				VISIT 2 DOSE 2			VISIT 3	CONTACT	VISIT 4	VISIT 5	VISIT 6	Study conclusion contact
Timing of reporting	Day 0/ Month 0	Day 6 post Dose 1	Day 29 post Dose 1		Day 0/ Month 2	Day 6 post Dose 2	Day 29 post Dose 2	Month 3	Month 8	Month 14	Month 26	Month 38	
Reporting of pregnancies													
Recording of intercurrent medical conditions													
Recording of HZ Complications* (including AE/SAE information)													

* HZ complications are defined in Section 5.5.2.5

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 14. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.3.2. Evaluation of adverse events and serious adverse events

8.3.2.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of soliciting AEs, the subject should be asked a non-leading question such as:

'Have you felt different in any way since receiving the vaccine or since the previous visit?'

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE on the eCRF or SAE Report screens as applicable. It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals instead of the appropriate completed AE/SAE screens in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

8.3.2.2. Assessment of adverse events

8.3.2.2.1. Assessment of intensity

Intensity of the following AEs will be assessed as described:

Table 15 Intensity scales for solicited symptoms

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C/°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Gastrointestinal symptoms normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Myalgia	0	Normal
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Shivering	0	None
	1	Shivering that is easily tolerated
	2	Shivering that interferes with normal activity
	3	Shivering that prevents normal activity

*Fever is defined as: rectal temperature ≥38°C (100.4°F)/axillary temperature ≥37.5°C (99.5°F)/oral temperature ≥37.5°C (99.5°F)/tympanic temperature on oral setting ≥37.5°C (99.5°F)/tympanic temperature on rectal setting ≥38°C (100.4°F).The preferred route for recording temperature in this study will be oral.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals using GSK Biologicals' standard grading scale based on the US Food and Drug Administration (FDA) guidelines for Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers enrolled in Preventive Vaccine Clinical Trials" [FDA, 2007].

0	:	< 20 mm diameter
1	:	≥ 20 mm to ≤ 50 mm diameter
2	:	> 50 mm to ≤ 100 mm diameter
3	:	> 100 mm diameter

Temperature (measured by oral, axillary or tympanic route) will be scored at GSK Biologicals as follows:

0	:	< 37.5°C
1	:	37.5°C to 38.0°C
2	:	38.1°C to 39.0°C
3	:	> 39.0°C

The investigator will assess the maximum intensity that occurred over the duration of the event for all other AEs, i.e. unsolicited symptoms, including SAEs reported during the study. The assessment will be based on the investigator's clinical judgement.

The intensity of each AE and SAE recorded in the eCRF or SAE screens, as applicable, should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities. Such an AE would, for example prevent attendance at work and would necessitate the administration of corrective therapy.

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.2.

8.3.2.2.2. Assessment of causality

The investigator is obligated to assess the relationship between investigational vaccine and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship. Alternative plausible causes, based on natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational vaccine will be considered and investigated. The investigator will also consult the IB in the determination of his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccines administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational vaccine?

NO	:	The AE is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the AE.
YES	:	There is a reasonable possibility that the vaccine(s) contributed to the AE.

Non-serious and serious AEs will be evaluated as two distinct events. If an event meets criteria to be determined ‘serious’ (Section 8.1.2 for definition of serious adverse event), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors applicable to each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine, if applicable.
- Erroneous administration.
- Other cause (specify).

8.3.2.3. Assessment of outcomes

Outcome of any non-serious AE (i.e. unsolicited AE) occurring from Day 0 to Day 29 after each vaccination or any SAE reported during the entire study will be assessed as:

- Recovered/resolved.
- Not recovered/not resolved.
- Recovering/resolving.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

8.3.2.4. Medically attended visits

The subject will be asked if the subject received medical attention defined as hospitalization, an emergency room visit or a visit to or from medical personnel (medical doctor) for any reason, other than routine health care visits, from the first vaccination until Month 8, and this information will be recorded in the eCRF.

8.3.2.5. AEs of specific interest

Potential immune-mediated diseases (pIMDs) (formerly referred to as NOADs and other immune mediated inflammatory disorders) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in the table below.

However, the investigator will exercise his/her medical and scientific judgement in deciding whether other immune-mediated diseases have an autoimmune origin (i.e. pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

Table 16 List of Potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy), and neuritis (e.g. optic neuritis) Multiple sclerosis (including variants) Transverse myelitis Guillain-Barré syndrome, (including Miller Fisher syndrome and other variants) Other demyelinating diseases (including acute disseminated encephalomyelitis) Myasthenia gravis (including Lambert-Eaton myasthenic syndrome) Non-infectious encephalitis/ encephalomyelitis Neuritis (including peripheral neuropathies) Narcolepsy	Systemic lupus erythematosus Scleroderma (including, CREST syndrome and morphoea) Systemic sclerosis Dermatomyositis Polymyositis Antisynthetase syndrome Rheumatoid arthritis, Juvenile chronic arthritis, (including Still's disease) Polymyalgia rheumatica Reactive arthritis Psoriatic arthropathy Ankylosing spondylitis Relapsing polychondritis Mixed connective tissue disorder	Psoriasis Vitiligo Raynaud's phenomenon Erythema nodosum Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) Cutaneous lupus erythematosus Alopecia areata Lichen planus Sweet's syndrome
Liver disorders	**Gastrointestinal disorders**	**Metabolic diseases**
Autoimmune hepatitis Primary biliary cirrhosis Primary sclerosing cholangitis Autoimmune cholangitis.	Crohn's disease Ulcerative colitis Ulcerative proctitis Celiac disease	Autoimmune thyroiditis (including Hashimoto thyroiditis) Grave's or Basedow's disease Diabetes mellitus type I Addison's disease

Vasculitides	Others
Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis. Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome, thromboangiitis obliterans (Buerger's disease), necrotizing vasculitis, allergic granulomatous angiitis, Henoch-Schonlein purpura, anti-neutrophil cytoplasmic antibody positive vasculitis, Behcet's syndrome, leukocytoclastic vasculitis. Vasculitides secondary to other immune mediated diseases such as lupus vasculitis and rheumatoid vasculitis.	Autoimmune hemolytic anemia Autoimmune thrombocytopenias Antiphospholipid syndrome Pernicious anemia Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) Uveitis Autoimmune myocarditis/cardiomyopathy Sarcoidosis Stevens-johnson syndrome Sjögren's syndrome Idiopathic pulmonary fibrosis Goodpasture syndrome

When there is enough evidence to make any of the above diagnoses, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the eCRF a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available to investigators.

pIMDs that occur during the study (see also Section 8.3.1 for reporting period) will be reported promptly to GSK within the timeframes described in Table 17, once the investigator becomes aware of the pIMD.

Once onset of a new pIMD or exacerbation of a pre-existing pIMD is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the SAE screens of the eCRF WITHIN 24 HOURS after the he/she becomes aware of the diagnosis. A field on the SAE screen allows to specify that the event is a pIMD and whether it is serious or non serious. The SAE screens will always be completed as thoroughly as possible with all available details of the event, in accordance with the pIMD standard questionnaire provided. Even if the investigator does not have all information regarding a pIMD, the SAE screens should still be completed within 24 hours. Once additional relevant information is received, the SAE screens in the eCRF should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report.

Refer to Section 8.4.3 for back-up system and updating of SAE information after freezing of the subject's eCRF.

8.4. Reporting and follow-up of adverse events, serious adverse events and pregnancies

8.4.1. Prompt reporting of serious adverse events and other events to GSK Biologicals

SAEs will be reported promptly to GSK as described in Table 17 once the investigator determines that the event meets the protocol definition of an SAE.

Pregnancies will be reported promptly to GSK as described in Table 17 once the investigator becomes aware of a pregnancy in the time period defined in Section 8.3. The subject will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether that be full-term or premature, information on the status of the mother and child will be forwarded to GSK. Generally, follow-up should be no longer than 6 to 8 weeks following the estimated delivery date.

Table 17 Time frames for submitting SAEs and other events reports to GSK Biologicals

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours*	SAE screen	24 hours*	SAE screen
Pregnancy	24 hours*	Pregnancy Report Form	24 hours*	Pregnancy Report Form
pIMDs	24 hours**	SAE screen	24 hours**	SAE screen

* Time frame allowed after receipt or awareness of the information.
**Timeframe allowed after the diagnosis is established and known to the investigator

In case the electronic reporting system is temporarily unavailable, a back up system is in place. Please refer to Section 8.4.3 for a detailed description.

Please see the Sponsor Information Sheet for details on study contact for reporting SAEs.

Back-up Study Contact for Reporting SAEs
GSK Biologicals Clinical Safety & Pharmacovigilance
Fax: [redacted] or [redacted]
24/24 hour and 7/7 day availability

8.4.2. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.4.1. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to the investigational product and unexpected. The purpose of the report is to fulfil specific regulatory and Good Clinical Practice (GCP) requirements, regarding the product under investigation.

8.4.3. Completion and transmission of SAEs reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator will complete and submit the information in the SAE screens in eCRF within 24 hours. The SAE screens in eCRF will always be completed as thoroughly as possible with all available details of the event and will be submitted by the investigator. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the SAE screens in eCRF. The SAE screens in eCRF should be updated when additional relevant information is received WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report.

8.4.3.1. Back-up system in case the electronic SAE reporting system does not work

If the SAE reporting system has been down for 24 hours, the investigator or his/her delegate should fax an SAE report form directly to the GSK Central Safety department (please refer to Section 8.4.1) within 24 hours. The maximum timeline for reporting SAEs to central safety is therefore 48 hours.

NB. This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow.

As soon as the electronic reporting system is working again, the investigator or delegate must update the SAE screens in the eCRF within 24 hours.

The final valid information for regulatory reporting will be the information reported through the electronic system.

When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information is to be recorded on the paper SAE Report Form, with all changes signed and dated by the investigator. The updated SAE Report Form should be sent to GSK Biologicals WITHIN 24 HOURS of receipt of the follow-up information.

In rare circumstances, if the electronic system for reporting SAEs does not work and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by email or by mail. Initial notification via the telephone does not replace the need for the investigator to complete and submit SAE screens in the eCRF (or complete and sign the SAE Report Form if back-up system need to be used).

In the event of a death determined by the investigator to be related to vaccination, completion of SAE screens in the eCRF/sending of the fax (if electronic SAE reporting system does not work or after freezing of the subject's eCRF) must be accompanied by telephone call to the Study Contact for Reporting SAEs.

8.4.4. Follow-up of adverse events and serious adverse events

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until study conclusion.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

Cases of new onset of autoimmune diseases and other immune-mediated inflammatory disorders documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until study conclusion.

Investigators will follow-up subjects:

- With SAEs or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.
- Or, in the case of other non-serious AEs, cases of new onset of autoimmune diseases, until study conclusion or they are lost to follow-up.

Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such abnormalities noted for any subject must be made available to the Site Monitor.

GSK Biologicals may request that the investigator perform or arrange for the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

8.5. Treatment of adverse events

Treatment of any adverse event is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF. Refer to Section 6.6.

8.6. Unblinding

GSK Biologicals' policy (incorporating ICH E2A guidance, EU Clinical Trial Directive and Federal Regulations) is to unblind any serious adverse event (SAE) report associated with the use of the investigational product, which is unexpected and attributable/suspected, prior to regulatory reporting. The GSK Biologicals' Central Safety physician is responsible for unblinding the treatment assignment in accordance with specified time frames for expedited reporting of SAEs (refer to Section 8.4.1).

8.7. Emergency unblinding

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the study treatment is essential for the clinical management or welfare of the subject, as judged by the investigator.

The emergency unblinding process consists of the automated system (SBIR) that allows the investigator to have unrestricted, immediate and direct access to the subject's individual study treatment.

The investigator has the option of contacting a GSK Biologicals' On-call Central Safety Physician (or Backup) if he/she needs medical advice or needs the support of GSK to perform the unblinding (i.e. he/she cannot access the automated Internet-based system).

Any emergency unblinding must be fully documented by using the Emergency Unblinding Documentation Form, which must be appropriately completed by the investigator and sent within 24 hours to GSK Biologicals.

GSK Biologicals' Contact information for Emergency Unblinding 24/24 hour and 7/7 day availability
GSK Biologicals' Central Safety Physician: Outside US/Canada: [redacted] (GSK Biologicals Central Safety Physician on-call) US/Canada only: [redacted] (GSK Biologicals Central Safety Physician on-call)
GSK Biologicals' Central Safety Physician Back-up: Outside US/Canada: [redacted] US/Canada only: [redacted]
Emergency Unblinding Documentation Form transmission: Outside US & Canada: Fax: [redacted] or [redacted] US/Canada only: Fax: [redacted]

8.8. Subject card

Study subjects must be provided with the address and telephone number of the main contact for information about the trial.

Investigator/delegate should therefore provide a "subject card" to each subject. The aim of this card is to inform any physician having to deal with a subject in an emergency situation that the subject is in a clinical trial and that he/she can contact the trial investigator for more relevant information.

Subjects must be instructed to keep these cards in their possession at all times.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for the concluding visit/is available for the concluding contact foreseen in the protocol is considered to have completed the study.

9.2. Subject withdrawal

Subjects who are withdrawn because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as result of a SAE/AE until resolution of the event (Section 8.4).

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not come back for the concluding visit/was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject himself/herself, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event.
- Moved from the study area.
- Lost to follow-up.
- Death.
- ***Unblinding upon the subject's request to allow the subject to decide if he/she will consider immunization with a licensed HZ vaccine.***

(Amended 18 April 2014)

- Other (specify).

9.2.2. Subject withdrawal from investigational vaccine

A 'withdrawal' from the investigational vaccine refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from

the date of withdrawal. A subject withdrawn from the investigational vaccine may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the investigational vaccine will be documented on the Vaccine Administration screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the subject himself/herself, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Other (specify).

10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

10.1. Primary endpoint

- Confirmed HZ cases
  - Confirmed HZ cases during the study in the modified total vaccinated cohort (mTVc).

10.2. Secondary endpoints

- Occurrence of overall PHN
  - Incidence of PHN calculated using the mTVc;
- Duration of severe ‘worst’ HZ-associated pain
  - Duration of severe ‘worst’ HZ-associated pain following the onset of a confirmed HZ rash over the entire pain reporting period as measured by the ZBPI in subjects with confirmed HZ;
- Incidence of overall and HZ-related mortality
  - Incidence of overall and HZ-related mortality during the study;
- Incidence of HZ complications
  - Incidence of HZ complications during the study in subjects with confirmed HZ;
- Incidence of overall and HZ-related hospitalizations
  - Incidence of overall and HZ-related hospitalizations during the study;

- Duration of pain medication administered for HZ
  - Duration of pain medication administered for HZ during the study in subjects with confirmed HZ;
- Solicited local and general symptoms in a subset of subjects
  - Occurrence, intensity of each solicited local symptom within 7 days (Days 0 – 6) after each vaccination, in subjects included in the 7-day diary card subset;
  - Occurrence, intensity and relationship to vaccination of each solicited general symptom within 7 days (Days 0 – 6) after each vaccination, in subjects included in the 7-day diary card subset;
- Unsolicited AEs
  - Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days (Days 0 – 29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification, in all subjects;
- Serious AEs
  - Occurrence and relationship to vaccination of all SAEs from Month 0 to Month 14 in all subjects;
  - Occurrence of SAEs related to study participation or to a concurrent GSK medication/vaccine during the entire study period in all subjects;
  - Occurrence of any fatal SAEs during the entire study period in all subjects;
- Occurrence of pre-defined AEs
  - Occurrence and relationship to vaccination of any pIMDs during the entire study period in all subjects;
- Occurrence of medically attended visits
  - Occurrence and relationship to vaccination of medically attended visits (defined as hospitalizations, emergency room visits or visits to or from medical personnel), other than routine health care visits, from Month 0 to Month 8 in all subjects.

10.3. Exploratory endpoints

- Acute HZ severity
  - Acute HZ severity as determined by the mean Area Under Curve (AUC) of the severity-by-duration of HZ-associated pain as measured by the ZBPI during a 4-week period following the onset of confirmed HZ in subjects with confirmed HZ;
- Interference of HZ with QoL
  - Interference of HZ with QoL as measured by ZBPI in subjects with confirmed HZ;

  - Interference of HZ with QoL as measured by EQ-5D in subjects with confirmed HZ;
  - Interference of HZ with QoL as measured by SF-36 in subjects with confirmed HZ;
- HZ BOI
  - HZ BOI as determined by the mean AUC of the severity-by-duration HZ-associated pain during a 26 week period following the onset of the HZ rash in the mTVc;
- CMI in terms of frequencies of antigen-specific CD4 T cells at Months 0, 3, 14, 26 and 38
  - Frequencies of CD4 T cells with antigen-specific Interferon gamma (IFN-γ) and/or Interleukin-2 (IL-2) and/or Tumour Necrosis Factor alpha (TNF-α) and/or CD40 Ligand (CD40L) secretion/expression to gE and VZV as determined by ICS in a subset of subjects at Months 0, 3, 14, 26 and 38;
- Antigen-specific Ab concentrations at Months 0, 3, 14, 26 and 38
  - Anti-gE and anti-VZV Ab concentrations as determined by ELISA, in a subset of subjects at Months 0, 3, 14, 26 and 38;
- Anti-VZV neutralizing Ab titres at Months 0, 3, 14, 26 and 38
  - Anti-VZV neutralizing Ab titres as determined by the neutralization assay in a subset of subjects at Months 0, 3, 14, 26 and 38

10.4. Estimated sample size

10.4.1. Sample size assumptions

Table 18 presents the assumptions used for the sample size calculations for both studies ZOSTER -006 and ZOSTER-022. Simulations were performed to estimate the sample size required as a consequence of unequal VE estimates by age strata. A drop-out rate of 5% per year and an incidence of 5% for non-compliance to vaccine schedule were taken into account for sample size calculations.

Table 18 Assumptions for incidences under placebo, and VE used for trial simulations

Age	HZ Incidence (% / Year)	HZ VE	PHN Incidence in HZ subjects (% /Year)	On top PHN VE in HZ subjects (2)	Overall PHN VE
Overall(1)	~0.7	~68%	~11%	NA	~71%
50-59	0.5	82%	5%	5%	83%
60-69	0.8	72%	9.5%	5%	73%
70-79	1.1	58%	17%	35%	73%
≥80	1.1	36%	28%	25%	52%
≥70 (1)	1.1	~53%	~19%	NA	~71%

[1] The overall HZ incidence and the incidence in the ≥ 70YOA age strata depends on the age-stratification considered
[2] VE against PHN in people with HZ, i.e., a comparison of VE between placebo recipients with HZ who got PHN versus vaccine recipients with HZ who got PHN.

10.4.2. Significance level

The overall efficacy analyses will be performed at the 5% 2-sided significance level. No significance adjustment is planned in ZOSTER-006 or ZOSTER-022 for the efficacy analyses due to the futility analyses, since GSK has no current intention to submit the data to Regulatory Authorities for registration.

The scope of the statistical testing of ZOSTER-006, ZOSTER-022 and the pooling of the data from both studies are described in Section 10.4.4 and summarised in Table 19. The pooled analysis of studies ZOSTER-006 and ZOSTER-022 is planned provided the following conditions are met, as defined in Section 10.4.4:

1. Clinically meaningful overall HZ VE in subjects ≥ 50 YOA is reached in ZOSTER-006;
2. Clinically meaningful HZ VE is reached in subjects ≥ 70 YOA in ZOSTER-022**.**

(Amended 18 April 2014)

The pooled analysis of data in subjects ≥ 50 YOA accrued in study ZOSTER-006 and data in subjects ≥ 70 YOA collected in study ZOSTER-022 allows ***for the*** estimation of overall PHN VE ***(subjects ≥ 50 YOA)***, PHN VE in subjects ≥ 70 YOA ***and a more robust estimation of HZ VE in subjects ≥ 70 YOA (as*** HZ VE in subjects ≥ 70 YOA will be assessed in study ZOSTER-022***)***. **(Amended 18 April 2014)** An estimation of the confidence interval (CI), based on pooled data will be provided in addition. The statistical evaluation of the other objectives of the pooled analysis, including the overall PHN VE primary objective and the PHN VE in subjects with HZ secondary objective, will only be performed on the pooled data from both studies. According to these restrictions in the testing sequence, the type 1 error is maintained at 2.5% (1-sided). Each statistical evaluation in the pooled analysis is either preceded by an evaluation in ZOSTER-006, ZOSTER-022, or both; or is only performed on the pooled database during the pooled analysis. As a consequence, there is no increase in the significance level of each objective due to a possible multiple testing problem.

Table 19 Summary of statistical *inferential* evaluations of primary and secondary objectives for studies ZOSTER-006, ZOSTER-022 and the pooled analysis (Amended 18 April 2014)

Analysis	Endpoint	50-59 YOA	60-69 YOA	≥70 YOA	All age strata
ZOSTER-006	HZ VE	S	S	O	P
	PHN VE	-	-	-	-
	PHN VE in HZ subjects	-	-	-	-
ZOSTER-022	HZ VE	-	-	P	-
	PHN VE	-	-	-	-
	PHN VE in HZ subjects	-	-	-	-
Pooled analysis	HZ VE	-	-	R	-
	PHN VE	-	-	***P***	***S***
	PHN VE in HZ subjects	-	-	-	S*

P: Primary objective, well powered
R: Re-estimation of VE for an objective already demonstrated previously in ZOSTER-006 or ZOSTER-022.
S: Secondary objective, appropriately powered
S*: Secondary objective, low power
O: Study not well powered under current assumptions although may lead to significance
- : Estimates not relevant or not considered for a statistical evaluation

10.4.3. Success criteria

The ZOSTER-006 study is designed to demonstrate clinically meaningful overall HZ VE in subjects of ≥ 50 YOA. Clinically meaningful overall HZ VE will be demonstrated if the lower limit of the 95% CI is above 25%; however, the study has been powered for the more robust lower limit of 40%. That primary analysis will be supported by sensitivity analyses of the HZ VE in the 50-59 YOA and 60-69 YOA strata. Clinically meaningful HZ VE by age strata will be demonstrated if the lower limit of the 95% CI is above 10%. The ZOSTER-006 study is not powered to demonstrate significant HZ VE within the ≥ 70 YOA stratum. That objective is not within the scope of this study and is deferred to the analysis of ZOSTER-022 study data.

The ZOSTER-022 study is designed to demonstrate clinically meaningful HZ VE in subjects ≥ 70 YOA. Clinically meaningful HZ VE will be demonstrated in that age range if the lower limit of the 95% CI is above 10%. The ***pooled analysis of the ZOSTER-006 and*** ZOSTER-022 ***studies*** is powered to demonstrate statistical***ly*** significant PHN VE ***in subjects ≥ 70 YOA***. Statistical significance of PHN VE in ≥ 70 YOA randomized subjects will be demonstrated if the lower limit of the 95% CI is above 0%. The PHN VE co-primary objective ***of the pooled ZOSTER-006 and ZOSTER-022 studies*** will be tested provided the primary HZ VE is demonstrated ***in each study*** and no adjustment of significance level will be made. **(Amended 18 April 2014)**

Both studies ZOSTER-006 and ZOSTER-022 will be performed in parallel, in similar centres and using essentially identical study designs (aside from the age distribution of the enrolled population). The pooled analysis of those 2 studies is therefore deemed acceptable and will provide additional precision in estimating VE. Homogeneity of relative risk between the 2 studies will be demonstrated. ***The primary analysis to demonstrate efficacy for overall PHN in subjects ≥ 70 YOA will be performed on the pooled studies ZOSTER-006 and ZOSTER-022. In addition, t***he pooled analysis of

studies ZOSTER-006 and ZOSTER-022 is intended to provide consolidated estimations of the clinically meaningful HZ VE in all subjects ≥ 70 YOA in mTVc subjects randomized to studies ZOSTER-006 and ZOSTER-022. Clinically meaningful HZ VE in subjects ≥ 70 YOA will be demonstrated if the lower limit of the 95% CI is above 10% and clinically meaningful overall PHN VE ***in all subjects ≥ 70 YOA*** will be demonstrated if the lower limit of the 95% CI is above ***0***%. **(Amended 18 April 2014)**

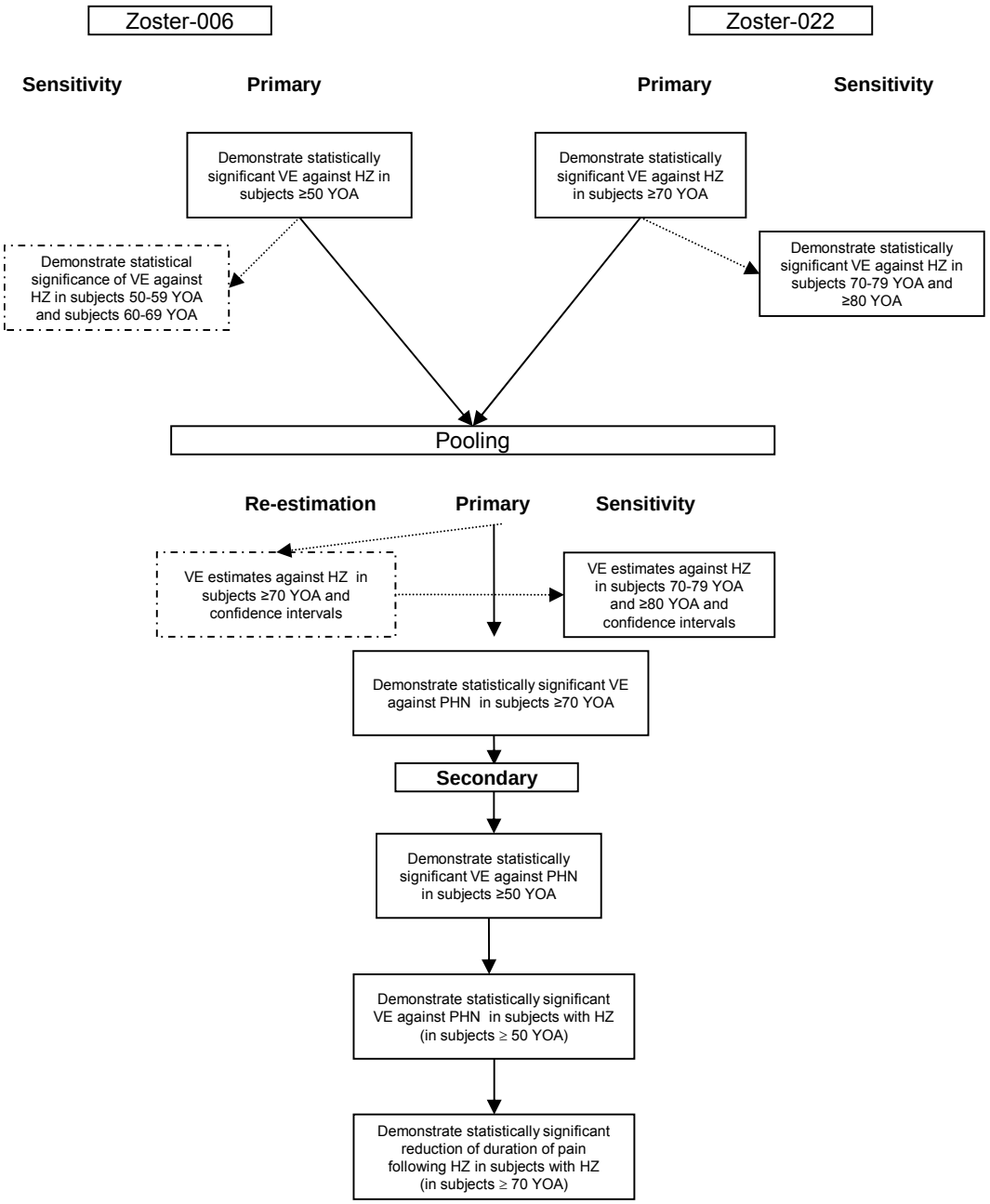
10.4.4. Gatekeeping strategy

The statistical testing for each study will proceed sequentially using an order for the gatekeeping families defined prospectively (see below). If more than one test is involved within the same family, the Hochberg's set up method [Hochberg, 1988] will be used to adjust the p-values for the multiple test schemes. All secondary objectives mentioned in protocols ZOSTER-006 and ZOSTER-022 will be evaluated within each report. However, the overall type 1 error of 5% two-sided can only be fully controlled for those objectives that are mentioned sequentially in the gatekeeping strategy presented below. If a gatekeeping family fails to be demonstrated, the remaining planned tests will be performed, but the type 1 error of the following families may not be fully controlled.

The enrolment of subjects ≥ 70 YOA in both studies and the need to provide an estimation of the HZ VE and PHN VE across the two studies, requires the gatekeeping strategy to be defined across the two studies and the pooling ***(see Figure 1)*** **(Amended 18 April 2014)**. The following pathway is proposed and will be confirmed prior to unblinding of the treatment assignment.

The primary objective of ZOSTER-006 and ***the*** primary objective of ZOSTER-022 should be demonstrated prior to testing the primary objective of the pooling. Sensitivity analyses will be performed by age strata for each of the primary objectives. **(Amended 18 April 2014)**

***Figure 1 Gatekeeping strategy* (Amended 18 April 2014)**



The primary objectives of the pooling include the re-estimation of HZ VE ***in subjects ≥ 70 YOA*** and ***estimation of*** PHN VE in subjects ≥ 70 YOA. ***The HZ VE is planned to be already demonstrated in ZOSTER-022 and the pooled PHN VE will be the primary analysis of PHN; as a consequence, they do not affect the overall type 1 error and are not considered within the main path of the gatekeeping strategy.***

The first hypothesis to be tested from the pooled dataset consists in the overall PHN VE in subjects ≥ ***70*** YOA. Further secondary objectives are then sequentially tested following demonstration of overall PHN VE ***in subjects ≥ 70 YOA***.

1. ***Demonstrate statistically significant reduction in incidence of PHN (90 days or more) in subjects ≥ 50 YOA***
2. Demonstrate statistically significant reduction in incidence of PHN (90 days or more) in subjects with HZ ***(in subjects ≥ 50 YOA)***
3. Demonstrate statistically significant reduction of duration of severe 'worst' pain following HZ in subjects with HZ ***(in subjects ≥ 70 YOA)***.

(Amended 18 April 2014)

10.4.5. Sample sizes

The sections below describe the estimated number of subjects required to achieve the objectives of studies ZOSTER-006, ZOSTER-022 and the pooling of data from both studies. The provisional country allocation and various subsets are also described. For operational reasons, the same subjects may be randomized to the more than one subset.

10.4.5.1. Primary objective

The final ***HZ efficacy*** analysis of the ZOSTER-006 study is planned after the accumulation of at least 196 confirmed HZ cases across all age strata (primary condition) in the primary cohort for efficacy. **(Amended 18 April 2014)** Other conditions for triggering the analyses are described in Section 10.4.5.6. It is estimated that 196 confirmed HZ cases would provide ~97% power to demonstrate an overall HZ VE of at least 40% assuming a true HZ VE of 68% (including essential sensitivity analyses in 50-59 and 60-69 YOA strata). Table 20 presents the sample sizes overall and according to the age-stratification ratio 8:5:3:1 (50-59, 60-69, 70-79 and ≥ 80 YOA) using a randomization ratio 1:1 for vaccine or placebo. The sample size was selected in order to provide the required number of HZ cases within a follow-up time of ~3 years. The stratification ratios were selected in order to achieve similar numbers of HZ cases in the three main age strata. If large disparities in the total number of HZ cases (placebo and vaccine groups combined) are observed during the trial between the age strata, sample size reassessment or modification of the stratification ratios may be considered.

Table 20 Expected number of HZ and PHN cases in ZOSTER-006 (Amended 18 April 2014)

Age strata	Sample size	Median number of HZ cases		Median number of PHN cases *(initial assumptions)*		*Expected number of PHN cases (projection based on current accrual rates)*	
		Placebo	All	Placebo	All	***Placebo***	***All***
50-59 YOA	7520	48	57	3	3	***4***	***5***
60-69 YOA	4700	48	62	4	6	***5***	***7***
70-79 YOA	2820	40	56	6	8	***4***	***5***
≥ 80 YOA	940	13	22	4	5	***1***	***2***
All	15980	149	196	17	23	***14***	***19***

Median number of cases calculated based on 1000 trial simulations.

The final ***HZ efficacy*** analysis of the ZOSTER-022 study is planned after the accumulation ***of*** at least 278 confirmed HZ cases (expected median number of cases is 310 HZ cases) across both 70-79 YOA (expected median of 222 HZ cases) and ≥ 80 YOA (expected median of 87 HZ cases) strata. All HZ cases should be accrued in the primary cohort for efficacy. **(Amended 18 April 2014)** Other conditions for triggering the analyses are described in Section 10.4.5.6. This number of HZ cases would provide ~99% power to demonstrate HZ VE of at least 10% under the assumptions described above in subjects ≥ 70 YOA.

The end of study analyses of the ZOSTER-006 and the ZOSTER-022 studies are planned after the accumulation at least 35 PHN cases in subjects ≥ 70 YOA in the pooled ZOSTER-006 and ZOSTER-022. All PHN cases should be accrued in the primary cohort for efficacy. Other conditions for triggering the analyses are described in Section 10.4.5.6. This number of PHN cases would provide ~90% power to demonstrate PHN VE with Lower Limit (LL) above 0%. **(Amended 18 April 2014)**

Table 21 presents the sample sizes overall and according to the age-stratification ratio 3:1 (70-79 and ≥ 80 YOA) and a randomization ratio 1:1. The sample size was selected in order to provide the required number of HZ cases within a follow-up time of ~3 years. If the accrual rate of HZ or PHN cases is much lower than expected, a blinded sample size reassessment may be considered for which the details would be available prior to the first interim analysis.

Table 21 Expected number of HZ and PHN cases in ZOSTER-022 (Amended 18 April 2014)

Age strata	Sample size	Median number of HZ cases		Median number of PHN cases *(initial assumptions)*		*Expected number of PHN cases (projection based on current accrual rates)*	
		Placebo	All	Placebo	All	***Placebo***	***All***
70-79 YOA	10884	157	222	32	40	***15***	***20***
≥ 80 YOA	3628	54	87	17	26	***5***	***8***
All	14512	210	310	49	65	***20***	***28***

Median number of cases calculated based on 1000 trial simulations.

The number of HZ cases, PHN cases and the total sample size for each age strata for the **pooled** analysis are driven by the number of the cases and sample size in both the ZOSTER-006 and ZOSTER-022 studies (see Table 22). The total number of PHN cases and the number of PHN cases in subjects ≥ 70 YOA that each study (ZOSTER-006 and ZOSTER-022) will contribute to the pooled analysis may vary from what has been described above. It is estimated however that the total number of PHN cases in ≥ 50 YOA subjects is approximately ***47***, among which at least ~***35*** PHN cases would be accrued in the ≥ 70 YOA age strata. A total of at least ***35*** PHN cases provide ***90***% power to demonstrate ***in subjects ≥ 70 YOA*** an overall PHN VE of at least ***0***%. **(Amended 18 April 2014)**

Table 22 Expected number of HZ and PHN cases in pooled ZOSTER-006 and ZOSTER-022 (Amended 18 April 2014)

Age strata	Sample size	Median number of HZ cases		Median number of PHN cases *(initial assumptions)*		*Expected number of PHN cases (projection based on current accrual rates)*	
		Placebo	All	Placebo	All	***Placebo***	***All***
50-59 YOA	7520	48	57	2	3	***4***	***5***
60-69 YOA	4700	48	61	4	6	***5***	***7***
70-79 YOA	13704	196	278	32	48	***19***	***25***
≥ 80 YOA	4568	57	110	17	31	***6***	***10***
All	30492	360	506	57	88	***34***	***47***

Median number of cases calculated based on 1000 trial simulations.

10.4.5.2. Secondary objectives

The ZOSTER-006 sample size is sufficient to demonstrate a HZ VE of at least 10% for the 50-59 YOA and 60-69 YOA age strata with powers of 99% and 98%, respectively.

The ZOSTER-022 sample size is sufficient to demonstrate a HZ VE of at least 10% for the ≥ 70 YOA stratum with a power of 99%.

The sample size of the pooled studies ZOSTER-006 and ZOSTER-022 provide ***10***% chance to demonstrate statistically significant PHN VE (LL above 0%) in those subjects presenting with an HZ episode. **(Amended 18 April 2014)**

10.4.5.3. Futility analyses and sample size re-assessment

The study may involve one (or more) unblinded futility analyses performed by the IDMC. One futility analysis is planned after at least 25% of the total number of HZ cases anticipated at final ***HZ efficacy*** analysis are observed in Zoster-006 (see Table 20), and when at least 20% of the total number of HZ cases anticipated at final ***HZ efficacy*** analysis within each age stratum (50-59 YOA, 60-69 YOA and 70+ YOA) are observed (see Table 20). **(Amended 18 April 2014)** Note that HZ cases from ZOSTER-022 may be used to meet the required number of 70+ YOA cases. The precise timing of that analysis will be determined by a blinded review of the HZ case accrual in ZOSTER-006 and/or ZOSTER-022. The futility decision rules will be described in the RAP. Essentially, no increase in the type 1 error of the final ***HZ efficacy*** analysis is incurred as no decision of early termination for efficacy will be made by GSK at any of those

analyses. **(Amended 18 April 2014)** Adequate trial duration is required to accumulate enough PHN information and safety information necessary for regulatory purposes. Conversely, a slight reduction in the power of the study can be caused due to the futility rules. A conservative futility boundary or a predictive power threshold [Proschan, 2006] in the range of ~30% is anticipated but the actual functional form of the beta-spending function or the predictive power threshold used for the trial will be defined in the RAP. Information collected in both trials may be combined to calculate the predictive power for each trial separately and together.

Table 23 below provides information about the ZOSTER-006 conditional power with respect to the overall HZ VE LL 40% (i.e. without consideration for by-age HZ VE LL 10%) calculated following 25% of accrual and for different values of the observed HZ VE or futility boundaries. Irrespective to the futility boundary considered, the conditional power calculated under the sample size (alternative) assumptions remains very high although the conditional power calculated under the observed HZ VE is close to zero. A more reasonable prediction for the power at the final ***HZ efficacy*** analysis that will be implemented is the expected conditional power or Bayesian predictive power, following integration of the conditional power on the posterior distribution of the VE in each age strata and accounting for the proportion density of each stratum in the total number of HZ cases at the final ***HZ efficacy*** analysis. **(Amended 18 April 2014)**

Table 23 Observed HZ VE at ZOSTER-006 Interim to trigger futility stopping and conditional power at the final *HZ efficacy* analysis calculated under alternative hypothesis and current observed VE (Amended 18 April 2014)

						VE Confidence Interval[e]	
Futility analysis	Rho[a]	# HZ cases	Observed VE[b]	CP under alternative[c]	CP under observed VE[d]	Lower Limit	Upper Limit
1	1	49	33.6%	87.2%	0.0%	-102.6%	70.8%
2	1	98	46.9%	78.8%	1.8%	0.2%	69.5%
1	2	49	24.7%	81.5%	0.0%	-137.4%	71.8%
2	2	98	44.6%	71.5%	0.6%	-4.2%	69.7%
1	3	49	17.0%	76.1%	0.0%	-168.1%	72.5%
2	3	98	42.5%	64.3%	0.2%	-8.2%	69.9%
1	4	49	9.7%	69.7%	0.0%	-201.7%	73.2%
2	4	98	40.4%	56.5%	0.0%	-12.3%	70.1%

a: Rho defines the form of the futility boundary. A conservative (O'Brian-Fleming) boundary is defined for Rho=3 and a more aggressive (Pocock) boundary is defined for Rho = 1.
b: Observed HZ VE that triggers futility conditions at each futility analysis.
c: Conditional power at the final ***HZ efficacy*** analysis calculated under the sample size (alternative) assumptions
d: Conditional power at the final ***HZ efficacy*** analysis calculated under the observed HZ VE at the interim (Amended 18 April 2014)
e: HZ VE repeated confidence interval and approximate VE posterior distribution at the interim over which the mean (expected) conditional power may be calculated.

Table 24 below provides information about the ZOSTER-022 conditional power with respect to the HZ VE LL 40% in subjects of ≥ 70 YOA (i.e., without consideration for statistically significant PHN VE in subjects of ≥ 70 YOA) calculated following 25% of

accrual and for different values of the observed HZ VE or futility boundaries. Irrespective to the futility boundary considered, the conditional power calculated under the sample size (alternative) assumptions remains very high although the conditional power calculated under the observed HZ VE is close to zero. A more reasonable prediction for the power at the final ***HZ efficacy*** analysis that will be implemented is the expected conditional power or Bayesian predictive power, following integration of the conditional power on the posterior distribution of the VE in each age strata and accounting for the proportion density of each stratum in the total number of HZ cases at the final ***HZ efficacy*** analysis. **(Amended 18 April 2014)**

Table 24 Observed HZ VE at ZOSTER-022 Interim to trigger futility stopping and conditional power at the final *HZ efficacy* analysis calculated under alternative hypothesis and current observed VE (Amended 18 April 2014)

Futility analysis	Rho[a]	# HZ cases	Observed VE[b]	CP under alternative[c]	CP under observed VE[d]	VE Confidence Interval[e]	
						Lower Limit	Upper Limit
1	1	77	18.7%	79.6%	0.1%	-85.7%	53.2%
2	1	155	31.3%	71.4%	3.4%	-9.6%	52.7%
1	2	77	8.5%	71.7%	0.0%	-112.6%	53.7%
2	2	155	28.5%	62.1%	1.0%	-14.1%	52.8%
1	3	77	-0.2%	64.1%	0.0%	-136.3%	54.0%
2	3	155	26.0%	53.2%	0.3%	-18.1%	52.9%
1	4	77	-8.4%	56.3%	0.0%	-160.8%	54.3%
2	4	155	23.5%	44.5%	0.1%	-22.3%	53.0%

a. Rho defines the form of the futility boundary. A conservative (O'Brian-Fleming) boundary is defined for Rho=3 and a more aggressive (Pocock) boundary is defined for Rho = 1.
b. Observed HZ VE that triggers futility conditions at each futility analysis.
c. Conditional power at the final ***HZ efficacy*** analysis calculated under the sample size (alternative) assumptions
d. Conditional power at the final ***HZ efficacy*** analysis calculated under the observed HZ VE at the interim (Amended 18 April 2014)

HZ VE repeated confidence interval and approximate VE posterior distribution at the interim over which the mean (expected) conditional power may be calculated.

The futility approach, whether by futility boundary or conditional or predictive power implemented is not-bounding with regards to the decision actually taken at the time of the analysis. The IDMC recommendations with regards to futility of the study may not be endorsed by GSK Steering Committee without affecting the overall significance level.

Blinded sample size reassessment may be performed by GSK in one or more age strata in order to keep the same trial duration if accrual is much lower than expected. The sample size re-evaluation will be done independently from the data provided to the IDMC. Conditions for the sample size reassessment need to be defined further.

10.4.5.4. Provisional region and sub-population allocations

The provisional region allocation for study ZOSTER-006 is presented in Table 25. Enrolment target numbers per region are approximate and may change depending on the

enrolment. In study ZOSTER-006, eligible subjects will be randomized to investigational vaccine/placebo according to a 1:1 ratio.

Subjects will be stratified by age: 50-59 YOA; 60-69 YOA; 70-79 YOA and ≥ 80 YOA in approximately an 8:5:3:1 ratio. The main ≥ 70 YOA stratum used for sample size calculation is subdivided into 70-79 and ≥ 80 YOA strata in order to demonstrate efficacy ≥ 80 YOA or in any of these 2 sub-strata taken separately. The study is however not powered to demonstrate efficacy in any of these 2 sub-strata taken separately. In addition, some small percentages of the sample will include frail elderly subjects.

Table 25 Provisional region allocation for study ZOSTER-006

Australasia		Europe		Latin America		North America	
Country	Sample Size	Country	Sample Size	Country	Sample Size	Country	Sample Size
Australia Hong Kong Japan S. Korea Taiwan	***~3410***	Czech Republic Estonia Finland France Germany Italy Spain Sweden United Kingdom	***~7345***	Brazil Mexico	***~2615***	Canada US	***~2610***

10.4.5.5. 7-day diary card subset

The number of subjects in this subset was defined based on the empirical rules that, in absence of a specific AE in a cohort of N subjects, the probability is 95% that the incidence of that AE is less than 1 / (N/3) [Hanley, 1983].

The provisional number of subjects in the 7-day diary card subset in study ZOSTER-006 is shown in Table 26.

Table 26 Provisional number of subjects in the 7-day diary card subset in study ZOSTER-006

Age cohort	50-59 YOA		60-69 YOA		70-79 YOA		≥ 80 YOA		All	
Treatment group	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo
ZOSTER-006	1410	1410	1410	1410	1410	1410	470	470	4700	4700

Note: In addition, study ZOSTER-022 will include a 7-day diary card subset of 1008 subjects (in respectively the 70-79 YOA and ≥ 80 YOA strata, there are 252 subjects in each treatment group).

10.4.5.6. Immunogenicity Subset

10.4.5.6.1. Assumptions and background information for humoral immunity

Assumptions to estimate the number of subjects to be included in the immunogenicity subset in study ZOSTER-006 and ZOSTER-022 were based on gE-specific humoral

immunogenicity data obtained in study ZOSTER-003 for subjects who received two doses of gE 50 μg/AS01$_B$.

10.4.5.6.2. Humoral immune response vaccine take

The humoral vaccine take is assessed in comparison to placebo group using anti-gE or anti-VZV Ab concentrations. The increase observed post dose 2 in study ZOSTER-003 in the gE 50μg/AS01$_B$ group as compared with placebo is about 10-fold for anti-gE Abs. The CV is about 100% (or In-based variance = 0.693 = 0.832²), accounting for higher variability in the current study as compared to study ZOSTER-003 due to, but not limited to, inter-country variations. A 4-fold increase in geometric mean over placebo as a lower bound for clinical relevance, in absence of other justification, adjusted for pre-vaccination level, is considered as a threshold for clinical relevance, and will be used as criteria to demonstrate vaccine take.

When expressed on the log-scale, the effect size for clinical significance is Ln(10) / 0.832 = 2.76. When accounting for the superiority requirement of a 4-fold increase over NaCl solution, the effect size is 2.76 – Ln(4) / 0.832= 1.10. Despite the number of blood samplings that should be administered in vaccine and placebo according to the study randomization ratio, it is also reasonable to analyze twice as much vaccine samples than placebo samples. The overall power of the test is conventionally set to ~95% and the type 1 error to 2.5%. Since we may be required to demonstrate that success criteria in all countries involved in the trial, accounting for ~15 countries, the power of the test in each country should be 0.95^(1/15) = 0.996.

Table 27 presents the number of subjects under vaccine (N1) and placebo (N2) required to demonstrate a 4-fold increase in anti-gE Ab concentration geometric means over saline. The number of evaluable blood samples required in each country at post dose 2 is ~55 for vaccine and ~28 for placebo for an overall power of 0.996^15 = 0.95. A slight increase in that number of subjects may be needed as the sample size should be a multiple of 3 for the age stratification. Overall, accounting for the same number of subjects to be sampled in vaccine and placebo groups in each of the 15 to 18 countries in order to maintain the blind, and to have a sufficiently large number of evaluable blood samples, the total number of subjects enrolled into the subset should approximately be 18 x 60 x 2 = ~2160**.** No comparisons are planned within each age strata at the country level.

Table 27 Power calculations for a T-test for Relevant Superiority

Power	N1/N2	Equivalence margin (E)	Actual difference (D)	Significance level		Standard deviation	
				alpha	beta	SD1	SD2
0.99839	61/32	13.90	23.00	0.02500	0.00161	8.32	8.32
0.99648	55/28	13.90	23.00	0.02500	0.00352	8.32	8.32
0.99413	51/26	13.90	23.00	0.02500	0.00587	8.32	8.32
0.99245	49/26	13.90	23.00	0.02500	0.00755	8.32	8.32
0.99031	47/24	13.90	23.00	0.02500	0.00969	8.32	8.32
0.95043	34/17	13.90	23.00	0.02500	0.04957	8.32	8.32
0.90324	28/14	13.90	23.00	0.02500	0.09676	8.32	8.32

Means & SD were multiplied by a 10-fold coefficient in order to allow more precision in the outputs.
N1, N2: number of subjects receiving vaccine (N1) and placebo (N2)

10.4.5.6.3. Humoral immune response inter-region variability

Following the objective of vaccine take, the vaccine geometric mean responses between countries can be compared. This comparison consists of selecting two countries, or group of countries and comparing their means in order to demonstrate equivalence since defining the success criteria in terms of "statistical significance" is not meaningful in this situation. The absence of statistical significance would not support the absence of clinical relevance between regions or countries.

Using Ratio of Geometric Means – Region-wise

An equivalence criteria of 2-fold is considered acceptable when referring to the ratio of geometric means between regions. This threshold ensures that any differences between countries are not clinically relevant as it corresponds to half of the 4-fold increase over placebo, considered as the minimally clinically relevant difference.

The same assumptions as above are used for the calculations. ZOSTER-010 data showed a ratio of geometric means equal to 1.26 between EU and US. A pairwise comparison between each of the 4 main regions may be considered, leading to 6 comparisons. The power of each test should be ~99% for a global power of ~95%.

Table 28 presents the sample size for each individual comparison, assuming absence of true difference between regions, assuming ratio of geometric means equal to 0, 90% (Ln = -0.10) and 75% (Ln = -0.29). A sample size of approximately 60 subjects under vaccine within each region would allow demonstrating equivalence of the two geometric means within a non-clinically relevant range of 2-fold, provided absence of difference in means (true difference = 0). Since each region includes several countries, a pool of at least 3 countries is sufficient within each region to allow the comparison when the ratios of geometric means reach 75%.

Table 28 Power Testing Equivalence Using a Parallel-Group Design (Region)

	Reference Group	Treatment Group						
Power	Sample Size (N1)	Sample Size (N2)	Lower Equiv Limit	Upper Equiv Limit	True Difference	Standard Deviation	Alpha	Beta
0.7490	60	60	-6.93	6.93	-2.90	8.32	0.0250	0.2510
0.9630	120	120	-6.93	6.93	-2.90	8.32	0.0250	0.0370
0.9957	180	180	-6.93	6.93	-2.90	8.32	0.0250	0.0043
0.9996	240	240	-6.93	6.93	-2.90	8.32	0.0250	0.0004
0.9714	60	60	-6.93	6.93	-1.00	8.32	0.0250	0.0286
0.9998	120	120	-6.93	6.93	-1.00	8.32	0.0250	0.0002
1.0000	180	180	-6.93	6.93	-1.00	8.32	0.0250	0.0000
1.0000	240	240	-6.93	6.93	-1.00	8.32	0.0250	0.0000
0.9897	60	60	-6.93	6.93	0.00	8.32	0.0250	0.0103
1.0000	120	120	-6.93	6.93	0.00	8.32	0.0250	0.0000
1.0000	180	180	-6.93	6.93	0.00	8.32	0.0250	0.0000
1.0000	240	240	-6.93	6.93	0.00	8.32	0.0250	0.0000

Note: Means and Standard Deviation were multiplied by 10 to achieve sufficient precision

If those comparisons should be made within each age strata, leading to a total of 3*6 comparisons, the power of each comparison should be closer to 99.7% in order to maintain the overall power to 0.997^18 = 0.95. The number of countries to be involved in the comparisons should then be at least 4.

Using Ratio of Geometric Means – Country-wise

The same calculations may be performed on a country basis. The table below provides the power for a comparison of one country versus the rest of the world, assuming 15 countries and a ratio of geometric mean equal to 0.90 (LN = -0.10) and 75% (LN = -0.29). A sample of 60 subjects in the country selected is sufficient to allow the comparison versus 900 subjects with a power of at least 95%.

Table 29 Power Testing Equivalence Using a Parallel-Group Design (Country)

	Reference Group	Treatment Group						
Power	Sample Size (N1)	Sample Size (N2)	Lower Equiv Limit	Upper Equiv Limit	True Difference	Standard Deviation	Alpha	Beta
0.9553	60	900	-6.93	6.93	-2.87	8.32	0.0250	0.0447
0.9757	70	900	-6.93	6.93	-2.87	8.32	0.0250	0.0243
0.9868	80	900	-6.93	6.93	-2.87	8.32	0.0250	0.0132
0.9929	90	900	-6.93	6.93	-2.87	8.32	0.0250	0.0071
0.9962	100	900	-6.93	6.93	-2.87	8.32	0.0250	0.0038
0.9996	60	900	-6.93	6.93	-1.00	8.32	0.0250	0.0004
0.9999	70	900	-6.93	6.93	-1.00	8.32	0.0250	0.0001
1.0000	80	900	-6.93	6.93	-1.00	8.32	0.0250	0.0000
1.0000	90	900	-6.93	6.93	-1.00	8.32	0.0250	0.0000
1.0000	100	900	-6.93	6.93	-1.00	8.32	0.0250	0.0000

Note: Means and Standard Deviation were multiplied by 10 to achieve sufficient precision

10.4.5.6.4. Number of subjects in the Immunogenicity subset

Table 30 provides the provisional number of subjects in the Immunogenicity subset in study ZOSTER-006. CMI analysis will be performed in the Immunogenicity subset of three countries (Czech Republic, Japan and United States). These countries will have approximately 156 subjects per country enrolled in the immunogenicity subset. Other countries will have approximately 138 subjects per country enrolled in the immunogenicity subset.

Subjects will be randomized to be part of the Immunogenicity subset (Section 5.3.4). Blood samples obtained from subjects included in the Immunogenicity subset will be used to assess humoral immune responses. The number of placebo subjects and vaccine subjects that will have their blood sampled will be equal in order to maintain the blind. However, only a fraction of the placebo samples will be analyzed as a reduced sample is sufficient to characterise the background gE or VZV-specific immunogenicity levels in the placebo group.

Table 30 Provisional number of subjects in the Immunogenicity subset in study ZOSTER-006 (Amended 18 April 2014)

Age cohort	50-59 YOA		60-69 YOA		≥ 70 YOA		All		
Treatment group	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	***Total***
CMI countries[1]	26	26	26	26	26	26	78	78	***156***
Non-CMI countries[2]	23	23	23	23	23	23	69	69	***138***
All countries [1+2] (Total of 18 countries)							***1269***	***1269***	***2538***

[1] Czech Republic, Japan, United States

[2] Australia, Hong Kong, S. Korea, Taiwan, Estonia, Finland, Germany, Italy, Spain, Sweden, United Kingdom, France, Brazil, Mexico, Canada

10.4.5.7. CMI Subset

10.4.5.7.1. Assumptions and background information for CMI

Assumptions to estimate the number of subjects to be included in the CMI subset in study ZOSTER-006 were based on gE-specific CMI data obtained in study ZOSTER-003 for subjects who received two doses of gE 50 μg/$AS01_B$.

The frequency of CD4 T-cells producing at least 2 cytokines following induction with gE/$AS01_B$ will be estimated in both placebo and vaccine recipients, after adjustment for background CD4 T-cell frequency and pre-vaccination CD4 T-cell responses. The increase in CMI responses observed previously following administration of 2 doses of $gE_{[50\ \mu g]}$ /$AS01_B$ compared with saline is about 5.5-fold, and the coefficient of variation is about 100%. Therefore, a 1.5-fold increase over placebo in the frequency of activated CD4 T-cells is considered as a minimum target for vaccine take and was used as threshold for immunologic superiority. These figures were used for the sample size calculation.

When expressed on the log-scale, the effect size for clinical significance is Ln(5.5)/ 0.832 = 2.05. When accounting for a target of a 1.5-fold increase over saline, the effect size is 2.05 – Ln(1.5) /0.832 = 1.562. While the number of blood samplings will be collected in vaccine and placebo recipients according to the study randomization ratio, it is appropriate to analyze twice as many vaccine samples than placebo samples using an immunogenicity sample-randomization ratio of 2. Although this endpoint is purely exploratory, the overall power of this test is set to ~95% and the type 1 error to 2.5% per convention.

Table 31 presents the number of subjects under vaccine (N1) and placebo (N2) required to demonstrate a 1.5-fold increase over saline in frequency of gE-specific CD4 cells producing at least 2 cytokines. If the test is performed for each of the 3 age-ranges, the power of each test should be 98.1% in order to maintain the overall power at 0.981^3 = 0.94 (i.e., 94%). Twenty-one subjects in each of the 3 main age strata equals will have received vaccine or placebo, respectively, for a total number of 3 * 21 * 2 = 126 subjects. For this exploratory objective, the comparison is based upon one country only and, for instance, does not account for comparison across multiple countries and regions.

Table 31 Power Calculations for CMI subset

Power	N1/N2	Equivalence margin (E)	Actual difference (D)	Significance level		Standard deviation	
				Alpha	beta	SD1	SD2
0.99320	25/14	4.05	17.00	0.02500	0.00680	8.32	8.32
0.98871	23/12	4.05	17.00	0.02500	0.01129	8.32	8.32
0.98145	21/12	4.05	17.00	0.02500	0.01855	8.32	8.32
0.97242	20/10	4.05	17.00	0.02500	0.02758	8.32	8.32
0.95163	17/10	4.05	17.00	0.02500	0.04837	8.32	8.32

10.4.5.7.2. Number of subjects in the CMI subset

The CMI analyses will be performed in the Immunogenicity subset in three countries (Czech Republic, Japan and United States) at designated sites that have access to a PBMC processing facility within the acceptable time window from sample collection to PBMC processing. The CMI subset in these countries is expected to include 156 subjects to account for anticipated lost or non-evaluable samples, see Table 32.

Table 32 Provisional number of subjects in the CMI subset in study ZOSTER-006 (Amended 18 April 2014)

Age cohort	50-59 YOA		60-69 YOA		≥ 70 YOA		All		
Treatment group	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	***Total***
Each participating country	26	26	26	26	26	26	78	78	***156***
All countries (Total of 3 countries)							***234***	***234***	***468***

10.4.6. Conditions for triggering analyses

A comprehensive understanding of the extent to which the candidate vaccine prevents HZ in the various age strata involves the availability of results from both studies (ZOSTER-006 and ZOSTER-022). The database freeze and statistical analyses would then be triggered when **both** studies have achieved their conditions for triggering analyses. However, if one of the studies reached the conditions required for triggering the analyses and a delay of more than approximately 6 months is predicted prior to those conditions are reached for the second study, then GSK may decide to proceed with the analysis of the study that reaches its conclusion first. The conditions described below are minimum requirements prior to ***the specified analyses***. **(Amended 18 April 2014)** Additional HZ cases and/or PHN cases may be accrued as a result of the decision to wait for **both** studies to achieve the requirements simultaneously.

The following conditions are planned prior to final HZ ***efficacy*** analyses of study ZOSTER-006. The number of HZ and PHN cases mentioned refers to the cases in the primary cohort for efficacy.

1. At least 196 HZ cases across all age group for the overall HZ analysis;
2. ~75% of the initial sample size (not accounting for any sample-size reassessment) in each strata with at least 36 months follow-up and the remaining subjects have

completed at least 30 months follow-up after Dose 2 in order to ensure enough safety data;

3. Approximately 60 HZ cases in subjects 50-59 YOA and approximately 60 HZ cases in subjects 60-69 YOA for the HZ analysis by-age in 50-59 and 60-69 YOA age strata respectively;

(Amended 18 April 2014)

The ZOSTER-006 study will continue until an adequate number of HZ cases will be accrued in ZOSTER-022 and an adequate number of PHN cases will be accrued in both ZOSTER-006 and ZOSTER-022.

The end of study analysis of ZOSTER-006 will occur when the following conditions are met:

1. ***All previous conditions are met for final HZ efficacy analysis in study ZOSTER-022;***
2. ***A total of at least 35 PHN cases in subjects ≥ 70 YOA when pooled with ZOSTER-022 PHN cases are accrued.***

The end of study analysis cannot be performed before the final HZ efficacy analysis.

(Amended 18 April 2014)

The following conditions are planned prior to final HZ ***efficacy*** analyses of study ZOSTER-022. The number of HZ and PHN cases mentioned refers to the cases in the primary cohort for efficacy.

(Amended 18 April 2014)

1. At least 278 HZ cases accrue over both 70-79 and ≥ 80 YOA strata;
2. ~75% of the initial sample size (not accounting for any sample-size reassessment) in each stratum with at least 36 months of follow-up and the remaining subjects have completed at least 30 months follow-up after Dose 2 in order to ensure enough safety data.

The end of study analysis of ZOSTER-022 will occur when the following condition is met:

1. ***A total of at least 35 PHN cases in subjects≥ 70 YOA when pooled with ZOSTER-006 PHN cases are accrued.***

The end of study analysis cannot be performed before the final HZ efficacy analysis.

In study ZOSTER-022, depending on accrual of HZ and PHN cases, final HZ efficacy analysis may occur at the same time as the end of study analysis.

(Amended 18 April 2014)

10.4.7. Control of type I error for the two-steps analyses (Amended 18 April 2014)

Although, the analyses of ZOSTER-006 will be performed in two steps. Each objective will be assessed only once. Therefore no adjustment of type I error is needed.

(Amended 18 April 2014)

10.4.8. Maintaining the blind (Amended 18 April 2014)

It is planned to maintain the whole team (Central, Local, Investigators) and subjects blinded up to end of study.

A firewall team will be set up in order to allow the planned analyses to be performed and results reported to the relevant authorities while the study blind is maintained to the whole team and subjects. All details of this approach can be found in the firewall charter.

(Amended 18 April 2014)

10.4.9. *List of objectives assessed at each analysis step* (Amended 18 April 2014)

Table 33 ***provides, for studies ZOSTER-006 and ZOSTER-022, an overview of the analyses which will be performed at final HZ efficacy analysis (step 1) and end of study analysis (step 2), respectively.***

For ZOSTER-006, step 1 will include analyses of the following objectives:

- ***all HZ VE objectives;***
- ***all reactogenicity/safety and immunogenicity objectives.***

At step 2 all objectives of study ZOSTER-006 will be analyzed. Objectives already analyzed at step 1 will be re-analyzed (confirmatory descriptive in case of inferential analysis at step 1 or descriptive analysis otherwise).

At step 2, overall PHN VE in subjects ≥ 70 YOA, and other pre-specified endpoints will be analyzed in the pooled analyses of studies ZOSTER-006 and ZOSTER-022.

(Amended 18 April 2014)

***Table 33 Overview of analyses performed at each analysis step (ZOSTER-006, ZOSTER-022, pooled analysis of ZOSTER-006 and ZOSTER-022)* (Amended 18 April 2014)**

			First step* Final HZ efficacy analysis		Second step** End of study analysis	
			Analysis of objective Yes (Y) No (N) Not applicable (NA)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive	Analysis of objective Yes (Y) No (N)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive
ZOSTER-006						
Primary						
	Efficacy					
		To evaluate VE in the prevention of HZ compared to placebo in adults ≥ 50 YOA, as measured by the reduction in HZ risk.	Y	I	Y	CD
Secondary						
	Efficacy					
		To evaluate VE in the prevention of HZ compared to placebo in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, as measured by the reduction in HZ risk;	Y	I	Y	CD
		To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;	N	-	Y	D
		To evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;	N	-	Y	I
		To evaluate VE in the reduction of overall and HZ-related mortality and hospitalizations compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;	N	-	Y	I

			First step* Final HZ efficacy analysis		Second step** End of study analysis	
			Analysis of objective Yes (Y) No (N) Not applicable (NA)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive	Analysis of objective Yes (Y) No (N)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive
		To evaluate VE in the reduction in incidence of HZ-associated complications compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;	N	-	Y	I
		To evaluate VE in the reduction in use of pain medications compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;	N	-	Y	I
	Safety					
		To evaluate vaccine safety and reactogenicity.	Y	D	Y	D
Exploratory						
	Efficacy					
		To evaluate VE in reducing the severity of acute HZ-associated pain compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;	N	-	Y	I
		To evaluate VE in improving Quality of Life (QoL) compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;	N	-	Y	I
		To evaluate VE in the mitigation of Burden-Of-Illness (BOI) caused by HZ compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA.	N	-	Y	I

			First step* Final HZ efficacy analysis		Second step** End of study analysis	
			Analysis of objective Yes (Y) No (N) Not applicable (NA)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive	Analysis of objective Yes (Y) No (N)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive
	Immunogenicity					
		To evaluate vaccine induced cell mediated and humoral immune responses and the persistence of each type of response after two injections of study vaccine in subjects ≥ 50 YOA, and by age strata;	Y	I, D	Y	CD, D
		To evaluate anti-varicella-zoster virus (VZV) neutralizing antibody (Ab) titres in a subset of subjects at Month 0 (pre-vaccination), and at Months 3, 14, 26 and 38, in subjects ≥ 50 YOA, and by age strata.	Y	I, D	Y	CD, D
ZOSTER-022***						
Primary						
	Efficacy					
		To evaluate VE in the prevention of HZ compared to placebo in adults ≥ 70 YOA, as measured by the reduction in HZ risk.	Y	I	Y	CD
Secondary						
	Efficacy					
		To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 70 YOA;	N	-	Y	D
		To evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥ 70 YOA, with confirmed HZ	N	-	Y	I
		To evaluate VE in the reduction of overall and HZ-related mortality and hospitalizations compared to placebo in subjects ≥ 70 YOA	N	-	Y	I

			First step* Final HZ efficacy analysis		Second step** End of study analysis	
			Analysis of objective Yes (Y) No (N) Not applicable (NA)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive	Analysis of objective Yes (Y) No (N)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive
		To evaluate VE in the reduction in incidence of HZ-associated complications compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;	N	-	Y	I
		To evaluate VE in the reduction in use of pain medications compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;	N	-	Y	I
	Safety					
		To evaluate vaccine safety and reactogenicity.	Y	D	Y	D
Exploratory						
	Efficacy					
		To evaluate VE in reducing the severity of acute HZ-associated pain compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;	N	-	Y	I
		To evaluate VE in improving Quality of Life (QoL) compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;	N	-	Y	I
		To evaluate VE in the mitigation of BOI caused by HZ compared to placebo in subjects ≥ 70 YOA;	N	-	Y	I
	Immunogenicity					
		To evaluate vaccine induced humoral immune responses and the persistence of each type of response after two injections of study vaccine in subjects ≥ 70 YOA and by age strata;	Y	I, D	Y	CD, D
		To evaluate anti-varicella-zoster virus (VZV) neutralizing antibody (Ab) titres in a subset of subjects at Month 0 (pre-vaccination), and at Months 3, 14, 26 and 38, in subjects ≥ 70 YOA and by age strata.	Y	I, D	Y	CD, D

			First step* Final HZ efficacy analysis		Second step** End of study analysis	
			Analysis of objective Yes (Y) No (N) Not applicable (NA)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive	Analysis of objective Yes (Y) No (N)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive
Pooled analysis of ZOSTER-006 and ZOSTER-022						
Co-primary						
	Efficacy					
		To evaluate VE in the prevention of PHN compared to placebo in subjects ≥ 70 YOA across both phase III studies.	NA		Y	I
		To consolidate VE estimation in the prevention of HZ compared to placebo in subjects ≥ 70 YOA across both phase III studies;	NA		Y	CD
Secondary						
	Efficacy					
		To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 50 YOA;	NA		Y	I
		To evaluate VE in the prevention of PHN compared to placebo in subjects ≥ 50 YOA with confirmed HZ;	NA		Y	I
		To evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;	NA		Y	CD
	Safety					
		To evaluate vaccine safety and reactogenicity in subjects ≥ 70 YOA.	NA		Y	D

			First step* Final HZ efficacy analysis		Second step** End of study analysis	
			Analysis of objective Yes (Y) No (N) Not applicable (NA)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive	Analysis of objective Yes (Y) No (N)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive
Exploratory						
	Efficacy					
		To evaluate VE in reducing the severity of acute HZ-associated pain compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;	NA		Y	CD
		To evaluate VE in improving QoL compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;	NA		Y	CD
	Immunogenicity					
		To evaluate vaccine induced humoral immune responses and the persistence of each type of response after two injections of study vaccine in subjects ≥ 50 YOA and by age cohort;	NA		Y	CD
		To evaluate anti-varicella-zoster virus (VZV) neutralizing antibody (Ab) titres in a subset of subjects at Month 0 (pre-vaccination), and at Months 3, 14, 26 and 38, in subjects ≥ 50 YOA and by age strata;	NA		Y	CD
		To assess correlation of the humoral immune responses at Month 3 with protection against HZ.	NA		Y	D

* It is predicted that the first step for Zoster-006 will occur about one year before the first step for Zoster-022.
** The second analysis step for both studies will occur at the same time.
*** Depending on accrual of HZ and PHN cases, in study ZOSTER-022, step 1 may occur at the same time as step 2.

10.5. Study cohorts to be evaluated

10.5.1. Total Vaccinated cohort

The Total Vaccinated cohort (TVc) will include all vaccinated subjects with respect to the vaccine actually administered.

The TVc for analysis of efficacy and immunogenicity will include vaccinated subjects for whom data related to efficacy and immunogenicity endpoints are available.

The TVc for analysis of safety will include all subjects with at least one vaccine administration documented.

10.5.2. Modified Total Vaccinated cohort

The mTVc will be the primary population for efficacy analysis, which excludes subjects in the TVc for efficacy analysis who were not administered with the second vaccination or who develop a confirmed case of HZ prior to 1 month after the second vaccination.

Rationale for using mTVc for primary analysis:

Although the TVc (Intent-to-treat [ITT] population) analysis of efficacy is the one recommended according to ICH, the true assessment of the VE, according to the recommended schedule, can only be performed based on the mTVc, where subjects not completing the vaccination schedule due to an HZ episode or withdrawal will be excluded, as was done in an earlier HZ vaccine efficacy study [Oxman, 2005]. The analysis on the TVc is planned for sensitivity analyses and is expected to provide consistent results with the primary analyses. A delay of 1 month was selected prior to which any subject with confirmed HZ would be excluded from mTVc.

For those reasons, GSK Biologicals believes that the VE estimate for registration purposes should be based on mTVc, provided there is no essential VE difference between the mTVc and TVc analyses. Our proposal is to compare VE analyses on mTVc and TVc, and review the frequency for exclusion from mTVc. If the results are consistent between both cohorts then the VE estimate based on mTVc would be considered for registration purposes.

10.5.3. According To Protocol cohort for analysis of efficacy

The According To Protocol cohort (ATPc) for analysis of efficacy will include all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom efficacy data concerning endpoint measures are available, i.e., excluding all subjects who developed a confirmed case of HZ prior to 1 month after the second vaccination. The list of criteria used to exclude subjects from ATP will be defined prospectively in the ***Statistical*** Analysis Plan (***S***AP) prior to database freeze. **(Amended 18 April 2014)**

The ATPc will be the analysis set for supportive efficacy analysis, only including subjects who developed a confirmed case of HZ during the follow-up period starting from 1 month after the second vaccination (Month 3).

10.5.4. According To Protocol cohort for analysis of safety

The ATPc for analysis of safety will include all subjects:

- who have received at least one dose of study vaccine/placebo according to their random assignment;
- with sufficient data to perform an analysis of safety (at least one dose with safety follow-up);
- for whom administration site of study vaccine/placebo is known;
- who have not received other medication/vaccine forbidden in the protocol (Section 6.6.1);
- for whom the randomization code has not been broken.

10.5.5. According To Protocol cohort for analysis of immunogenicity

For study ZOSTER-006, the ATPc for analysis of immunogenicity will include all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom immunogenicity results are available at Month 3 for CMI and/or humoral immunogenicity.

10.6. Derived and transformed data

10.6.1. Handling of missing data

For a given subject and a given efficacy measurement, missing or non-evaluable measurements will not be imputed for the primary analysis. The missing endpoint and censoring are supposed to occur independently, and the pattern of the missingness being either Completely At Random (MCAR) or Missing At Random (MAR) only.

For the analysis of solicited symptoms, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVc will include only subjects/doses with documented safety data (i.e., symptom screen/sheet completed).

For the analysis of unsolicited AEs/SAEs/concomitant medication, all vaccinated subjects will be considered and subjects who did not report an event will be considered as subjects without an event.

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

The reasons for and timings of missing data will be reviewed and discussed. The likely patterns for missing data will be assessed and compared with the actual missing data pattern in light of CHMP /EWP/1776/99 and implementation recommendations.

Sensitivity analyses will be pre-specified prior to unblinding for each main efficacy endpoint in order to assess the sensitivity of the conclusions to missing-data pattern. When repeated measurements are planned, primary methodology will include mixed effect model for repeated measurement analysis [Mallinckrodt, 2008].

10.6.2. Efficacy

The HZ incidence rate is determined with reference to the first confirmed HZ case observed in the patient, should several HZ cases occur in the same subject.

The HZ-free period for a subject is calculated from HZ onset to time zero relative to the cohort considered: first vaccination for TVc and beyond the HZ-case exclusion period following the second injection for mTVc and ATP.

The number of Person-Years at risk over an interval of time is the sum of the confirmed HZ-free episodes over all subjects at risk during that interval, either up to the cut-off date for the analysis, the censoring date or the occurrence of the first HZ case for a subject.

The following outputs will be derived from the efficacy data recorded using the ZBPI:

HZ burden-of-illness score

For each confirmed case of HZ, responses to the "worst pain" question in the ZBPI are used to calculate a "HZ severity-of-illness" score, defined as the area under the curve (AUC) of HZ-associated pain plotted against time during the 182-day period after the onset of the case. Subjects developing HZ will present "severity-of-illness" scores ranging from 0 up to, theoretically, 1820. A score of 0 is recorded for subjects in whom HZ did not develop during the study period.

HZ severity score

The methodology described for the HZ burden-of-illness score will be applied to the 4 weeks during which a daily measure is taken and provide the HZ severity score. The HZ severity score will apply only to subjects with HZ. Subjects not infected with HZ will not take part in this analysis.

10.6.3. Humoral immune response

The current cut-off values that apply for gE and VZV Ab responses are described in Table 7 of Section 5.8.3. Those values may changes as improvements are introduced to the analytical methods. The final cut-off values that are used for the analyses will be stated in the study report.

- A seronegative subject is a subject whose Ab concentration is below the cut-off value.
- A seropositive subject is a subject whose Ab concentration is greater than or equal to the cut-off value.
- The seropositivity rate is defined as the percentage of seropositive subjects.

- The VZV gE-specific humoral immune response to vaccine for subjects who are seropositive at baseline is defined as a 4-fold increase in the anti-gE Ab concentration at the endpoint as compared to the pre-vaccination anti-gE antibody concentration. The VZV gE-specific humoral immune response to vaccine for subjects who are seronegative at baseline is defined as a 4-fold increase in the anti-gE Ab concentration at the endpoint as compared to the anti-gE Ab cut-off value for seropositivity.
- The VZV-specific humoral immune response to vaccine for subjects who are seropositive at baseline is defined as a 4-fold increase in the anti-VZV Ab concentration at the endpoint as compared to the pre-vaccination anti-VZV Ab concentration. The VZV-specific humoral immune response to vaccine for subjects who are seronegative at baseline is defined as a 4-fold increase in the anti-VZV Ab concentration at the endpoint as compared to the anti-VZV Ab cut-off value for seropositivity.
- The Geometric Mean Concentrations (GMCs) calculations are performed by taking the anti-log of the mean of the log concentration transformations. For descriptive statistics only, Ab concentrations below the cut-off of the assay will be given an arbitrary value equal to half the cut-off for the purpose of GMC calculation. For inferential analyses, those concentrations below the cut-off will be considered as missing to avoid potential influential data.

10.6.4. Cellular-mediated immune response

- ***For the inferential analysis, t***he frequency of ***CD4 [2+] T cells, i.e.,*** CD4 T cells producing at least 2 activation markers ***among*** IFN-γ, IL-2, TNF-α and/or CD40L, upon in vitro stimulation with the antigen (induction condition) is calculated by adding an offset of 0.5 to the number of activated CD4***[2+]*** T cells (numerator) divided by the total number of CD4 T cells involved (denominator). A similar calculation will be made for the frequency of CD4 ***[2+]*** T cells upon in vitro stimulation in medium only (background condition).

(Amended 18 April 2014)

$$Freq_{Induction}^{CD4[2+]} = \frac{n_{Induction}^{2+} + 0.5}{N_{Induction}^{CD4}} \qquad \log(Freq_{Induction}^{CD4[2+]}) = \log(\frac{n_{Induction}^{2+} + 0.5}{N_{Induction}^{CD4}})$$

$$Freq_{Bachground}^{CD4[2+]} = \frac{n_{Background}^{2+} + 0.5}{N_{Bachground}^{CD4}} \qquad \log(Freq_{Background}^{CD4[2+]}) = \log(\frac{n_{Background}^{2+} + 0.5}{N_{Background}^{CD4}})$$

$n_{Induction}^{2+}$ = number of CD4 T cells secreting at least 2 activation markers after induction with the antigen

$n_{Background}^{2+}$ = number of CD4 T cells secreting at least 2 activation markers in medium condition

N^{CD4} = Total number of CD4 T cells involved in the assay (induction or background)

(Amended 18 April 2014)

- ***For the descriptive analyses, the frequency of CD4[2+] T cells upon in vitro stimulation with the antigen (induction condition) is calculated by dividing the number of activated CD4[2+] Tcells (numerator) over the total number of CD4 T***

cells involved (denominator). The same calculation will be performed for the frequency computation for any kinds of cells and for each individual activation marker as appropriate. **(Amended 18 April 2014)**

$$Freq_{Induction}^{CD4[2+]} = \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}}$$

$n_{Induction}^{2+}$ = number of CD4 T cells secreting at least 2 activation markers after induction with the antigen

N^{CD4} = Total number of CD4 T cells involved in the assay (induction)

(Amended 18 April 2014)

- The frequency of **antigen-specific** (gE or VZV) CD4***[2+]*** T cells for each individual subject is calculated as the difference between the frequency of CD4***[2+]*** T cells, upon in vitro stimulation with the antigen (induction condition)**,** minus the frequency of CD4***[2+]*** T cells**,** upon in vitro stimulation in medium only (background condition). ***The differences less or equal to one (1) are imputed to 1 antigen-specific CD4[2+] T cell per 10^6 CD4 T cells. The same calculation will be performed for the frequency computation for any kinds of cells and for each individual activation marker as appropriate.*** **(Amended 18 April 2014)**

$$Freq_{Specific}^{CD4[2+]} = \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} - \frac{n_{Background}^{2+}}{N_{Background}^{CD4}} \qquad if \ \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} > 1 + \frac{n_{Background}^{2+}}{N_{Background}^{CD4}}$$

$$Freq_{Specific}^{CD4[2+]} = 1 \qquad if \ \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} \le 1 + \frac{n_{Background}^{2+}}{N_{Background}^{CD4}}$$

$n_{Induction}^{2+}$ = number of CD4 T cells secreting at least 2 activation markers after induction with the antigen

$n_{Background}^{2+}$ = number of CD4 T cells secreting at least 2 activation markers in medium condition

N^{CD4} = Total number of CD4 T cells involved in the assay (induction or background)

(Amended 18 April 2014)

- The Geometric Mean (GM) frequency calculations are performed by taking the anti-log of the mean of the log frequency transformations;
- ***The CMI vaccine response to gE will be based on the gE-specific data as computed above. The cut-off for the assay (320 positive events/10^6 CD4 T cells) will be used for vaccine response assessment. The vaccine response is defined as the percentage of subjects who have:***
  - ***at least a 2-fold increase as compared to the cut-off, for subjects with pre-vaccination T cell frequencies below the cut-off.***
  - ***at least a 2-fold increase as compared to pre-vaccination T cell frequencies, for subjects with pre-vaccination T cell frequencies above the cut-off.***

(Amended 18 April 2014)

- ***The CMI vaccine response to VZV will be based on the VZV-specific data as computed above. The cut-off for the assay (320 positive events/10^6 CD4 T cells) will be used for vaccine response assessment. The vaccine response is defined as the percentage of subjects who have:***
  - ***at least a 2-fold increase as compared to the cut-off, for subjects with pre-vaccination T cell frequencies below the cut-off.***
  - ***at least a 2-fold increase as compared to pre-vaccination T cell frequencies, for subjects with pre-vaccination T cell frequencies above the cut-off.***

(Amended 18 April 2014)

- A CMI responder is a subject with a CMI response greater than or equal to the cut-off value.

10.7. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in the protocol will be described and justified in the final study report.

10.7.1. Prior to Final *HZ efficacy* Analysis (Amended 18 April 2014)

Blinded review of safety and efficacy data will be performed in order to anticipate any data issues and rate of accrual of HZ and PHN events within each age strata.

Unblinded evaluation of safety, efficacy and risk-benefit for the subjects will be performed by the IDMC on an ongoing basis. Operational details for IDMC will be provided in the IDMC Charter.

10.7.2. Statistical considerations for the interim futility analyses

The IDMC may be also involved in evaluation of VE at specified interim timepoints (futility analysis) and may recommend discontinuation of a clinical study that has demonstrated its inability to achieve its primary and main secondary endpoints. The futility rules will be described in the RAP.

GSK has no plan to proceed with early registration for efficacy (i.e., following an interim analysis) due to the expected low accrual rate of PHN cases and the need to collect a sufficient number of events to achieve robust estimation of PHN VE. If a futility analysis occurs and leads to a recommendation by the IDMC to filing prior to study end for ethical reasons, it is mandated that, prior to final ***HZ efficacy*** analysis, the significance level for all primary objectives but also key secondary objectives is set to 0.0001 for both HZ and overall PHN, considering the alternative hypotheses of true vaccine efficacies above 40%. As a consequence, the significance level of the final ***HZ efficacy*** analysis will be adjusted to 4.9998% 2-sided. Practically speaking, however, that adjustment makes no essential difference as using a significance level of 5% 2-sided that will be referred to in other part of this document. **(Amended 18 April 2014)**

10.7.3. *End of study* analysis (Amended 18 April 2014)

When the conditions for triggering the ***end of*** analysis of efficacy have been reached, the ***end of study*** analysis cut-off date will be defined. Any HZ episode occurring prior to the ***end of study*** analysis cut-off date will be followed, as described in the ***S***AP, until a 4-week pain-free period is documented and the HZ rash resolves OR until the cut-off date for ***end of study*** analysis. For all subjects with ongoing HZ-associated pain at the time of cut-off date for ***end of study*** analysis, questionnaire data will be collected until a 4-week pain-free period is documented OR until at least Day HZ-90 in order to document potential PHN episodes. **(Amended 18 April 2014)**

Following achievement of criteria triggering analyses, final data collection and data cleaning, the write access to the clinical database will be removed and all eCRF data will become available for ***end of study*** analysis. **(Amended 18 April 2014)** The merging of immunogenicity data to the eCRF data will occur after that database lock.

10.7.4. Study reports (Amended 18 April 2014)

Depending on the further evolution of the case accrual rate, the generated data may be presented in one or more study reports per study (ZOSTER-006 and ZOSTER-022).

- ***The first study report for each study will contain assessment of the HZ VE objectives (ZOSTER-006) or the HZ VE objective (ZOSTER-022) and of safety, reactogenicity and immunogenicity objectives.***
- ***A final study report for each study will contain the assessment of remaining objectives not assessed at the first step, and in addition, but not limited to, the confirmatory descriptive re-analysis of the previously assessed objectives. The final study report for each study will also contain the results presented in the first report (to provide a comprehensive all in one report). Assessment of the objectives of the pooled analyses of both studies will be included in the final ZOSTER-022 study report. Analysis of correlate of protection may require extensive exploratory analyses and therefore may be available as an annex report after completion of this final ZOSTER-022 study report.***

(Amended 18 April 2014)

10.8. Statistical methods

All analyses will be presented overall and by age strata. The main age strata for reporting purposes are 50-59, 60-69 and ≥70 YOA. In addition, the results for the ≥ 70 YOA stratum will also be presented separately for 70-79 and ≥ 80 YOA subjects. The study is not powered prospectively to demonstrate efficacy in these 2 sub-strata taken separately. Another set of analyses in subjects ≥ 60 YOA will also be presented.

Any exploratory or sensitivity analysis may be performed in addition to the analyses described below on an ad-hoc basis. The significance level of those analyses may not however be fully controlled.

10.8.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age, gender, geographic ancestry and ethnicity) of each study cohort will be tabulated overall and by region.

The mean age (plus range and standard deviation) of the enrolled subjects, as a whole, and per treatment group and stratified by age group will be calculated.

The distribution of subjects enrolled among the study sites will be tabulated as a whole and per vaccine group.

No inferential analyses of demographic data or baseline characteristics are planned.

10.8.2. Analysis of efficacy

All efficacy analyses will be presented overall and by age strata.

When overall VE is presented, the age stratification factor will include the 3 main age levels. When VE by age is presented, the same model will be run using only the data pertaining to the strata under consideration.

Additional tables will present the overall VE by region and overall VE by time (e.g., using 1-year interval). The methodology will be described in the ***S***AP. **(Amended 18 April 2014)**

All p-values reported are related to the null hypothesis test VE = 0 or absence of effect of the vaccine and will account for p-value adjustment for multiple testing scheme when applicable. Both raw-confidence intervals and confidence intervals adjusted for multiple testing or other kind of significance adjustment will be produced.

10.8.2.1. Reduction in HZ risk

Descriptive statistics

For each treatment group, the number of subjects at risk, person-time, number of confirmed events (HZ) and incidence rate, and incidence of confirmed HZ cases will be tabulated overall and by age strata. The results will be presented over the whole study and by visit interval. Similar tables will describe the median time-to-event and hazard rate.

Survival curves for each vaccine group will be calculated non-parametrically, tabulated and presented graphically overall and by age strata using the Kaplan-Meier (i.e., Product-Limit) method.

Primary Inferential Analyses

When the disease incidence is very low, large sample size is required together with longer trial duration. As a consequence, all participants cannot be expected to be followed for the same duration throughout the end of the trial. For sufficiently large sample size and small incidence of disease, the number of cases in the vaccine and placebo groups may be approximated by independent Poisson distributions. For such low

incidence rates, both binomial and Poisson distribution are equivalent. Under that model, it can be demonstrated that the number of vaccine group, given the total number of cases, follows a binomial distribution and resolves into a single-parameter estimation problem [Chan, 2003].

Under that model, the primary analysis method of the vaccine VE will consider the exact inference on the relative risk stratified for age strata and regions conditionally to the total number of HZ cases observed and time at risk. The method is implemented in the Poisson procedure of the StatXact package provided by Cytel. Relative risks will be calculated overall and by age-strata. Stratification will include age and regions for the overall analysis and region alone when analysis by age strata. The stratification will account for possible differences in HZ incidence across strata and/or regions.

These analyses will adjust for the number of person-time in each vaccine group and strata when applicable. Similarity of the relative risks across the strata analyzed will be assessed graphically and by means of exact tests for homogeneity of the relative risks. Absence of clinically meaningful difference in relative risks across strata and p-values larger than 5% (2-sided) will justify assuming the relative risks are similar across the strata. In other situations, the impact of potential heterogeneity on the study conclusions will be assessed using sensitivity analyses.

Sensitivity analysis of the VE will be provided by region to support registration and for visual inspection of the consistency of the VE across regions. The study is not powered to demonstrate significance of VE in any of those regions using only the data of that region in isolation.

Sensitivity analysis of the overall VE after each multiple of 12 months following last vaccination will be provided in order to assess consistency of VE over time.

Secondary Inferential Analyses

The elapsed time following the HZ-case exclusion period after the second vaccination to the first HZ episode may be analyzed using Cox's proportional hazard regression stratified for age strata and region with vaccine groups as covariates. Wald test and CIs will be produced.

Ties will be handled using the Efron method. Cox adjusted survival curves will be produced for each combination of vaccine group and age category.

10.8.2.2. Reduction in overall PHN risk

The overall reduction in PHN risk will be evaluated similarly to the HZ risk using the exact inference on the relative risk stratified for age strata and regions conditionally to the total number of HZ cases observed and time at risk. Similarly to the HZ VE, a Poisson distribution for the number of PHN cases under placebo and vaccine groups is assumed. Since the incidence of PHN is approximately 10% to 25% of the incidence of HZ, the Poisson approximation of the overall number of PHN cases with regards to the mTVc is similarly valid. The inference of the PHN VE is partially confounded with the analysis of HZ risk as it includes the efficacy of the vaccine against HZ in all subjects randomized

and the efficacy of the vaccine against PHN in those subjects that presented with HZ. However, the overall PHN analysis is deemed relevant for the following reasons:

1. An analysis performed on randomized cohort ensures comparability of the vaccine groups under evaluations. An analysis performed on the subset of subjects who presented with HZ may be biased due to the selection of that subset due to the disease.
2. It matters to provide Health Authorities with overall benefit on PHN risk, whether the primary efficacy is against HZ or against PHN.

10.8.2.3. Reduction in Burden-of-Illness

The "Chop-lump" test [Follmann, 2009] for the overall reduction in Burden-of-Illness scores in all subjects between vaccine and placebo will be implemented and compared to the original analysis of the Burden-of-Illness proposed by Chang [Chang,1994]. That analysis is exploratory and will be described in the ***S***AP. **(Amended 18 April 2014)** The purpose of this analysis is to compare with results published elsewhere [Oxman, 2005] and no further change to the methodology is this considered appropriate.

The HZ "Burden-Of-Illness (BOI) score" represents the average severity of illness among all subjects in the vaccine or placebo groups. It is calculated according to the "modified" scale described by Coplan [Coplan, 2004] as the sum of the HZ "severity-of-illness" scores of all members of the treatment group divided by the total number of subjects in the group.

The pain experienced by the subjects over the period that precedes a 24 hour window prior to the visit to the investigator will be captured in a single measure. VE with respect to the BOI due to HZ (VE BOI) is defined as the relative reduction in the BOI score in the vaccine group as compared with that in the placebo group and calculated as 1 - relative risk (i.e., 1- the HZ BOI score in the vaccine group divided by the HZ BOI score in the placebo group).

The same definition of clinically relevant improvement as given for HZ severity applies to BOI.

10.8.2.4. Reduction in HZ severity score

Based on Rowbotham [Rowbotham, 2001] and Farrar et al. [Farrar, 2001], a reduction of 1.74 units or 28% on pain score between baseline and endpoint were best associated with clinically relevant improvement, according to the Patient's Global Impression of Change (PGIC) category of "much improved" or better. The authors also concluded that, in studies with no minimum baseline requirement, the relationship between percentage changes and PGIC is more consistent than with the raw change. Dworkin et al, [Dworkin, 2008] reach a similar conclusion. Therefore, a percentage reduction in pain between vaccine and placebo of ~28% may be considered as clinically relevant in this study.

Additional implementation details will be provided in the ***S***AP. **(Amended 18 April 2014)**

The statistical methodology for the analysis of HZ severity will be described in the ***S***AP and is similar to the methodology described previously for BOI assessment in [Chang, 1994]. **(Amended 18 April 2014)** The method for accounting for the potential differential in use of antiviral treatment or pain medications between the vaccine and placebo groups will be pre-specified. Contrary to the BOI analysis, the HZ severity analysis only applies to subjects with HZ (i.e., a score of zero is not assigned to subjects who do not present with HZ) and only includes the first 4 weeks following the HZ episode.

Additional analyses may be performed using partial AUC, calculated from 0 to specific elapsed time after HZ onset. That approach accounts partially for any difference in pain score profiles or pattern (e.g., long duration with low scores versus short score with high scores) even though subjects may have the same overall AUC.

10.8.2.5. Reduction in incidence of HZ associated complications

At the end of the trial, it is reasonable to assume that a final assessment of the presence or absence of HZ associated complication will be made for most patients with confirmed HZ. As a consequence, the number HZ associated complications in subjects with HZ under placebo or vaccine may be considered as a binomial distribution rather than a Poisson distribution.

The overall incidence of HZ associated complications, in subjects with an HZ episode, overall and by sub-categories will be presented and compared with placebo using asymptotic standardized unconditional binomial test [Miettinen, 1985]. The analysis will be stratified by age group and weights associated to each stratum will be pre-specified. The statistical methodology will be further described in the ***S***AP. **(Amended 18 April 2014)**

10.8.2.6. Reduction of duration of severe 'worst' pain in subjects with an HZ episode

This analysis aims at demonstrating the effect of the vaccine on the reduction of the duration of pain, irrespective of whether the pain is acute or chronic. Similarly to the approach taken for the analysis of incidence of PHN, this analysis will involve any subject reporting ZBPI pain scores of 3 or more at any time during the study.

The time-to-cessation of severe 'worst' pain will be analyzed using a survival methodology. The primary analysis will consist in a Cox-proportional model to assess the hazard rate reduction in ZBPI worst pain duration due to the vaccine in those subjects that presented HZ.

A change-point piecewise exponential model [Arani, 2001; Desmond, 2002] may be used as sensitivity analysis to compare hazard rates related to acute (0-30 days), sub-acute (30-120 days) and chronic (120+ days) pain between vaccine group and placebo. The cut-off points 30 days and 120 days were suggested according to Desmond [Desmond, 2002]. Those cut-off points may additionally be estimated using the data. The comparisons across both sub-acute pain and chronic pain will be combined using a likelihood-ratio test.

Both methodologies will be further detailed in the ***S***AP. **(Amended 18 April 2014)**

10.8.2.7. Reduction in PHN incidence in subjects with an HZ episode

At the end of the trial, it is reasonable to assume that a final assessment of the presence or absence of PHN will be made for most patients who experienced an HZ episode. As a consequence, the number of PHN cases in subjects with HZ under placebo and vaccine maybe considered as a binomial distribution rather than a Poisson distribution.

The incidence of PHN in subjects with an HZ episode, overall and by sub-categories will be presented and compared with placebo using asymptotic standardized unconditional binomial test [Miettinen, 1985]. The analysis will be stratified by age group and weights associated to each stratum will be pre-specified. The statistical methodology will be further described in the ***S***AP. **(Amended 18 April 2014)**

10.8.2.8. Improvement of subject's quality of life by ZBPI

Descriptive statistics and inferential analysis of QoL subscale of ZBPI (item 9: questions A to G) total scores and scores per item over time will be provided overall and by age group.

10.8.3. Analysis of immunogenicity

The primary analysis will be based on the ATPc for analysis of immunogenicity (Section 10.5.5). If the percentage of enrolled subjects excluded from this ATPc is more than 5%, a second analysis based on the TVc will be performed to complement the ATP analysis.

10.8.3.1. Cell-mediated immune response

CMI response will only be assessed and analyzed in the CMI component of the Immunogenicity subset as defined in Section 4.1.

Descriptive statistics

- For CMI response, the following parameters will be tabulated by treatment group, overall and by age group at Months 0, 3, 14, 26 and 38:
- descriptive statistics of the frequency of CD4 T cell secreting at least two different cytokines (IFN-γ, IL-2, TNF-α,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least IFN-γ and another cytokine (IL-2, TNF-α,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least IL-2 and another cytokine (IFN-γ, TNF-α,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least TNF-α and another cytokine (IFN-γ, IL-2,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least CD40L and another cytokine (IFN-γ, IL-2, TNF-α) to both VZV and gE antigens;
- proportion of responders with exact 95% CI.

Inferential Analyses

If the data allows, inferential analysis on the log-transformed frequency of CD4 T cells producing at least two different cytokines following induction with antigen will be performed overall and by age strata or sub-strata, in subjects infected with HZ and healthy subjects. Least-squares means and 95% CI are back-transformed to provide geometric means and ratios. Covariates will include the log-transformed pre-vaccination frequency following induction with the antigen and the non-specific background log-transformed frequency. Sensitivity analyses may include additional effects for appropriate interactions in the model in order to provide estimations and 95% CI by region.

10.8.3.2. Humoral immune response

Humoral immune response will be assessed and analyzed in the Humoral Immunogenicity subset as defined in Section 4.1.

Descriptive statistics

The following parameters will be tabulated by treatment group, overall and by age group at Month 0, Month 3, Month 14, Month 26 and Month 38:

- Geometric mean concentrations (GMCs) of anti-gE Ab with 95% CIs;
- Humoral seropositivity rates with exact 95% CIs;
- Vaccine response rates with 95% CIs;
- Tabulations will be presented overall and by region.

Inferential Analyses

If the data allows, inferential analysis on the log-transformed Ab concentrations will be performed overall and by age strata or sub-strata, in subjects infected with HZ and healthy subjects. Least-squares means and 95% CI are back-transformed to provide geometric means and ratios. Covariates will include the log-transformed pre-vaccination concentrations. Sensitivity analyses may include additional effects for regions and appropriate interactions in the model in order to provide estimations and 95% CI by region.

The analysis for immunogenicity will be performed at final HZ efficacy analysis. A confirmatory descriptive analysis for immunogenicity will be performed at end of study analysis.

An additional humoral immunogenicity analysis will be performed on the pooled data of both ZOSTER-006 and ZOSTER-022 and the results will be provided in the final study report for ZOSTER-022.

(Amended 18 April 2014)

10.8.3.3. VZV neutralizing antibody response

Descriptive statistics

The following parameters will be tabulated by treatment group, overall and by age group at Month 0, Month 3, Month 14, Month 26 and Month 38:

- Geometric mean titres (GMTs) of anti-VZV neutralizing Abs with 95% CIs;
- Tabulations will be presented overall and by region.

10.8.3.4. Correlate of protection

An exploratory analysis will be implemented in an attempt to correlate humoral immune responses to vaccination and subsequent HZ risk [Dunning, 2006]. A specific ***S***AP will describe the methodologies to be used for that purpose. **(Amended 18 April 2014)** The exploratory analyses may be initiated during the course of the trial by SDAC to support IDMC.

Serum blood samples will be collected from all subjects at Month 0 (pre-vaccination) and Month 3, and may be used for correlate of protection analysis. Additional subject samples may be retrieved and analyzed based on some demographics and baseline characteristics to match more exactly with characteristics of those who developed HZ.

The analysis for correlate of protection will be performed on the pooled data of both ZOSTER-006 and ZOSTER-022 and ***may be available as*** an annex report. **(Amended 18 April 2014)**

10.8.4. Quality of life

10.8.4.1. SF-36 health survey

The methodology used for the analysis of the SF-36® questionnaire is detailed by Ware et al. [Ware, 2000]. The SF-36® yields an 8-scale profile of scores (physical functioning, role physical, bodily pain, general health perceptions, vitality, social functioning, role emotional, and mental health) as well as a reported health transition score.

Details on descriptive statistics and statistical analysis of the effect of the vaccine on the difference over pre-vaccination scores will be provided in the ***S***AP. **(Amended 18 April 2014)**

10.8.4.2. EQ-5D questionnaire

The EQ-5D questionnaire is analyzed based on three different types of scores:

- 5-dimensional descriptive system: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression,
- A weighted health state index computed by applying scores from EQ5D "value sets" elicited from general population samples in United Kingdom [Dolan, 1995]
- A Visual Analog Scale (VAS) ranging from 0 to 100, with 100 representing the best imaginable health state and 0 representing the worst imaginable health state.

Details on contingency tables for each of the 5-dimension and descriptive statistics for weighted health state index and VAS will be provided in the ***S***AP. **(Amended 18 April 2014**) Similar details will be provided for the change from pre-vaccination. Further specifications of statistical analyses will also be provided.

10.8.5. Analysis of safety

The primary analysis for safety will be based on the TVc. A second analysis based on this ATPc will be performed to complement the TVc analysis.

When appropriate, tabulations will be presented overall and by time of occurrence relative to last vaccination (e.g., using windows such as Days 0 – 6, Days 0 – 29 and more than 30 days post-vaccination).

10.8.5.1. Within groups assessment

For each treatment group, the following results will be tabulated overall and by age strata.

- The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general adverse event (solicited and unsolicited) and with any AE during the solicited follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall.
- The percentage of doses followed by at least one local AE (solicited and unsolicited), by at least one general AE (solicited and unsolicited) and by any AE will be tabulated, overall vaccination course, with exact 95% CI.
- The percentage of subjects reporting each individual solicited local and general AE during the solicited 7-day (Days 0-6) follow-up period will be tabulated with exact 95% CI.
- The percentage of doses followed by each individual solicited local and general AE during the solicited 7 day (Days 0-6) follow-up period will be tabulated, overall vaccination course, with exact 95% CI.
- For all solicited symptoms, the same tabulation will be performed for grade 3 solicited AEs and for solicited general AEs with relationship to vaccination.
- Duration and prevalence of fever will be presented.

- The proportion of subjects with at least one report of unsolicited AE during the 30-day (Days 0 – 29) follow-up period after each vaccination classified according to the MedDRA System Organ Class and Preferred Terms will be tabulated, with exact 95% CI.
- The distribution of the number of unsolicited AEs per subject will be tabulated.
- The same tabulation will be performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination. The proportion of AEs resulting in a medically attended visit (other than routine health maintenance visits) will also be tabulated.
- Incidences of SAEs during the 30-day (Days 0 – 29) follow-up period after each vaccination, up to 8 months and during any time during the study classified according to the MedDRA System Organ Class and Preferred Terms will be tabulated, with exact 95% CI.
- A separate tabulation will report major categories of SAEs that occur with higher frequencies in elderly subjects including: cardiac, vascular, respiratory, neurological, congestive heart failure, myocardial infarction, varicella or HZ-like rash, cerebral or vascular events.
- Incidences of SAEs by major categories including: cardiac, vascular, respiratory, neurological, congestive heart failure, myocardial infarction, varicella or HZ-like rash, cerebral vascular. Listing will also be provided, sorted by patients and sorted by preferred term.
- Incidence of withdrawal due to AEs. Listing will also be provided, sorted by subjects and sorted by MedDRA Preferred Term.
- The proportion of subjects with at least one report of pIMDs during the entire study period will be tabulated overall and by time window. Listing will also be provided, sorted by subjects and sorted by MedDRA Preferred Term.
- The proportion of subjects with concomitant medication will be tabulated, until 30 days after each vaccine dose and overall, with exact 95% CI.
- Proportion and incidence rate of subjects with fatal outcome, HZ-related complications and overall and HZ-related hospitalizations, will be tabulated overall and by time window.
- Proportion of subjects experiencing an HZ episode using pain medications by type (opiods, non-narcotics, antidepressants, miscellaneous) will be tabulated.

10.8.5.2. Additional exploratory safety comparisons

The standardized asymptotic 95% CI for the difference between the two groups and the associated 2-sided p-value to detect group difference will be computed for the following endpoints.

- The proportion of subjects with at least one report of unsolicited AE classified by the MedDRA presented by System Organ Class and Preferred Term.

- Incidences of SAEs classified according to the MedDRA System Organ Class and Preferred Terms.

The objective of these analyses is to identify a safety signal as defined by the Council for the International Organization of Medical Sciences (CIOMS) VI working group, i.e., a report or reports of an event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continues surveillance. It is recognized that the use of any method to identify safety signals has the potential to identify a large number of events which may or may not have a causal relationship to drug treatment due to multiplicity of endpoints. In order to put any safety signal in perspective a permutation test will be conducted to quantify the probability to observe at least one false safety signal according to the threshold p-value defining a signal. In addition, clinical significance and biological plausibility will need to be accounted before establishing causality.

Other exploratory safety analyses may be described in the ***S***AP. **(Amended 18 April 2014)**

11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

11.1. Case Report Form/Remote Data Entry instructions

Remote Data Entry (RDE), a validated computer application, will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

11.2. Monitoring by GSK Biologicals

Monitoring visits by a GSK Site Monitor are for the purpose of confirming that GSK Biologicals' sponsored studies are being conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical practice (GCP) and the applicable regulatory requirement(s)

(verifying continuing compliance with the protocol, amendment(s), reviewing the investigational product accountability records, verifying that the site staff and facilities continue to be adequate to conduct the study).

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a RDE review and a Source Document Verification (SDV). By SDV we understand verifying RDE entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the RDE. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the RDE will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For RDE, the monitor will mark completed and approved screens at each visit.

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF entries will serve as the source document.

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any amendments, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Archiving of data at study sites

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g. audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting

systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic for studies with an eCRF); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by ICH GCP, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

11.4. Audits

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.5. Posting of information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov before enrolment of subjects begins.

11.6. Ownership, confidentiality and publication

11.6.1. Ownership

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

11.6.2. Confidentiality

Documented evidence that a potential investigator is aware and agrees to the confidential nature of the information related to the study must be obtained by means of a confidentiality agreement.

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (i) information which becomes publicly available through no fault of the investigator or site staff; (ii) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (iii) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (iv) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

11.6.3. Publication

For multicentre studies, the first publication or disclosure of study results shall be a complete, joint multicentre publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a 'Publication'), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period to review the proposed Publication (at least twenty-one working days, or at least fifteen working days for abstracts/posters/presentations). Proposed Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

11.6.4. Provision of study results to investigators, posting to the clinical trials registers and publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to the GSK Clinical Study Register at the time of the first regulatory approval or within 12 months of any decision to terminate development. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 12 months of the first approval or within 12 months of any decision to terminate development. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

12. COUNTRY SPECIFIC REQUIREMENTS

All countries will comply with AE and SAE reporting as described in Section 8 of the protocol. Additionally, countries and sites will follow all applicable local regulations and guidelines for AE and SAE reporting as required by their respective healthcare authorities and ethics committees.

12.1. Requirements for France

This section includes all the requirements of the French law (n° 2004-806 of 09 August 2004), and identifies, item per item, the mandatory modifications or additional information to the study protocol.

Concerning the « STUDY POPULATION»

- In line with the local regulatory requirements, the following text about «PAYMENT TO SUBJECTS » is added:

  If the subjects will be paid for the inconvenience of participating in the study. The amount of payment is stated in the informed consent form. Subjects not completing the study for whatever reason could be paid at the discretion of the Investigator, generally on a pro rata basis.

- In line with the local regulatory requirements, the following text about **« NATIONAL FILE »** is added:

  All subjects participating in studies could be identified and monitored under the « Fichier national ».

  The following details will be described**:**

  – first 3 letters of name and first 2 letters of surname,

  – date of birth,

  – reference of the study and dates of beginning and termination,

  – exclusion period,

  – the total amount of honorarium.

- In line with the local regulatory requirements, the following text in section «OTHER STUDY ELIGIBILITY CRITERIA CONSIDERATIONS » is added:

  A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category.

  It is the investigator's responsibility to ensure and to document (in source document - patient notes) that the patient is either affiliated to or beneficiary of a social security category.

Concerning the "DATA ANALYSIS AND STATISTICAL CONSIDERATIONS" and specially in the "SAMPLE SIZE ASSUMPTION"

- The expected number of patients to be recruited in France is declared to the French regulatory authority.

Concerning the "STUDY CONDUCT CONSIDERATIONS"

- In section "Regulatory and Ethical Considerations, Including the Informed Consent Process"

Concerning the process for informing the patient or his/her legally authorized representative, the following text is added:

- French Patient Informed Consent form is a document in triplicate which summarizes the main features of the study and allows collection of the patient's written consent. It also contains a reference to the authorisation of Afssaps and the approval from the French Ethics committee and the maintenance of confidentiality of the returned consent form by GSK France.

Concerning the process for obtaining subject informed consent:

- When **biomedical research is carried out on an adult in the care of a "tutelle" guardian**, consent is given by their legal representative and, if the committee mentioned in article L. 1123-1 considers that the research in question, because of the gravity of the restraints or the specificity of the medical acts involved, entails a serious risk of affecting their private life or the integrity of their body, by the family council if it has been instated, or by the judge of "tutelle" guardians.

- When biomedical research is carried out on an adult in the care of a "curatelle" guardian, consent is given by the subject assisted by his guardian.

  However, if the adult in the care of a "curatelle" guardian is invited to participate in research which the committee mentioned in article L. 1123-1 considers, because of the gravity of the restraints or the specificity of the medical acts involved, to entail a serious risk of affecting their private life or the integrity of their body, the matter is submitted to the judge of guardians who decides whether the adult is capable of giving his consent. In the case of incapacity, the judge will decide whether or not to authorise the biomedical research.

- When biomedical research, which complies with the conditions laid down in article L. 1121-8, is considered for **an adult incapable** of expressing his consent and not under a legal protection order, consent is given by a person of confidance as defined in article L. 1111-6 and, failing this, by a person who maintains close and stable links with the subject. However, if the committee mentioned in article L. 1123-1 considers that the research in question, because of the gravity of the restraints or the specificity of the medical acts involved, entails a serious risk of affecting their private life or the integrity of their body, consent is given by the judge of guardians.

Concerning the management of the Patient Informed Consent forms, the following text is added:

- The first copy of the Patient Informed Consent form is kept by the investigator. The second copy is kept by the Director of the Medical Department of GlaxoSmithKline France and the last copy is given to the patient or his/her legally authorized representative.

- The second copy of all the consent forms will be collected by the investigator at the end of the trial under the Clinical Research Assistant’s (CRA's) control, and placed in a sealed envelope bearing only:

  the study number,

  the identification of the Centre : name of the principal investigator and number of centre),

  the number of informed consents,

  the date,

  and the principal investigator’s signing.

  Then, the CRA hands the sealed envelope over to the Director of the Medical Department, for confidential recording, under his responsibility.

In section concerning the “ NOTIFICATION TO THE HOSPITAL DIRECTOR ” the following text is added (if applicable)

- In accordance with Article L1123-13 of the Public Health Code, the Hospital Director is informed of the commitment to the trial in his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-63).

In section concerning the " INFORMATION TO THE HOSPITAL PHARMACIST " the following text is added (if applicable)

- In accordance with Article R.1123-64 of the Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in his establishment. The Pharmacist is supplied with a copy of the protocol (which allows him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the CIB), the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

In section " DATA MANAGEMENT " the following text is added

- " within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacist if applicable, involved in this clinical trial, and data regarding the patients recruited in this clinical trial (patient number, treatment number, patient status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by Laboratoire GlaxoSmithKline or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Act n° 78-17 of 6th January 1978 further modified, each of these people aforesaid has a right of access, correction and opposition on their own data through Laboratoire GlaxoSmithKline (Clinical Operations Department)."

12.2. Requirements for Germany

EXPLANATORY STATEMENT CONCERNING GENDER DISTRIBUTION (ARTICLE 7, PARAGRAPH 2 (12) OF THE GERMAN GCP ORDER)

- There is no intention to conduct specific analyses investigating the relationship between the gender of the subjects and the efficacy, immunogenicity or safety of the GSK Biologicals' gE/AS01$_B$ vaccine. The ratio of male to female subjects recruited into the study ZOSTER-006 is expected to be in line with the demographics of the population aged ≥ 50 YOA in the Member State.

12.3. Requirements for Japan

Regulatory and Ethical Considerations

The study will be conducted in accordance with Good Clinical Practice (GCP), Article 14-3 and 80-2 of the Pharmaceutical Affairs Law, all applicable subject privacy requirements, and the guiding principles of the declaration of Helsinki.

Clinical Trial Notification to Regulatory Authority

GSK will submit the CTN to the regulatory authorities in accordance with Article 80-2 of the Pharmaceutical Affairs Law before conclusion of any contract for the conduct of the study with study sites.

Informed Consent of Subjects

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

Informed Consent

Prior to the start of the study, the investigator (or subinvestigator) should fully inform the potential subject of the study including the written information given approval by the IRB. The investigator (or subinvestigator) should provide the subject ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. After giving informed consent based on his/her free will, the subject should sign and personally date the consent form. If the subject wishes to consider the content of the written information at home, he/she may sign the consent form at home. The person who conducted the informed consent discussion should sign and personally date the consent form. If the subject is unable to read, an impartial witness should be present during the entire informed consent discussion, and the witness should sign and personally date the consent form. The investigator (or subinvestigator) should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the subject.

If information becomes available that may be relevant to the subject's willingness to continue participation in the study (revision of informed consent form and other written information)

If information becomes available that may be relevant to the subject's willingness to continue participation in the study, the investigator (or subinvestigator) should immediately inform the subject of it to confirm the willingness to continue participation in the study, and document the communication of this information (in medical records). If necessary, the investigator should revise the written information to be provided to subjects, promptly report it to the sponsor, and obtain approval from the IRB. The investigator should not enroll any new subject in the study before the IRB’s approval. After the IRB approves the revision of the written information to be provided to subjects, the investigator (or subinvestigator) should inform each subject participating in the study of the revised written information, and obtain written informed consent.

Study Monitoring

By monitoring the parties involved in the study including medical institutions, investigators, subinvestigators, study collaborators, and storage managers, monitors will:

1. Oversee the process of obtaining written informed consent, the control of investigational products and the progress of the study (including withdrawals and adverse events, and ensure that the conduct of the study is in compliance with GCP, Revised GCP, this protocol, and any other written agreement between the sponsor and the investigator/institution.

2. Collect and provide information that is necessary to conduct the study properly (information on investigational products' safety, efficacy and quality).
3. Verify that the investigator/institution has adequate qualifications and resources and remain adequate throughout the study period, and that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the study and remain adequate throughout the study period.
4. Verify that source documents and other study records are accurate, complete, kept up-to-date and maintained.
5. Determine whether the person responsible for retaining records is maintaining the essential documents at each medical institution.
6. Check the accuracy and completeness of the CRF entries, source documents and other study-related records against each other.

The investigator and institution should agree to allow the monitor direct access to essential documents and other relevant documents.

Direct access to essential documents by monitors and the scope of those documents will be specified separately in the written procedures for monitoring prepared for this study.

The monitor will also review EQ-5D, SF-36 and ZBPI questionnaires for extraneous written comments that could indicate possible AEs. Information collected in the CRF, and in EQ-5D, SF-36 and ZBPI questionnaires will be handled as independent components of this study. Except for header section information (e.g., subject identification code (subject number), treatment number, visit date), neither the monitor nor the investigator (or subinvestigator) will attempt to reconcile responses to individual questions/items recorded on EQ-5D, SF-36 and ZBPI questionnaires or health outcomes portions of diary cards (if applicable) with other data recorded in the CRFs. EQ-5D, SF-36 and ZBPI questionnaires itself generally serve as the source document; therefore, unless otherwise specified elsewhere, no other source document is available for data validation.

Source Data Recorded Directly on CRF

The following data may be recorded directly on the CRFs and considered to be source data.

1. Assessment of causality between adverse events and the investigational product.

Deviations from and Changes of Protocol

Deviations from Protocol

The investigator (or subinvestigator) may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to subjects without agreement by the sponsor or prior IRB approval. As soon as possible, the implemented deviation or change and the reasons for it should be submitted to the head of the medical institution and the IRB for approval, and via the head of the medical institution to the sponsor for agreement.

The investigator (or subinvestigator) should document all deviations from the approved protocol. The investigator should document the reason only for the deviation from, or the change of, the protocol to eliminate an immediate hazard(s) to subjects, and submit it to the sponsor and the head of the medical institution, and retain its copy.

Changes of Protocol

1. If it becomes necessary to make any changes significantly affecting the conduct of the study, and/or increasing the risk to subjects, the sponsor should promptly document the changes and reasons for them and amend the protocol after discussion with the [coordinating [investigator, committee members] and] investigators, and notify the heads of the medical institutions and investigators of the changes of the protocol [sample informed consent form and other written information, if necessary]. The investigator should not implement any significant changes without approval from the IRB.
2. For changes other than the above 1), the sponsor should document the changes and reasons for them and inform the heads of the medical institutions and investigators of the changes of the protocol. Such changes require prior approval from the IRB, except where necessary to eliminate an immediate hazard(s), or when the change(s) involves only logistical or administrative aspects of the study. The investigator should promptly report the changes implemented without prior approval to the IRB for approval.

Study Period

June, 2010 ~ ***December, 2015 (estimation at the time of protocol amendment 4)***
(Amended 18 April 2014)

13. REFERENCES

Araújo LQ, MacIntyre CR, Vujacich C. Epidemiology and burden of herpes zoster and post-herpetic neuralgia in Australia, Asia and South America. *Herpes* 2007;14(Suppl 2): 40A–44A.

Arani RB., Soong S-J, Weiss HL, et al. Phase specific analysis of herpes zoster associated pain data: a new statistical approach. *Statist., Med.* 2001;20:2429–2439.

Carter WP, Germann CA, Baumann MR. Ophthalmic diagnoses in the ED: herpes zoster ophthamicus. *Am. J. Ophthalmol.* 2008; ***26(5):*** 612– 617. **(Amended 18 April 2014)**

CDC. Prevention of herpes zoster. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2008;57:1–30.

Garcia Cenoz M, Castilla J, Montes Y, et al. Varicella and herpes zoster incidence prior to the introduction of systematic child vaccination in Navarre, 2005-2006. *An Sist Sanit Navar*. 2008;31:71-80.

Chan ISF, Wang WWB, Heyse J. Encyclopedia of Biopharmaceutical Statistics. *Vaccine Clinical Trials*. 2003;1005–1022.

Chang MN, Guess HA, Heyse JF. Reduction in burden of illness: a new efficacy measure for prevention trials. *Stat Med.*1994;13:1807–1814.

Cohen JI, Straus SE, Arvin AM. Varicella zoster virus and its replication. 2007; p. 2774-2818. In D. M. Knipe and P. M. Howley (ed.), *Fields virology*, 5th ed. Lippincott/The Williams & Wilkins Co., Philadelphia, PA.

Coplan PM, Schmader K, Nikas A, et al. Development of a measure of the burden of pain due to herpes zoster and postherpetic neuralgia for prevention trials: adaptation of the brief pain inventory. *J Pain*. 2004;5(6):344–356.

Dolan P, Gudex C, Kind P, Williams A; A social Tariff for EuroQoL: Results from a UK General Population Survey. The University of York, center for Health Economics. 1995.

Desmond Renee A, Weiss Heidi L, Arani Ramin B, Soong Seng-jaw, Wood Martin J, Fiddian Paul A, Gnann John W, Whitley Richard J. Clinical Applications for Change-Point Analysis of Herpes Zoster Pain. *Journal of Pain and Symptom Management.* 2002, 23:510–516.

Dunning A. A model for immunological correlates of protection. *Statist. Med. 2006*, 25:1485–1497.

Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis.* 2007;44 Suppl 1:S1–26.

Dworkin et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. *The Journal of Pain*. 2008;9(2):105–121.

EMEA. Zostavax Summary of Product Characteristics. http://www.emea.europa.eu/humandocs/PDFs/EPAR/zostavax. Website accessed 24 March 2009.

Farrar JT, Young JP Jr, LaMoreau L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on a 11-point numerical pain rating scale. *Pain*. 2001;94:149–158.

FDA, U.S. Department of Health and Human Services, Center for Biologics Evaluation and Research. Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Version of September 2007.

Follmann DA, Fay MP, Proschan, MA. Chop-lump tests for Vaccine trials. *Biometrics.* 2009;65: 885–893.

Gilden D, Cohrs RJ, Mahalingam R, et al. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. *Lancet Neurology*. 2009;8(8):731–740.

Hanley and Lippman-Hand. If nothing goes wrong, is everything all right? Interpreting zero numerators. *JAMA.* 1983;249:1743–1745.

Heid CA, Stevens J, Livak KJ et al. Real time quantitative PCR. *Genome Res*. 1996;6(10):986–994.

Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika.* 1988;75:800–802.

Kang CI, Choi CM, Park TS, et al. Incidence of herpes zoster and seroprevalence of varicella-zoster virus in young adults of South Korea. *Int J Inf Dis.* 2008;12(3):245–247.

Levin MJ, Oxman MN, Zhang JH, et al; Veterans Affairs Cooperative Studies Program Shingles Prevention Study Investigators. Varicella-zoster virus-specific immune responses in elderly recipients of a herpes zoster vaccine. *J Infect Dis* 2008; 197:825–835.

Mallinckrodt C, Lane P, Schnell D, Peng Y, Mancuso J. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials, *DIJ.* 2008;42:303–319.

Miettinen OS, Nurminen M. Comparative analysis of two rates. *Statistics in Medicine*. 1985; 4:213–226.

Oxman MN, Levin MJ, Johnson GR, et al. Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352:2271–2284.

Proschan MA, Lan GKK, Turk Wittes J. Statistical Monitoring of Clinical Trials A Unified Approach; Springer-Verlag, 2006

Rowbotham MC. What is a "Clinically meaningful" reduction in pain? *Pain*. 2001;94:131–132.

Schmader K, Sloane R, Pieper C, et al. The impact of acute herpes zoster pain and discomfort on functional status and quality of life in older adults. *Clin J Pain*. 2007;23(6):490–496.

Schmader KE, Dworkin RH. Natural history and treatment of herpes zoster. *The Journal of pain*. 2008;9(1):S3–S9.

Scott F, Johnson R, Leedham-Green M, et al. The burden of herpes zoster: A prospective population based study. *Vaccine.* 2006; 24:1308–1314.

Sperber SJ, Smith BV, Hayden FG. Serologic response and reactogenicity to booster immunization of healthy seropositive adults with live or inactivated varicella vaccine. *Antiviral Res*. 1992;17:213–222.

TGA eBS Australian Register of Therapeutic Goods Medicines. Public summary ZOSTAVAX FROZEN zoster virus vaccine live min 19400 PFU/0.65mL powder for injection vial. https://www.ebs.tga.gov.au/ebs/ANZTPAR/PublicWeb.nsf/cuMedicines?OpenView. Website accessed 25 March 2009.

Toyama N, Shiraki K, and Members of the Society of the Miyazaki Prefecture Dermatologists. Epidemiology of herpes zoster and its relationship to varicella in Japan: A 10-year survey of 48,388 herpes zoster cases in Miyazaki prefecture. *J Med Virol.* 2009;81(12)2053–2058.

Ware JE, Kosinski M, Dewey JE. How to score Version 2 of the SF-36® Health Survey. Lincoln, RI: Quality Metric Incorporated, 2000.

Zostavax (Zoster Vaccine Live) Prescribing information. June 2011

Appendix A LABORATORY ASSAYS

Specific Ab (anti-VZV and anti-gE) measurements

Anti-VZV ELISA: Anti-VZV Ab concentrations will be measured using a commercial ELISA kit (*Enzygnost*/Dade Behring), which is based on a single point quantification Ab method (sera tested at a 1:231 dilution). The assay cut-off is 25 milli-international units (mIU)/mL. The assay will be performed on human serum at GSK Biologicals' laboratory or another laboratory designated by GSK Biologicals.

Anti-gE ELISA: Anti-gE Ab concentrations will be measured using an anti-gE ELISA. Diluted blood serum samples of study subjects will be added to microtitre wells pre-coated with gE antigen. Secondary peroxidase-conjugated anti-human Abs will be added, which bind to the primary human anti-gE Abs. After incubation of the microtitre wells with a chromogen substrate solution, the enzymatic reaction will be stopped. Optical densities will be recorded and anti-gE Ab concentrations are calculated from a standard curve. The assay cut-off is ***97*** mIU/mL. **(Amended 18 April 2014)** The assay will be performed on human serum at GSK Biologicals' laboratory or another laboratory designated by GSK Biologicals.

Intracellular cytokine staining (ICS)

CMI responses will be performed by GSK Biologicals (or designated laboratory) on thawed Peripheral Blood Mononuclear Cells (PBMCs) by ICS. The assay will be performed on samples collected during the course of the study. This assay provides information on the frequency of CD4 T cells responding to culture medium or antigens (gE peptide pool or VZV lysate) by secreting cytokine molecules involved in immunity such as IFN-γ, IL-2, TNF-α, and CD40L.

Briefly, PBMC collected from the subjects are stimulated for two hours using culture medium (for evaluation of the non-specific response), a pool of overlapping peptides covering the entire sequence of the vaccine antigen gE or a VZV lysate. Then, an intracellular block (brefeldin A) is added to inhibit cytokine secretion for a subsequent overnight incubation. Cells are then harvested, stained for surface markers (CD3, CD4 and CD8) and fixed. The fixed cells are then permeabilised and stained with anti-cytokine Abs, washed and analyzed by cytofluorometry.

The results of ICS assays are expressed as the frequency of specific CD4 T cells per million total CD4 T cells.

Anti-VZV neutralizing antibody assay

Anti-VZV neutralizing Abs will be quantified using a plaque reduction neutralization test (PRNT). Briefly, two-fold serum serial dilutions are incubated with a fixed amount of VZV. The mixture is then added to a monolayer of Vero cells in a 96-well plate and incubated for 2 days. The cells are then fixed, and viral replication is detected using a mixture of murine anti-VZV monoclonal Abs and anti-mouse Abs conjugated to horseradish peroxidase (HRPO). The HRPO activity is detected using a precipitated peroxidase substrate resulting in a brown coloration of VZV-infected cells. The plaques,

visualized as collections of stained cells, are counted, and the ratio of the number of plaques for each serum dilution to the number of plaques when no serum is added (control wells) is calculated. The neutralizing Ab titre is reported as the reciprocal of the serum dilution that reduces the number of plaques by 50% (ED50).

PCR Assay for Confirmation of suspected case of HZ

HZ cases will be confirmed by a Polymerase Chain Reaction (PCR) based algorithm that assesses the presence of VZV DNA in samples, and the adequacy of the samples (by assessing the presence of β-actin DNA). Herpes Simplex Virus (HSV) qPCR will be performed on VZV negative/ β -actin positive samples for exploratory purpose to assess if the rash lesions are due to HSV(1 or 2) and not to VZV; it is not part of the decision making process for HZ case confirmation. HSV qPCR testing is optional and requires specific consent from the individual subjects.

VZV, HSV1/2 and β-actin DNA in HZ clinical specimens will be assessed using real-time PCR detection by the 5' nuclease assay based on the Taqman probe technology [Heid, 1996]. If the VZV PCR is negative, β-actin PCR will be performed to assess adequacy of the sample and if a specimen is found to be VZV–PCR negative and β-actin–PCR negative, it is considered to be inadequate. If VZV PCR is negative and β-actin PCR is positive, a generic PCR for HSV1/2 will be performed.

In the Taqman-based PCR experiments, the formation of a PCR product is monitored in real-time during amplification by means of fluorogenic probes that bind specifically to the amplified product. The reporter fluorophore is at the 5' end of the Taqman probe and the quencher is at the 3' end. As long as the probe is intact, no fluorescence is produced by the fluorophore. During the PCR polymerization step, the Taq DNA polymerase displaces the Taqman probe by 3-4 nucleotides, and the 5' nuclease activity of the DNA polymerase separates the fluorophore from the quencher, and a measurable fluorescent signal proportional to the DNA copy number is produced.

As mentioned above, the 5' nuclease-based PCR assay allows the determination of the DNA copy number within samples, but in the present study the VZV, HSV1/2 and β-actin DNA PCR data on samples from suspected HZ lesions (swabs of vesicles, papules and crusts, and crusts themselves) will be used qualitatively only according to the above mentioned approach.

Appendix B ASCERTAINMENT OF HZ CASES INCLUDING PCR TESTING ALGORITHM TO CLASSIFY HZ SUSPECTED CASES

A suspected case of HZ is defined as new unilateral rash accompanied by pain (broadly defined to include allodynia, pruritus or other sensations) and no alternative diagnosis. This suspected case will be documented by digital photography of the rash and by collecting any relevant information as described in the clinical protocol.

To classify the suspected case of HZ, the samples from the rash lesions will be collected for laboratory testing by PCR (3 samples, collected on the same day, per subject). If during clinical evaluation at Visit HZ-1, the investigator determines that adequate rash lesion samples cannot be collected (i.e., less than three lesions present, or if only papules are present), the subject should be asked to return to the study site for collection of additional samples prior to or at the Visit HZ-2 if there is rash progression (i.e., appearance of new/additional lesions if originally less than three lesions present, or appearance of vesicles if originally only papules present). When the subject returns for repeat sample collection, three samples from separate lesions should be collected. See the Study Procedures Manual for further details on sample collection.

Each rash lesion will be tested using standardized and validated molecular assays according to the PCR testing algorithm described below.

A hierarchical case definition algorithm, similar to the algorithm used by Merck in their Shingle Prevention Study (*Zostavax* efficacy study) [Oxman, 2005] will be used to classify each suspected case of HZ as a confirmed HZ case or not.

- If at least 1 sample coming from a given subject is “VZV positive” by PCR (as defined below), the PCR algorithm will classify the “suspected HZ case” as a “confirmed case of HZ”.
- If all the samples coming from a given subject are “VZV negative” (as defined below), then β-actin PCR will be performed. If one or more “VZV negative” samples are “β-actin positive”, this means that the sampling procedure is valid-and that the “suspected HZ case” will be classified as “not a case of HZ”. HSV qPCR will be performed on VZV negative/ β-actin positive samples for exploratory purpose to assess if the rash lesions are due to HSV and not to VZV; it is not part of the decision making process for HZ case confirmation. HSV qPCR testing is optional and requires specific consent from the individual subjects.
- If PCR results for a particular subject do not confirm or exclude a “suspected HZ case” (i.e. samples coming from a given subject are considered as “inadequate” as both VZV and β-actin PCR results are negative, or no samples are available for the subject), only then will the classification by the HZAC be used to confirm or exclude the suspected HZ case. The HZAC will consist of three to five physicians with HZ expertise. For every suspected HZ case, each HZAC member will be asked to make a clinical determination of whether the case is HZ based on review of the available clinical information. A “suspected HZ case” will be considered as “HZ” if all HZAC members concur (unanimous decision); otherwise, it will be classified as “not HZ”.

This algorithm includes the following steps (see Figure 2):

1. DNA extraction from the rash lesion.

VZV real-time PCR assay (qPCR) targeting the orf62 gene is performed to detect VZV in the rash lesion:

1. If the VZV qPCR signal is ≥ the cut-off level, i.e. the technical limit of detection (LOD) of the assay (10 VZV DNA copies), the sample will be considered as "VZV positive".
2. If the VZV qPCR signal is above 0 copy/qPCR but below the cut-off level of the assay, it will be considered as "VZV borderline" and will be re-tested twice in order to obtain 3 results per sample. The sample will be considered as "VZV positive" if at least 2 results out of the three obtained are ≥ the cut-off level of the assay and it will be considered "VZV negative" if fewer than 2 samples are ≥ the cut-off level of the assay.
3. If the VZV qPCR signal is equal to 0 copies/qPCR, the sample will be considered as "VZV negative". If every sample is VZV negative, then extracted DNA from the samples will be assessed for the presence of β-actin DNA to confirm the validity of the rash lesion sampling procedure (see step 3).

As described above, if all the samples are VZV negative for a given subject, then β-actin qPCR will be performed on "VZV negative" samples to confirm the validity of the sampling procedure.

1. If the β-actin qPCR signal is below the cut-off level of the assay (β-actin Negative), the sample will be considered as "inadequate" as no β-actin DNA from human cells is detected within the rash lesion sample. If all samples are β-actin Negative, then the classification by the HZAC will be used to confirm or exclude the HZ case.
2. If the β-actin qPCR signal is ≥ the cut-off level of the assay (β-actin Positive), the sample will be considered as "valid" but without any VZV DNA. The extracted DNA may then be assessed for the presence of HSV-1/2 within the rash lesion (see below). If at least one sample is β-actin Positive, then the HZAC classification of a suspected HZ case, will not be part of the decision-making process for HZ case confirmation.

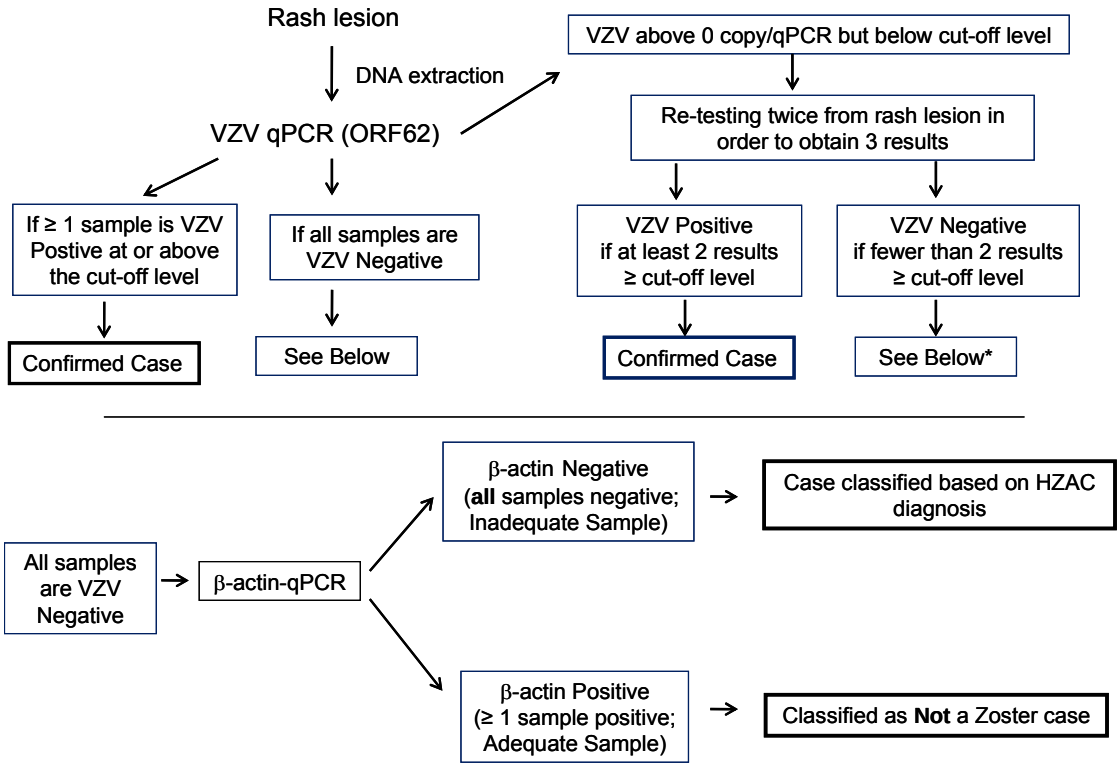
As described above the HSV qPCR assay may be performed for exploratory purpose on "VZV negative/ β-actin positive samples:

1. If the HSV qPCR signal is below the cut-off level of this assay, the sample will be considered as "HSV negative".

If the HSV qPCR signal is ≥ the cut-off level of this assay, the sample will be considered as "HSV positive".

Note: The cut-off level of the VZV qPCR, β-actin qPCR and HSV qPCR assays is defined as the technical limit of detection of these assays (LOD; i.e. lowest concentration that can be detected by PCR in at least 95% of the tests).

Figure 2 Algorithm for HZ case definition by PCR



VZV: Varicella Zoster Virus; Q-PCR: real-time (quantitative) PCR; HSV: Herpes Simplex Virus
* If the VZV qPCR signal is above 0 copy/qPCR but below the cut-off level of the assay, it will be considered as "VZV borderline" and will be re-tested twice in order to obtain 3 results per sample. The sample will be considered as "VZV positive" if at least 2 results out of the three obtained are ≥ the cut-off level of the assay and it will be considered "VZV negative" if fewer than 2 samples are ≥ the cut-off level of the assay. See then below 'All samples are VZV Negative'.
Note: The cut-off level of the VZV qPCR assay is defined as the technical limit of detection of the assay (LOD of 10 VZV DNA copies; i.e. lowest concentration that can be detected by PCR in at least 95% of the tests)

Appendix C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change 1**	
eTrack study number and Abbreviated Title	110390 (ZOSTER-006)
IND number	BB-IND 13857
EudraCT number	2008-000367-42
Administrative change number:	Administrative Change 1
Administrative change date:	20-APR-2010
Co-ordinating author:	[redacted] Scientific Writer

Rationale/background for changes:

- The original protocol (7 April 2010) had an incorrect EudraCT number (2008-00367-42), which was missing a zero. The correct number 2008-000367-42 has been included (instead of 2008-00367-42 as stated in the original protocol).
- The title of the sponsor signatory has been updated.

Title Page

EudraCT number 2008-***0***00367-42

Protocol Sponsor Signatory Approval Page

EudraCT number 2008-***0***00367-42

[redacted]
Vice President ***and Director***
~~Global Clinical Development~~
Late Clinical Development
GlaxoSmithKline Biologicals

Protocol Investigator Agreement Page

EudraCT number 2008-***0***00367-42

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 1

eTrack study number and Abbreviated Title(s)	110390 (ZOSTER-006)
IND number	BB-IND 13857
EudraCT number	2008-000367-42
Amendment number:	Amendment 1
Amendment date:	16-DEC-2010
Co-ordinating author:	[redacted] Scientific Writer

Rationale/background for changes:

- At the request of GSK Japan, signature lines were included for the GSK Japan Representative on the Investigator Agreement Page.
- A clarification has been added regarding the completion of the ZBPI beyond 24hrs prior to clinical evaluation at Visit HZ-1 (Sections 5.5.2.2 and 5.6).
- The process for ascertainment of HZ cases including the PCR testing algorithm to confirm or exclude suspected HZ cases and the circumstances under which suspected HZ cases will be referred to the HZ Ascertainment Committee (HZAC) has been updated and further clarified (Sections 5.5.2.3, Appendix A and Appendix B) (Figure 1 has been updated and both the original and amended versions are presented). It has been further clarified that**,** if based on qPCR test results the diagnosis of HZ can be excluded, exploratory testing may be performed to assess if the rash lesions are due to Herpes Simplex Virus (HSV); and that this testing is optional (Sections 5.5.2.3, 5.6, 5.8, 5.8.2, Appendix A and Appendix B)..
- Section 5.5.3 has been updated to maintain consistency with the current IDMC charter.
- Sections 5.6 and 5.7.3.6. have been updated to state that the treatment number must be recorded in the eCRF at <u>each</u> vaccination visit, rather than the <u>first</u> vaccination visit only.
- The procedures in case of temperature deviation during vaccine storage have been updated to reflect the most current standards for GSK Biologicals in Section 6.2.
- Section 6.3 was updated to clarify that the non-dominant arm is the preferred injection site for every dose.
- At the request of the US FDA, Sections 5.7.3.7 and 6.5 were updated to specify that subjects with a SAE (as judged by the investigator) related to the first dose of the vaccine should not receive a second dose.
- To reflect the most current standards for GSK Biologicals, wording regarding the description of potential immune-mediated diseases (pIMDs) [formerly referred to as new onset of autoimmune diseases (NOADs) and other immune mediated inflammatory disorders] has been updated, and the procedure has been added to report pIMDs to GSK Biologicals within 24 hrs of awareness using SAE screens (Sections 8.3.2.5 and 8.4.1; and Synopsis, List of Abbreviations, Sections 5.6, 5.7.3.9, 5.7.3.14, 5.7.3.16, 6.6, 6.6.2, 8.3.1, 10.2 and 10.8.5.1).

- The contact details for reporting of emergency code break have been updated in Section 8.7.
- The provisional regional allocation has been updated to reflect the most recent estimates for the study in Section 10.4.5.4. A clarification has been added that enrolment target numbers per region are approximate and may change depending on the enrolment (Sections 4.1 and 10.4.5.4).
- In Section 10.4.5.6.3, the subsection 'Using the Ratio of Responder Rates - Country-wise' has been deleted, as the responder rate will not be used to compare vaccine responses between countries.
- Clarification has been added to Section 10.4.5.7.1 with regards to the 1.5-fold increase used for the sample size calculation.
- Details in Sections 10.8.4.1 and 10.8.4.2 regarding the analysis of quality of life questionnaires (SF-36 and EQ-5D) have been removed from the protocol as they will be presented in the RAP.
- At the request of GSK Taiwan, additional wording was added to Section 12 (Country Specific Requirements) that countries should follow local regulations and guidelines for AE and SAE reporting as required by their respective healthcare authorities and ethics committees.
- Inconsistencies, redundancies and typographical errors have been corrected or clarifications have been added in the following Sections: Title page, List of Abbreviations; 3, 4.1, 4.3, 5.5.1, 5.5.2.1, 5.5.2.2, 5.5.2.5, 5.6, 5.7.2.2, 5.7.3, 5.7.3.1, 5.7.3.2, 5.7.3.6, 5.7.3.10, 5.7.3.11, 5.7.3.14, 5.7.3.16, 5.8.2, 5.8.3, 5.8.4.1, 7, 8.1.1 , 8.2.1, 8.3.2.2.1, 10.4.1, 10.4.5.3, 10.4.5.5, 10.6.2, 10.7.2, 10.7.3, and Appendix B.

The numbering of protocol sections and tables has been updated, as applicable.

Amended text has been indicated in *bold italics* and deleted text has been indicated in strikethrough (e.g. ~~text)~~ in the following sections:

Title Page

Contributing authors

- [redacted]***, Biostatistician***
- [redacted]***, Project Manager Clinical Laboratory***

Protocol Amendment Investigator Agreement

Study Representative (Japan) _____

Signature _____

Date _____

Synopsis

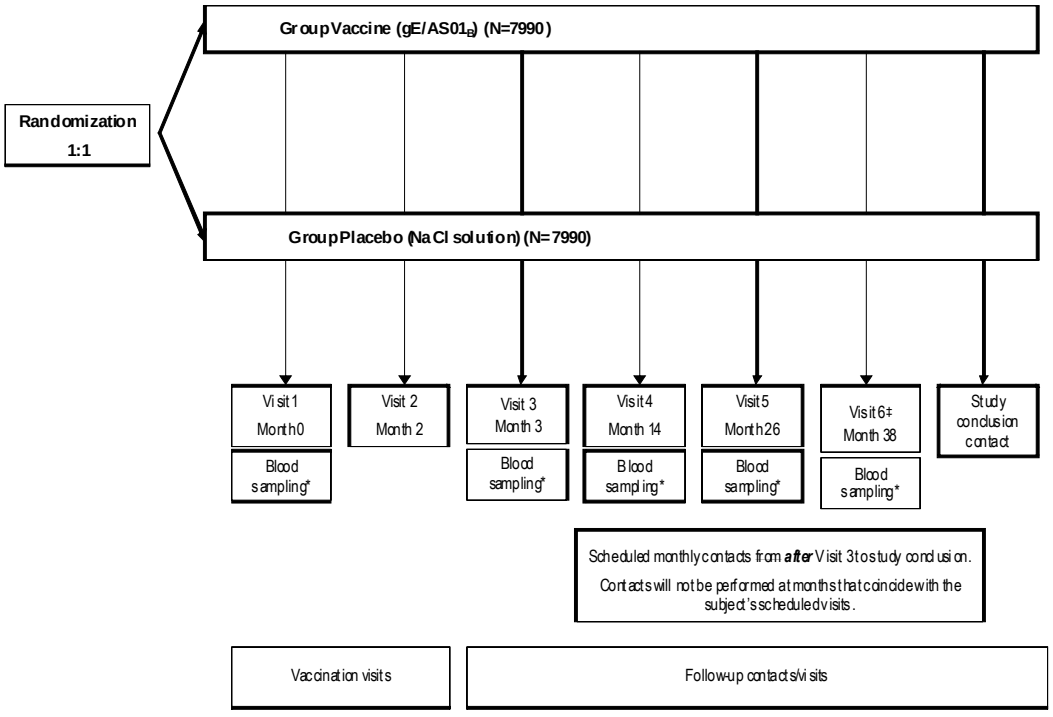
- Occurrence of pre-defined AEs
  - Occurrence and relationship to vaccination of any ***potential immune-mediated diseases (pIMDs)***[1] ~~new-onset of autoimmune diseases (NOADs) and other immune mediated inflammatory disorders~~ during the entire study period in all subjects**;**

Footnote 1: ***Formerly referred to as new onset of autoimmune diseases (NOADs) and other immune mediated inflammatory disorders.***

LIST OF ABBREVIATIONS

LOD	***Limit Of Detection***
PIMD	***Potential Immune-Mediated Disease***

3 Study Design Overview



4.1 Number of subjects/centres

Target enrolment is approximately ***15,980*** ~~16,000~~ eligible subjects using a 1:1 randomization ratio (vaccine:placebo).

Table 1 Subsets in study ZOSTER-006

Subset name	Description
7-day diary card	Diary card completion for recording of solicited adverse events (AEs) (from Day 0 to Day 6 after each vaccination)
Immunogenicity	Blood samples (approximately 10 mL) collected at Visit 1, 3, 4, 5 and 6 will be analyzed to assess humoral immune response
CMI *component of the Immunogenicity subset*	Blood samples (approximately 20 mL) collected at Visit 1, 3, 4, 5 and 6 will be analyzed to assess CMI response

Note: Blood samples (approximately 10 mL) will be collected from all subjects at Visits 1 and 3, and will be used to assess correlate of protection.

Overview of the recruitment plan

Furthermore, enrolment target numbers per region (see Section 10.4.5.4) are approximate and may change depending on the enrolment.

4.3 Exclusion criteria for enrolment

- Administration or planned administration of any other immunizations within 30 days before the first or second study vaccination or scheduled within 30 days after study vaccination. However, licensed non-replicating vaccines (i.e., inactivated and subunit vaccines, including inactivated and subunit influenza vaccines ***for seasonal or pandemic flu***, with or without adjuvant ~~for seasonal or pandemic flu~~) may be administered up to 8 days prior to each dose and/or at least 14 days after any dose of study vaccine;
- Chronic administration (defined as > ***15*** consecutive ~~15~~ days) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose**.**

5.5.1 Data collection

~~Starting at~~ ***After*** Visit 3 monthly contacts between the subjects and the investigator and/or his delegate will take place to collect information on any event of interest that may have occurred [see Table 2 and Section 5.7.4.14 for details].

For all subjects:

- **EQ-5D and SF-36 questionnaires:** To be completed by all subjects at study entry. Also, to be completed by all subjects at Visits 4, 5 and 6 (subjects with an ongoing ***clinically diagnosed suspected*** HZ episode will follow a weekly schedule and do not need to additionally complete the questionnaires at these visits).

EQ-5D and SF-36 will remain as source documents. The information from these questionnaires will only be transcribed into the eCRF for subjects who have ***clinically diagnosed suspected*** ~~confirmed~~ HZ during the study.

For all subjects in case of a suspected or confirmed case of HZ:

- **Zoster Brief Pain Inventory (ZBPI) questionnaire:** To be completed by subjects with clinically diagnosed suspected HZ on Day HZ-0 (Visit HZ-1) and daily from

Day HZ-1 (day after the Visit HZ-1) up to Day HZ-28, and weekly from Day HZ-29 onwards until the case of suspected HZ is disproved, OR until a 4-week pain-free period is documented, OR until the cut-off date for final analysis. For all subjects with ***ongoing*** HZ-associated pain ***at the time of*** the cut-off date for final analysis, ZBPI data will be collected until ***suspected HZ is disproved, OR until a 4-week pain-free period is documented OR until*** at least Day HZ-90 ~~regardless of the cut-off date for final analysis .~~ ***(see Section 5.5.2.2 for more details)***

- **EQ-5D and SF-36 questionnaires: To be completed w**eekly by the subjects with clinically diagnosed suspected HZ from Day HZ-0 onwards until the case of clinically diagnosed suspected HZ is disproved, OR until a 4-week pain-free period is documented, OR until the cut-off date for final analysis. For all subjects with ***ongoing*** HZ-associated pain ***at the time of*** the cut-off date for final analysis, EQ-5D and SF-36 data will be collected until ***suspected HZ is disproved, OR until a 4-week pain-free period is documented OR until*** at least Day HZ-90 ~~regardless of the cut-off date for final analysis..~~ ***(see Section 5.5.2.2 for more details)***

5.5.2 Evaluation and confirmation of suspected and confirmed HZ cases

5.5.2.1 Definitions

The end date of a HZ episode is defined as the first time at which a subject had no rash (papules, vesicles, ulcers or crusts) and after which he/she did not develop a rash at the same location at any later visit/contact. This end date will be recorded in the eCRF.

5.5.2.2. Evaluation of suspected case of HZ

All HZ cases that occur during the study period up to the cut-off date for final analysis will be followed and evaluated. ***Please refer to the SPM for information about recording*** ~~Any~~ HZ cases that occur after the cut-off date for final analysis. ~~will be recorded in the study database and~~ ***Such cases will be*** referred to the local physician for follow-up.

- The study staff/investigator will ask the subject to complete a ZBPI questionnaire at Visit HZ-1 to rate HZ-associated pain ***within the last 24 hours. If the time between the HZ onset and clinical evaluation at Visit HZ-1 is greater than 24 hours, the subject will be asked to complete a second ZBPI also for the elapsed time between the HZ onset and 24 hours before Visit HZ-1;***

- The subject will be given a supply of ZBPI, EQ-5D and SF-36 questionnaires. The ZBPI questionnaires will be used to collect information on the severity of HZ-associated pain, the duration of HZ-associated pain ~~and rash~~, and the impact of the HZ episode on subject's QoL.

- The subject will be asked to complete the ZBPI questionnaires daily from Day HZ-1 (day after the Visit HZ-1) up to Day 28, and weekly from Day HZ-29 onwards until:
  - The cut-off date for final analysis. ~~For all subjects with HZ-associated pain, ZBPI pain data will be collected until at least Day HZ-90, regardless of the cut-off date for final analysis;~~

  For all subjects with ongoing HZ-associated pain at the time of cut-off date for final analysis~~, If a subject with clinically diagnosed suspected HZ has not completed follow-up until at least Day HZ-90 at the cut-off date for final analysis, and the case is not disproved~~, follow-up for such a subject will continue until ***suspected HZ is disproved, OR until a 4-week pain-free period is documented OR until at least*** ~~the~~ Day HZ-90~~. follow-up is completed~~. The study conclusion contact for such a subject will thus occur after he/she completes ~~Day HZ-90~~ follow-up ***as descrived above.***

After Visit HZ-1 until Visit HZ-7, visits/contacts will take place for follow-up of the HZ episode according to the schedule presented in Table 3. ***Follow-up of HZ-associated pain and complications will continue irrespective of whether the rash has ended in some cases***. Follow-up of HZ-associated pain persisting beyond Visit HZ-7 or other complications will be done at monthly contacts between the subjects and the investigator and/or his delegate that are planned ~~starting at~~ ***after*** Visit 3.

Collection of subsequent HZ ***episode***-related information will be stopped and no further information on that suspected HZ episode will be encoded in the clinical database.

- The study staff/investigator will: 1) record relevant information regarding the clinically diagnosed suspected HZ case (such as the location and nature of HZ lesions, ***the end date of the rash,*** HZ-related complications, if any); 2) record concomitant medications/vaccinations, including concomitant medication the subject has already received and/or will receive for HZ treatment or treatment of any HZ-related complications (Section 6.6); 3) record intercurrent medical conditions (Section 6.7); and 4) check if the subject received any medical attention [hospitalization, emergency room visit, or a visit to or from medical personnel (medical doctor)] for HZ or any HZ-related complication. ~~Concomitant medication the subject has already received and/or will receive for HZ treatment will be recorded in the eCRF.~~

5.5.2.3 Confirmation of *clinically diagnosed* suspected case of HZ

A ***clinically diagnosed*** suspected case of HZ can be confirmed in two ways:

- By Polymerase Chain Reaction (PCR):

  In addition, if based on qPCR test results the diagnosis of HZ can be excluded, Herpes Simplex Virus (HSV) qPCR may be performed to assess if the rash lesions are due to HSV (1 or 2). This exploratory testing is not part of the process for HZ case confirmation (see Appendix A and Appendix B). This testing is optional and requires specific consent from the individual subjects.

- By the HZ Ascertainment Committee:

  All clinically diagnosed suspected HZ cases will be referred to the HZ Ascertainment Committee (HZAC). The HZAC will classify all referred cases as either "HZ" or "not HZ". However, the HZAC classification will serve as the final case definition only when the case cannot be confirmed or excluded by PCR, e.g., when all samples from a given subject are inadequate (as when both VZV and β-actin PCR results are negative), or when no samples are available for a given subject. Therefore, definitive PCR results, when available, will determine the final HZ case assignment. In such cases, the HZAC classification will not contribute to HZ case determination decision.

  ~~All cases of clinically diagnosed suspected HZ that cannot be confirmed or excluded by PCR [if the PCR specimen is inadequate (i.e., negative for both virus and β-actin DNA) or is missing] will be reviewed by the HZ Ascertainment Committee (HZAC).~~ The HZAC will consist of three to five physicians with HZ expertise. HZAC members, participating as investigator in this study, will not evaluate cases from their own study site. HZAC members will be blinded to treatment assignments. For every such case, each reviewing HZAC member will be asked to make a clinical determination of whether the case is HZ based on review of the available clinical information (***e.g.,*** summary of the rash and pain evaluations, digital photographs of the subject's rash, and clinical progress notes). ~~A unanimous diagnosis of "a confirmed case of HZ" or "not a case of HZ" will constitute a confirmed clinical diagnosis. HZAC members will discuss each non-unanimous case~~. A ***clinically diagnosed*** suspected case of HZ will be considered ***as*** ~~a~~ "~~clinically confirmed case of~~ HZ" if ~~the majority of~~ the HZAC members concur ***unanimously***; otherwise, it will be classified as "not ~~a case of~~ HZ". ***As described above, the HZAC case assignment will only be considered as the final case assignment if definitive PCR results are not available.*** Further details will be provided in the HZAC charter.

5.5.2.4 Evaluation of severity of HZ-associated pain using the Zoster Brief Pain Inventory

In each case of clinically diagnosed suspected HZ, the subjects will be asked to assess their HZ-associated pain and interference of HZ with their QoL by completing the ZBPI questionnaire either themselves or assisted, by an aide (Section 5.5.1) until the suspected case of HZ diagnosed is disproved, HZ-associated pain ceases (defined as a 28-day [or 4-week] pain free period) or until the cut-off date for final analysis ~~(for all subjects with HZ-associated pain, ZBPI pain data will be collected until at least Day HZ-90, regardless of the cut-off date for final analysis)~~ (***see further details in*** Section 5.5.2.2).

5.5.2.5 HZ complications

The presence of HZ complications listed below will be documented in the eCRF ~~at each contact/study visit~~, independently from the AE reporting ***of those HZ complications (refer to the SPM for details).***

5.5.3 Independent Data Monitoring Committee

~~The GSK Biologicals biostatistician and a member~~ ***One or more members*** of the Zoster vaccine program will attend the IDMC meeting open sessions to immediately reply to any questions from the IDMC members.

~~The futility rules will be described in the IDMC Charter.~~

Vaccine efficacy for futility analysis, and other analyses described in the protocol to be done in preparation of IDMC review, will be further detailed in the IDMC Reporting and Analysis Plan (RAP).

5.6 Outline of study procedures

Table 2 List of study procedures

(Bullet added at Visit 2 for Recording of treatment number)

Type of contact	VISIT 1	VISIT 2
Timepoints	Day 0*/ Month0	Month 2
Sampling timepoints	Pre-Vacc	Post-Vacc 1
Randomization[d]	○	
Recording of treatment number	●	●
Reporting of ***potential immune-mediated diseases (pIMDs)†*** ~~new onset of autoimmune diseases (NOADs) and other immune mediated inflammatory disorders~~ ***according to guidelines In Section 8.3.2.5***	● [d]	●
Transcription[g] by study staff/investigator of EQ-5D and SF-36 questionnaires completed ~~- by all subjects~~ ~~- by subjects who do not have an ongoing HZ episode~~	●	

Note: ~~Starting at~~ ***After*** Visit 3, monthly contacts between the subjects and the investigator and/or his delegate will be scheduled for the subject to respond to a standard set of questions, in a language that is understandable to the subject, to collect information on safety and the occurrence of HZ, and to follow-up ongoing HZ cases (Section 5.5.1).

† formerly referred to as new onset of autoimmune diseases (NOADs) and other immune mediated inflammatory disorders.

[g] EQ-5D and SF-36 will remain as source documents. The information from these questionnaires will only be transcribed in the eCRF for subjects who have a ***clinically diagnosed suspected HZ*** ~~zoster~~ event during the study.

Table 3 Study procedures to be performed during the follow-up period for each suspected HZ case

(Asterisk added after 'Section 5.7.3.11' for the listed study procedure)

Type of contact
Timepoints
Collect HZ lesion samples (3 replicate samples) for confirmation by PCR of a case of clinically diagnosed suspected HZ as specified in Section 5.7.3.11*, ***and for exploratory HSV qPCR*** **

Note: If the case of clinically diagnosed suspected HZ is disproved, or if HZ-associated pain ceases (defined as a 28-day [or 4-week] pain free period), subsequent ***HZ*** follow-up visits or contacts will be cancelled. When case of clinically diagnosed suspected HZ is disproved, collection of HZ-related information will be stopped and no further information on that suspected HZ episode will be encoded in the clinical database.

**** If during clinical evaluation at Visit HZ-1, the investigator determines that only papules are present, three samples should be collected (if possible). The investigator has the option of collecting three additional samples if the rash progresses to vesicles or crusts are present prior to or at the Visit HZ-2.. See the SPM for further details on PCR sample collection. ** If based on qPCR test results the diagnosis of HZ can be excluded, Herpes Simplex Virus (HSV) qPCR may be performed to assess if the rash lesions are due to HSV (1 or 2). This exploratory testing is not part of the decision making process for HZ case confirmation (see Appendix A and Appendix B). This testing is optional and requires specific consent from the individual subjects.***

† Subjects with clinically diagnosed suspected HZ will be asked to complete the ZBPI questionnaire at Day HZ-0 (Visit HZ-1) ***to rate HZ-associated pain within the last 24 hours (If the time between the HZ onset and clinical evaluation at Visit HZ-1 is greater than 24 hours, the subject will be asked to complete a second ZBPI also for the elapsed time between the HZ onset and 24 hours before Visit HZ-1)***; daily from Day HZ- 1 to Day HZ-28, and weekly from Day HZ-29 onwards until ***suspected HZ is disproved***, a 4-week pain-free period is documented or until the cut-off date for final analysis. ***For all subjects with ongoing HZ-associated pain at the time of cut-off date for final analysis, ZBPI data will be collected until suspected HZ is disproved, OR until a 4-week pain-free period is documented OR until at least Day HZ-90***. ~~(ZBPI pain data will be collected until at least Day HZ-90)~~ ***(See Section 5.5.2.2)***

‡Subjects with clinically diagnosed suspected HZ will be asked to complete the EQ-5D and SF-36 questionnaire weekly from Day HZ-0 onwards until ***suspected HZ is disproved,*** a 4-week pain-free period is documented or until the cut-off date for final analysis. ***For all subjects with ongoing HZ-associated pain at the time of cut-off date for final analysis, EQ-5D and SF-36 data will be collected until suspected HZ is disproved, OR until a 4-week pain-free period is documented OR until at least Day HZ-90***. (~~EQ-5D and SF-36 data will be collected until at least Day HZ-90).~~***(See Section 5.5.2.2).***

Each clinically diagnosed suspected HZ that occurs up to the cut-off date for final analysis will be followed at least until ***Visit HZ-7 (***the study visit at Day HZ-91***)***. ***Follow-up of HZ-associated pain and complications will continue irrespective of whether the rash has ended in some cases***. ***(See Section 5.5.2.2).***

The study staff/investigator will dispense additional questionnaires and provide instructions for the subject to return the completed questionnaires to the study site. The subjects will be given a new supply of questionnaires as necessary. Follow-up of HZ-associated pain persisting beyond ***Visit HZ-7 (***Day HZ-91***)*** or other complications will be done at monthly contacts that are planned ~~starting at~~ ***after*** Visit 3 between the subjects and the investigator and/or his delegate.

Time intervals between study visits/contacts related to study procedures performed in subjects participating in the study are presented in Table 4. In addition; ~~starting at~~ ***after*** Visit 3, monthly contacts between the subjects and the investigator and/or his delegate will be scheduled.

Follow-up for the occurrence of any SAEs will begin at Day 0 and continue until Month 14. Follow-up for the occurrence of SAEs related to study participation, or related to a concurrent GSK medication/vaccine or any fatal SAE, will continue until study conclusion. Follow-up for the occurrence of ***potential immune-mediated diseases (pIMDs), formerly referred to as*** new onset of autoimmune diseases and other immune mediated inflammatory disorders**,** will begin at Day 0 and continue until study conclusion.

Table 5 Intervals between contacts with subjects in case of suspected HZ

Table Footnotes

Note: If a case of clinically diagnosed suspected HZ is disproved or if pain ceases (i.e., after a 4-week pain-free period is documented), subsequent follow-up ***HZ*** visits or contacts may be cancelled. Follow-up of HZ-associated pain persisting beyond ***Visit HZ-7 (***Day HZ-91***)*** or other complications will be done at monthly contacts between the subjects and the investigator and/or his delegate that are planned ~~starting at~~ ***after*** Visit 3

5.7.2.2. Collect demographic data

Record demographic data such as ***information regarding*** date of birth, gender, geographic ancestry and ethnicity in the subject's eCRF.

5.7.2.3 Medical history

~~Perform a history-directed medical examination~~ ***Review*** and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study in the eCRF

5.7.3. Procedures during the study

Note that ***the urine pregnancy test*** ~~some of the procedures to be performed during the vaccination visits, i.e., Visits 1 and 2, (such as history directed physical examination and urine pregnancy test) are~~ ***is*** performed prior to ~~the first~~ vaccination and ~~are~~ ***is*** described in Section 5.7.2.

5.7.3.1 Check and record concomitant medication/vaccination and intercurrent medical conditions

Any subject with a clinically diagnosed ***suspected*** HZ episode between Visit 1 and Visit 2 should not receive the second vaccination.

5.7.3.2. Check contraindications to vaccination

See Section 5.7.3.7 for ~~an~~ additional ***criteria*** ~~criterion~~ to be checked prior to administration of the second vaccination dose.

5.7.3.6. Treatment number assignment

At the first vaccination visit, the subject will be assigned a treatment number defining the treatment he/she will be receiving. The treatment number must be recorded in the eCRF at ~~the first~~ ***each*** vaccination visit.

If there is a need for a site to use a replacement vaccine ~~at the subsequent visit~~, then that treatment number needs to be transcribed into the eCRF (see Section 6.4).

5.7.3.7. Vaccination

- Any subject with clinically diagnosed ***suspected*** HZ episode between Visit 1 and Visit 2 should not receive the second dose.
- ***Any subject with an SAE related to the first dose of vaccine (as judged by the investigator) should not receive the second dose (Section 6.5).***

5.7.3.9 Recording of *potential immune-mediated diseases (pIMDs)* ~~new onset of autoimmune diseases (NOADs) and other immune mediated inflammatory disorders~~

As specified in the List of Study Procedures (Table 2, Section 5.6), ***potential immune-mediated diseases (pIMDs), formerly referred to as*** NOADs and other immune mediated inflammatory disorders**,** occurring from administration of the first dose of vaccine/placebo onwards until end of the trial will be recorded.

Refer to Section8.3.2.5 for information on recording of ***pIMDs*** ~~NOADs and other immune mediated inflammatory disorders~~.

5.7.3.10 Recording of data from completed EQ-5D and SF-36 questionnaires

EQ-5D and SF-36 questionnaires: To be completed by all subjects at study entry. Also, to be completed by all subjects at Visits 4, 5 and 6 (subjects with an ongoing ***clinically diagnosed suspected*** HZ episode will follow a weekly schedule and do not need to additionally complete the questionnaires at these visits).

EQ-5D and SF-36 will remain as source documents. The information from these questionnaires will only be transcribed into the eCRF for subjects who have ***clinically diagnosed suspected*** ~~confirmed~~ HZ during the study.

5.7.3.11. Follow up of suspected HZ cases and HZ-associated pain

For all subjects with ***ongoing*** HZ-associated pain ***at the time of cut-off date for final analysis, ZBPI data will be collected until suspected HZ is disproved, OR until a 4-week pain-free period is documented OR until at least*** Day HZ-90. ~~For all subjects with HZ-associated pain, ZBPI pain data will be collected until at least Day HZ-90, regardless of the cut-off date for final analysis~~. In addition, subjects with clinically diagnosed

suspected HZ will be asked to complete EQ-5D and SF-36 questionnaires weekly. ***Refer to Section 5.5.2.2 for more details.***

Three replicate rash lesion samples (see Table 6) should be collected on the same day ~~according to the guidelines provided in the SPM~~. ***If during clinical evaluation at Visit HZ-1, the investigator determines that only papules are present, three samples should be collected (if possible). The investigator has the option of collecting three additional samples if the rash progresses to vesicles or crusts are present prior to or at the Visit HZ-2. See the SPM for further details on sample collection.***

5.7.3.14 Reminder for monthly follow-up contacts/yearly follow-up visits

The subject will be reminded that, ~~starting at~~ ***after*** Visit 3, monthly contacts between the subjects and the investigator and/or his delegate will take place (except at months that coincide with the subject's scheduled visits) in order to collect all relevant information on any event of interest that may have occurred [including SAEs (Section 8.3), ***pIMDs*** ~~NOADs and other immune mediated inflammatory disorders~~ (Section 8.3.2.5), occurrence or follow up of a suspected episode of HZ (Section 5.5.2), intercurrent medical conditions (Section 6.7), medically attended visits (up to Month 8 only, Section 8.3.2.4), the use of concomitant medications and/or vaccinations (Section 6.6) or pregnancy (Section 8.3)], and that information will be recorded in the appropriate section of the subject's eCRF.

5.7.3.16 Study conclusion

When the cut-off date for final analysis is established, the study sites will contact the subjects for the study conclusion contact ***as soon as possible***. If a subject with clinically diagnosed suspected HZ has not completed follow-up until at least Day HZ-90 at the cut-off date for final analysis, ~~and the case is not disproved,~~ follow-up for such a subject will continue until ~~the~~ Day HZ-90 (***or sooner (1) if the case is disproved or (2) if the subject has no HZ-associated pain for 4 consecutive weeks)*** ~~follow-up is completed~~. The study conclusion contact for such a subject will thus occur after he/she completes ~~Day HZ-90~~ follow-up ***as described above***.

- Recording of ***pIMDs*** ~~NOADs and other immune mediated inflammatory disorders~~ (Section 5.7.3.9).

After ~~At~~ study conclusion, if the study vaccine demonstrates sufficient evidence of efficacy and safety such that a clinically important benefit may be reasonably expected, placebo recipients ***may*** ~~will~~ be offered cross-over immunization with the study vaccine.

5.8 Biological sampling handling and analyis

Herpes Simplex Virus (HSV) qPCR (see Section 5.8.2) may be performed on Varicella Zoster Virus (VZV) negative β-actin positive samples for exploratory purpose to assess if the rash lesions are due to HSV (1 or 2) and not toVZV; it is not part of the decision making process for HZ case confirmation. This testing is optional and requires specific consent from the individual subjects (see Appendix A and Appendix B).

5.8.2 Biological samples

Table 6 Biological samples

Sample type	Quantity (approximate volume)	Unit	Timepoint	Subset Name*
Clinical specimens of HZ lesions	3 replicate samples, taken on the same day, of the highest priority lesion type available (1) vesicle fluid; 2) crust; 3) crust swab; 4) papule swab) †	NA	***S***~~s~~cheduled in case of suspected HZ for diagnosis	Subjects clinically diagnosed as having a suspected case of HZ

† If during clinical evaluation at Visit HZ-1, the investigator determines that only papules are present, three samples should be collected (if possible). The investigator has the option of collecting three additional samples if the rash progresses to vesicles or crusts are present prior to or at the Visit HZ-2. See the SPM for further details on sample collection

5.8.3 Laboratory assays

Table 9 Molecular Biology (PCR tests)

System	Component
HZ lesion sample	Varicella Zoster Viirus.DNA
HZ lesion sample	Herpes Simplex Virus.DNA**

***** Herpes Simplex Virus (HSV) qPCR may be performed on VZV negative/β-actin positive samples for exploratory purpose to assess if the rash lesions are due to HSV (1 or 2) and not to VZV; it is not part of the decion making process for HZ case confirmation (see Appendix A and Appendix B). This exploratory testing is optional and requires specific consent from the individual subjects.***

5.8.4.1 Immunological read-outs

- For a subgroup of subjects included in the CMI component of the Immunogenicity subset, ***gE and VZV specific*** CMI response will be measured at specified timepoints.
- For the correlates of protection analysis, analysis of the humoral immune responses at ***prevaccination and*** Month 3 will be performed on samples collected from vaccinated subjects who develop confirmed HZ and compared with the humoral immune responses at ***prevaccination and*** Month 3 from matched subjects that did not develop HZ.

6.2 Storage and handling of study vaccine

The study vaccines ~~will~~ ***must*** be stored at the defined temperature range (i.e. +2 to +8°C/36°F to 46°F) and must not be frozen. Please refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccine. The storage temperature of the vaccine will be monitored daily with ~~validated~~ temperature monitoring device(s) ***(at the minimum calibrated)*** and will be recorded as specified in the SPM.

The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact.

Any temperature deviation~~, i.e. temperature~~ outside the ~~defined~~ range ~~(~~***0***~~+2~~°C to +8°C/***32***~~36~~°F to 46°F~~)~~, must be reported to the sponsor as soon as detected. Following an exposure to ***such*** a temperature deviation, vaccines will not be used until ~~written~~ approval has been given by the Sponsor.

In case of temperature deviation between 0 and +2°C/32 and 36°F, the impacted study vaccine can still be administered, but the site must take adequate actions to go back to the defined range +2 to +8°C/36 to 46°F and avoid re-occurrence of such a temperature deviation.

Please ~~R~~***r***efer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the ***Temperature deviation process,*** packaging and accountability of the study vaccine.

6.3 Dosage and administration of study vaccine

The entire volume of the reconstituted vaccine should be withdrawn, the needle can be replaced, and any solution in excess of 0.5mL should be expelled. ~~After confirming that the needle is not in a blood vessel, t~~***T***he reconstituted vaccine ***or a 0.5mL dose of the NaCl solution placebo*** should be administered by IM injection ***into the deltoid muscle using a standard aseptic technique***, preferably ~~into the deltoid muscle of~~ ***in*** the non-dominant arm~~, using a standard aseptic technique. A 0.5 mL dose of the NaCl solution placebo should be injected IM. The injection site should be on the same arm for all injections for an individual subject.~~ In rare situations when there is no other alternative, the ~~second~~ injection may be given ***in the dominant arm***~~on the different arm~~.

6.5 Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of gE/AS01$_B$. If any of these events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 8.4.4).

- ***If the subject experiences an SAE judged to be vaccine-related by the investigator (Sections 8.1.2 and 8.3.2.2.2);***

See **Section 5.7.3.7 for an additional criterion to be checked** prior to administration of the second vaccination dose.

6.6 Concomitant medication/vaccination

Concomitant medication administered for the treatment of ***pIMDs*** ~~NOADs or other immune mediated inflammatory disorders~~ at any time during the study must be recorded in the eCRF. Refer to Section 8.3.2.5 for information regarding ***pIMDs*** ~~NOADs and other immune mediated inflammatory disorders~~ **.**

6.6.2 Time window for recording concomitant medication/vaccination in the eCRF

Concomitant medication, administered for the treatment of HZ or any related HZ-complications, or for the treatment of ***pIMDs*** ~~NOADs or other immune-mediated inflammatory disorders~~, from Day 0 until Study conclusion contact, must be recorded in the eCRF.

7 Health economics

For subjects with clinically diagnosed suspected HZ, both questionnaires will be completed weekly from Day HZ-0 onwards until the case of clinically diagnosed suspected HZ is disproved, OR until a 4-week pain-free period is documented, OR until the cut-off date for final analysis. For all subjects with ***ongoing*** HZ-associated pain ***at the time of the cut-off date for final analysis, EQ-5D and SF-36*** data will be collected until ***suspected HZ is disproved, OR until a 4-week pain-free period is documented OR until*** at least Day HZ-90 ~~regardless of the cut-off date for final analysis..~~

8.1.1 Definition of an adverse event

The occurrence of HZ or PHN will not constitute an AE or SAE. However, ***HZ*** complications ***other than PHN (see Section 5.5.2.5)*** ~~or presentations of HZ or PHN that, in the opinion of the investigator, are not typical of these diseases may~~ ***will*** be ***considered as*** AEs or SAEs.

8.2.1 Disease-related events or outcomes not qualifying as serious adverse events

The occurrence of HZ or PHN will not constitute an ***AE or*** SAE. However, ***HZ*** complications ***other than PHN(see Section 5.5.2.5)*** ~~or presentations of HZ or PHN that, in the opinion of the investigator, are not typical of these diseases may~~ ***will*** be ***considered as AEs or*** SAEs.

8.3.1 Time period for detecting and recording adverse events, serious adverse events and pregnancies

pIMDs ~~NOADs and other immune mediated inflammatory disorders~~ will be evaluated in all subjects during the entire study period (Section 8.3.2.5)

An overview of the protocol-required reporting periods for AEs and SAEs, ***pIMDs*** ~~NOADs and other immune mediated inflammatory disorders~~, medically attended visits,

pregnancies, and intercurrent medical conditions in study ZOSTER-006 is shown in Table 14.

Table 14 Reporting periods for AEs, SAEs, *pIMDs* ~~new onset of autoimmune diseases~~, medically attended visits, pregnancies and intercurrent medical conditions in study ZOSTER-006

Study activity
Timing of reporting
Reporting of ***pIMDs*** ~~NOADs and other immune mediated inflammatory disorders~~

8.3.2.2.1 Assessment of intensity

The investigator will assess ~~of~~ the maximum intensity that occurred over the duration of the event for all other AEs, i.e. unsolicited symptoms, including SAEs reported during the study. The assessment will be based on the investigator's clinical judgement.

8.3.2.5 AEs of specific interest

Potential immune-mediated diseases (pIMDs) (formerly referred to as NOADs and other immune mediated inflammatory disorders) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in the table below.

However, the investigator will exercise his/her medical and scientific judgement in deciding whether other immune-mediated diseases have an autoimmune origin (i.e. pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

Table 16 List of potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy), and neuritis (e.g. optic neuritis) Multiple sclerosis (including variants) Transverse myelitis Guillain-Barré syndrome, (including Miller Fisher syndrome and other variants) Other demyelinating diseases (including acute disseminated encephalomyelitis) Myasthenia gravis (including Lambert-Eaton myasthenic syndrome) Non-infectious encephalitis/ encephalomyelitis Neuritis (including peripheral neuropathies)	Systemic lupus erythematosus Scleroderma (including, CREST syndrome and morphoea) Systemic sclerosis Dermatomyositis Polymyositis Antisynthetase syndrome Rheumatoid arthritis, Juvenile chronic arthritis, (including Still's disease) Polymyalgia rheumatica Reactive arthritis Psoriatic arthropathy Ankylosing spondylitis Relapsing polychondritis Mixed connective tissue disorder	Psoriasis Vitiligo Raynaud's phenomenon Erythema nodosum Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) Cutaneous lupus erythematosus Alopecia areata Lichen planus Sweet's syndrome
Liver disorders	**Gastrointestinal disorders**	**Metabolic diseases**
Autoimmune hepatitis Primary biliary cirrhosis Primary sclerosing cholangitis Autoimmune cholangitis.	Crohn's disease Ulcerative colitis Ulcerative proctitis Celiac disease	Autoimmune thyroiditis (including Hashimoto thyroiditis) Grave's or Basedow's disease Diabetes mellitus type I Addison's disease

Vasculitides	Others
Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis. Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome, thromboangiitis obliterans (Buerger's disease), necrotizing vasculitis, allergic granulomatous angiitis, Henoch-Schonlein purpura, anti-neutrophil cytoplasmic antibody positive vasculitis, Behcet's syndrome, leukocytoclastic vasculitis. Vasculitides secondary to other immune mediated diseases such as lupus vasculitis and rheumatoid vasculitis.	Autoimmune hemolytic anemia Autoimmune thrombocytopenias Antiphospholipid syndrome Pernicious anemia Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) Uveitis Autoimmune myocarditis/cardiomyopathy Sarcoidosis Stevens-johnson syndrome Sjögren's syndrome Idiopathic pulmonary fibrosis Goodpasture syndrome

When there is enough evidence to make any of the above diagnoses, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the eCRF a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available to investigators.

pIMDs that occur during the study (see also Section 8.3.1 for reporting period) will be reported promptly to GSK within the timeframes described in Table 17, once the investigator becomes aware of the pIMD.

Once onset of a new pIMD or exacerbation of a pre-existing pIMD is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the SAE screens of the eCRF WITHIN 24 HOURS after the he/she becomes aware of the diagnosis. A field on the SAE screen allows to specify that the event is a pIMD and whether it is serious or non serious. The SAE screens will always be completed as thoroughly as possible with all available details of the event, in accordance with the pIMD standard questionnaire provided. Even if the investigator does not have all information regarding a pIMD, the SAE screens should still be completed within 24 hours. Once additional relevant information is received, the SAE screens in the eCRF should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report.

Refer to Section 8.4.3 for back-up system and updating of SAE information after freezing of the subject's eCRF.

~~Adverse events of specific interest for safety monitoring include the NOADs and other immune mediated inflammatory disorders, such as those listed below.~~

~~Occurrences of AEs of specific interest will be reported throughout the entire study period, whether or not they are considered to be possibly related to the treatment administration. Medical documentation of the events will be reported in appropriate targeted follow-up forms included in the eCRF. These events have also to be reported as AE or SAE as appropriate in the eCRF.~~

~~AEs of interest to be reported and documented are the following:~~

~~Neuroinflammatory disorders: cranial nerve disorders, multiple sclerosis, demyelinating disease, transverse myelitis, Guillain-Barré syndrome, myasthenia gravis, encephalitis, neuritis.~~

~~Musculoskeletal disorders: systemic lupus erythematosus, cutaneous lupus, Sjogren's syndrome, scleroderma, dermatomyositis, polymyositis, rheumatoid arthritis, polymyalgia rheumatica, reactive arthritis, psoriatic arthropathy, ankylosing spondylitis, undifferentiated spondyloarthropathy.~~

~~Gastrointestinal disorders: Crohn's disease, ulcerative colitis, ulcerative proctitis, celiac disease.~~

~~Metabolic diseases: autoimmune thyroiditis, Grave's or Basedow's disease, Hashimoto thyroiditis, insulin-dependent diabetes mellitus (IDDM), Addison's disease.~~

~~Skin disorders: psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases.~~

~~Other: autoimmune haemolytic anemia, thrombocytopenias, antiphospholipid syndrome, vasculitis, pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune glomerulonephritis, autoimmune uveitis, autoimmune myocarditis, sarcoidosis, Stevens-Johnson syndrome.~~

~~Medical or scientific judgment should be exercised in deciding whether other disorders/diseases have autoimmune origin and should be reported as appropriate.~~

Section 8.4.1. Prompt reporting of serious adverse events and other events to GSK Biologicals

Table 17 Time frames for submitting SAEs and other events reports to GSK Biologicals

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours*	SAE screen	24 hours*	SAE screen
Pregnancy	24 hours*	Pregnancy Report Form	24 hours*	Pregnancy Report Form
pIMDs	***24 hours****	***SAE screen***	***24 hours****	***SAE screen***

* Time frame allowed after receipt or awareness of the information.

*****Timeframe allowed after the diagnosis is established and known to the investigator***

8.7 Emergency unblinding

GSK Biologicals Central Safety Physician (Study Contact for Emergency Code Break)
~~Mobile p~~***P***hones for 7/7 day availability: Outside US/Canada: [redacted] (GSK Biologicals Central Safety Physician ***on call***) For US/Canada only: [redacted] (~~Head Safety Evaluation and Risk Management North America~~ GSK Biologicals ***Central Safety Physician on call***)
Back-up ~~mobile~~ phone contact ~~(all countries)~~: [redacted] ***Outside US/Canada:*** [redacted] ***For US/Canada only:*** [redacted]

10.2 Secondary endpoints

- Occurrence of pre-defined AEs
  - Occurrence and relationship to vaccination of any ***pIMDs*** ~~NOADs and other immune mediated inflammatory disorders~~ during the entire study period in all subjects;

10.4.1. Sample size assumptions

Table 18 Assumptions for incidences under placebo, and VE used for trial simulations

Age	HZ Incidence (% / Year)	HZ VE	PHN Incidence in HZ subjects (% /Year)	On top PHN VE in HZ subjects (2)	Overall PHN VE ~~in HZ subjects~~

10.4.5.3 Futility analyses and sample size re-assessment

The study may involve one (or more) unblinded futility analyses performed by the IDMC. One futility analysis is planned after approximately 25% of the total HZ cases are observed and~~/or~~ when at least 20% of the total HZ cases are observed in each age stratum.

A conservative futility boundary or a predictive power threshold [Proschan, 2006] in the range of ~30% is anticipated but the actual functional form of the beta-spending function or the predictive power threshold used for the trial will be defined in the IDMC Charter***/IDMC RAP***.

10.4.5.4. Provisional region and sub-population allocations

Enrolment target numbers per region are approximate and may change depending on the enrolment.

Table 25 Provisional region allocation for study ZOSTER-006

Australasia		Europe		Latin America		North America	
Country	Sample Size	Country	Sample Size	Country	Sample Size	Country	Sample Size
Australia Hong Kong Japan S. Korea Taiwan	~~~3200~~ ***~3410***	Czech Republic Estonia Finland France Germany Italy Spain Sweden United Kingdom	~~~7560~~ ***~7345***	Brazil Mexico	~~~2620~~ ***~2615***	Canada US	~~~2620~~ ***~2610***

10.4.5.5. 7-day diary card subset

Table 26 Provisional number of subjects in the 7-day diary card subset in study ZOSTER-006

Age cohort	50-59 YOA		60-69 YOA		70-79 YOA		≥ 80 YOA		All	
Treatment group	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo
ZOSTER-006	1410	1410	1410	1410	1410	1410	470	470	~~4880~~ ***4700***	~~4880~~ ***4700***

Note: In addition, study ZOSTER-022 will include a 7-day diary card subset of ~~1000~~ ***1008*** subjects (in ~~each~~ ***respectively the 70-79 YOA and ≥ 80 YOA strata***, ~~250~~ ***there are 252*** subjects in each treatment group).

10.4.5.6.3. Humoral immune response inter-region variability

~~*Using Ratio of responder Rates – Country-wise*~~

~~When comparing responder rate, a non-inferiority limit of 15% may be considered. Based on ZOSTER-010 data, the responder rates were ~97% in EU (N=95) and 100% in US (N=37) and a value of 97% will be used as the reference value worldwide. A ~3% - 4% difference in point estimate may be observe between countries [eq. 96% in CZ (N=49) and 100% in SP (N=46)], as observed between EU and US.~~

~~Table 30 provides power for a sample of 60 - 100 subjects from one country in comparison with the rest of the world, assuming 15 countries. When considering a difference of 4%, the sample should be at least equal to 100 to achieve a power of 90%.~~

~~**Table 30 Sample Sizes for Non-Inferiority Tests (Responder Rates)**~~

	~~Sample Size~~	~~Sample Size~~	~~Grp 2~~	~~Equiv Grp 1~~	~~Actual Grp 1~~	~~Equiv Margin~~	~~Actual Margin~~	
	~~Grp 1~~	~~Grp 2~~	~~Prop~~	~~Prop~~	~~Prop~~	~~Diff~~	~~Diff~~	~~Target~~
~~Power~~	~~N1~~	~~N2~~	~~P2~~	~~P1.0~~	~~P1.1~~	~~D0~~	~~D1~~	~~Alpha~~
~~0.6449~~	~~60~~	~~900~~	~~0.9700~~	~~0.8200~~	~~0.9300~~	~~-0.1500~~	~~-0.0400~~	~~0.0250~~
~~0.7364~~	~~70~~	~~900~~	~~0.9700~~	~~0.8200~~	~~0.9300~~	~~-0.1500~~	~~-0.0400~~	~~0.0250~~
~~0.8088~~	~~80~~	~~900~~	~~0.9700~~	~~0.8200~~	~~0.9300~~	~~-0.1500~~	~~-0.0400~~	~~0.0250~~
~~0.8641~~	~~90~~	~~900~~	~~0.9700~~	~~0.8200~~	~~0.9300~~	~~-0.1500~~	~~-0.0400~~	~~0.0250~~
~~0.9050~~	~~100~~	~~900~~	~~0.9700~~	~~0.8200~~	~~0.9300~~	~~-0.1500~~	~~-0.0400~~	~~0.0250~~
~~0.7642~~	~~60~~	~~900~~	~~0.9700~~	~~0.8200~~	~~0.9400~~	~~-0.1500~~	~~-0.0300~~	~~0.0250~~
~~0.8471~~	~~70~~	~~900~~	~~0.9700~~	~~0.8200~~	~~0.9400~~	~~-0.1500~~	~~-0.0300~~	~~0.0250~~
~~0.9041~~	~~80~~	~~900~~	~~0.9700~~	~~0.8200~~	~~0.9400~~	~~-0.1500~~	~~-0.0300~~	~~0.0250~~
~~0.9415~~	~~90~~	~~900~~	~~0.9700~~	~~0.8200~~	~~0.9400~~	~~-0.1500~~	~~-0.0300~~	~~0.0250~~
~~0.9652~~	~~100~~	~~900~~	~~0.9700~~	~~0.8200~~	~~0.9400~~	~~-0.1500~~	~~-0.0300~~	~~0.0250~~

~~Score test [Miettinen,1985]~~

10.4.5.7.1. Assumptions and background information for CMI

The frequency of CD4 T-cells producing at least 2 cytokines following induction with gE/AS01$_B$ will be estimated in both placebo and vaccine recipients, ~~The cellular proportion of subjects achieving a cellular immune response to vaccination with gE/AS01$_B$ (cellular immunity take rate) will be compared to that of subjects in the Placebo group based on the frequency of gE specific CD4 cells,~~ after adjustment for background ***CD4 T-cell frequency*** and pre-vaccination ~~gE specific~~ CD4 ***T-cell*** responses. The increase in CMI response***s*** observed ***previously*** ~~post dose 2~~ following ***administration of 2 doses of*** ~~50 µg~~ gE$_{[50\ \mu g]}$ /AS01$_B$ compared with saline is about 5.5-fold, and the coefficient of variation is about 100%. ***Therefore, a 1.5-fold increase over placebo in the frequency of activated CD4 T-cells is considered as a minimum target for vaccine take and was used as threshold for immunologic superiority.*** These figures were used for the sample size calculation.

10.6.2 Efficacy

HZ burden-of-illness score

For each confirmed case of HZ, responses to the "worst pain" question in the ZBPI are used to calculate a "HZ severity-of-illness" score, defined as the area under the curve (AUC) of HZ-associated pain plotted against time during the 182-day period after the onset of ***the case*** ~~rash~~.

10.7.2. Statistical considerations for the interim futility analyses

The futility rules will be described in the IDMC Charter***/IDMC RAP***.

If a futility analysis occurs and leads to a recommendation by the IDMC to filing prior to study end for ethical reasons, it is mandated that, prior to final analysis, the significance level ~~required during the course of the trial for considering early analysis by IDMC~~ for all primary objectives but also key secondary objectives is ***set to*** 0.0001 for both HZ and ***overall*** PHN***, considering the alternative hypotheses of true vaccine efficacies above 40%.***

10.7.3. Final analysis

When the conditions for triggering the final analysis of efficacy have been reached, the final analysis cut-off date will be defined. Any HZ episode occurring prior to the final analysis cut-off dat~~a~~***e*** will be followed ~~for a minimal duration of 90 days~~, as described in the RAP, ***until the case of suspected HZ is disproved, OR until a 4-week pain-free period is documented, OR until the cut-off date for final analysis. For all subjects with ongoing HZ-associated pain-at the time of cut-off date for final analysis, ZBPI data will be collected until suspected HZ is disproved, OR until a 4-week pain-free period is documented OR until at least Day HZ-90***-in order to document potential PHN episodes**.**

10.8.4 Quality of life

10.8.4.1. SF-36 health survey

The methodology used for the analysis of the SF-36® questionnaire is detailed by Ware et al. [Ware, 2000]. ***The SF-36® yields an 8-scale profile of scores (physical functioning, role physical, bodily pain, general health perceptions, vitality, social functioning, role emotional, and mental health) as well as a reported health transition score.***

~~Table 33 presents the SF-36® items that were to be taken into account for each score. The SF-36 evaluates the following items: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health, reported health transition.~~

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

10.8.5 Analysis of safety

10.8.5.1 Within groups assessment

- The proportion of subjects with at least one report of ***pIMDs*** ~~NOADs and other immune mediated inflammatory disorders~~ during the entire study period will be tabulated overall and by time window. Listing will also be provided, sorted by subjects and sorted by MedDRA Preferred Term.

12 Country specific requirements

All countries will comply with AE and SAE reporting as described in Section 8 of the protocol. Additionally, countries and sites will follow all applicable local regulations and guidelines for AE and SAE reporting as required by their respective healthcare authorities and ethics committees.

Appendix A Laboratory Assays

PCR Assay for Confirmation of suspected case of HZ

HZ cases will be confirmed by a Polymerase Chain Reaction (PCR) based algorithm that assesses the presence of VZV DNA in samples, ***and*** the adequacy of the samples (by assessing the presence of β-actin DNA) ~~and, finally, the potential presence of Herpes Simplex Virus (HSV) -1 and -2 DNA~~. ***Herpes Simplex Virus (HSV) qPCR will be performed on VZV negative/ β -actin positive samples for exploratory purpose to assess if the rash lesions are due to HSV(1 or 2) and not to VZV; it is not part of the decision making process for HZ case confirmation. HSV qPCR testing is optional and requires specific consent from the individual subjects.***

As mentioned above, the 5' nuclease-based PCR assay allows the determination of the DNA copy number within samples, but in the present study the VZV, HSV1/2 and β-actin DNA PCR data on samples from suspected HZ lesions (swabs of vesicles, papules and crusts, and crusts themselves) will be used qualitatively only according to the above mentioned ~~algorithm~~ ***approach.***

Appendix B Ascertainment of HZ cases including PCR testing algorithm to classify HZ suspected cases

To classify the suspected case of HZ, the samples from the rash lesions will be collected for laboratory testing by PCR (~~minimum~~ 3 samples, collected on the same day, per subject). ***If during clinical evaluation at Visit HZ-1, the investigator determines that only papules are present, three samples should be collected (if possible). The investigator has the option of collecting three additional samples if the rash progresses to vesicles or crust are present prior to or at the Visit HZ-2. See the Study Procedures Manual for further details on sample collection.***

Each rash lesion will be tested using standardized and validated molecular assays according to the PCR testing algorithm described below.

A hierarchical case definition algorithm, similar to the algorithm used by Merck in their Shingle Prevention Study (*Zostavax* efficacy study) [Oxman, 2005] will be used to classify each suspected case of HZ as a confirmed HZ case or not.

- If at least 1 sample coming from a given subject is "VZV positive" by PCR ***(as defined below)***, ***the PCR algorithm will classify the*** ~~this~~ "suspected HZ case" ~~will be classified~~ as a "confirmed case of HZ".
- If ***all*** the samples coming from a given subject are "VZV negative" ***(as defined below)***, ***then β-actin PCR will be performed. If one or more "VZV negative" samples are*** ~~and~~ "β-actin positive", this means that the sampling procedure is valid~~ated~~ and that the "suspected HZ case" will be classified as "not a case of HZ". ***HSV qPCR will be performed on VZV negative/ β-actin positive samples for exploratory purpose to assess if the rash lesions are due to HSV and not to VZV; it is not part of the decision making process for HZ case confirmation.*** ~~Regarding the testing algorithm, the HSV qPCR assay will assess if the rash lesions were due to HSV and not to VZV.~~ ***HSV qPCR testing is optional and requires specific consent from the individual subjects.***
- If ~~all the~~ PCR results for a particular subject ~~could~~ ***do*** not confirm or exclude a "suspected HZ case" (i.e. samples coming from a given subject are considered as "inadequate" as both VZV and β-actin PCR results are negative, ***or no samples are available for the subject*** ~~or the samples are missing~~***),*** ~~this case will be referred to the HZ Ascertainment Committee (HZAC) to be classified~~, ***only then will the classification by the HZAC be used to confirm or exclude the suspected HZ case.*** The HZAC will consist of ***three to*** five physicians with HZ expertise. For every ~~such case~~ ***suspected HZ case,*** each HZAC member will be asked to make a clinical determination of whether the case is HZ based on ~~the~~ review of the available clinical information. A "suspected HZ case" will be considered as ~~a~~ "~~confirmed~~ HZ ~~case~~" if ~~at least 3~~ ***all*** HZAC members concur (~~majority vote~~ ***unanimous decision***); otherwise, it will be classified as "not ~~a case of~~ HZ".

This algorithm includes the following steps (see Figure 1):

1. DNA extraction from the rash lesion.
2. VZV real-time PCR assay (qPCR) targeting the *orf62* gene is performed to detect VZV in the rash lesion:
    1. If the VZV qPCR signal is ≥ ***the cut-off level*** ~~above the cut-off of positivity corresponding to~~***, i.e.*** the technical limit of detection ***(LOD)*** of the assay ***(10 VZV DNA copies)***, the sample will be considered as "VZV positive".

If the VZV qPCR signal is ***above 0 copy/qPCR but below the cut-off level of the assay***~~, included between 1 copy/qPCR and the cut-off of positivity~~, it will be considered as "VZV borderline" and will be re-tested twice in order to obtain 3 results per sample. The sample will be considered as "VZV positive" if at least 2 results out of the three obtained are ***≥ the cut-off level of the assay and it will be considered "VZV negative" if fewer than 2 samples are ≥ the cut-off level of the assay*** ~~above the cut-off of positivity~~.

If the VZV qPCR signal is equal to 0 copies/***q***PCR, the sample will be considered as "VZV negative"***. If every sample is VZV negative, then*** ~~and the~~ extracted DNA ***from the***

samples will be assessed for the presence of β-actin ***DNA*** ~~housekeeping gene~~ to ~~validate~~ ***confirm the validity of*** the rash lesion sampling procedure (see ~~item~~ ***step*** 3).

3. As described ~~here~~ above, ***if all the samples are VZV negative for a given subject,*** then β-actin qPCR will be performed ~~only~~ on "VZV negative" samples to ~~validate~~ ***confirm the validity of*** the sampling procedure.

    1. If the β-actin qPCR signal is below the ***cut-off level of the assay*** ~~cut-off of positivity of this assay~~ ***(β-actin Negative)***, the sample will be considered as "inadequate" as no ***β-actin*** DNA ~~coming~~ from human cells is detected within the rash lesion sample. ***If all samples are β-actin Negative, then the classification by the HZAC will be used to confirm or exclude the HZ case.***

If the β-actin qPCR signal is ***≥ the cut-off level of the assay*** ~~above the cut-off of positivity of this assay~~ ***(***β-***actin Positive)***, the sample will be considered as "valid" but ~~it does not contain~~ ***without*** any VZV DNA. ~~According to the testing algorithm, t~~***T***he extracted DNA ~~will~~ ***may then*** be assessed for the presence of HSV-1/2 within the rash lesion (see ***below*** ~~item 4~~). ***If at least one sample is β-actin Positive, then the HZAC classification of a suspected HZ case, will not be part of the decision-making process for HZ case confirmation.***

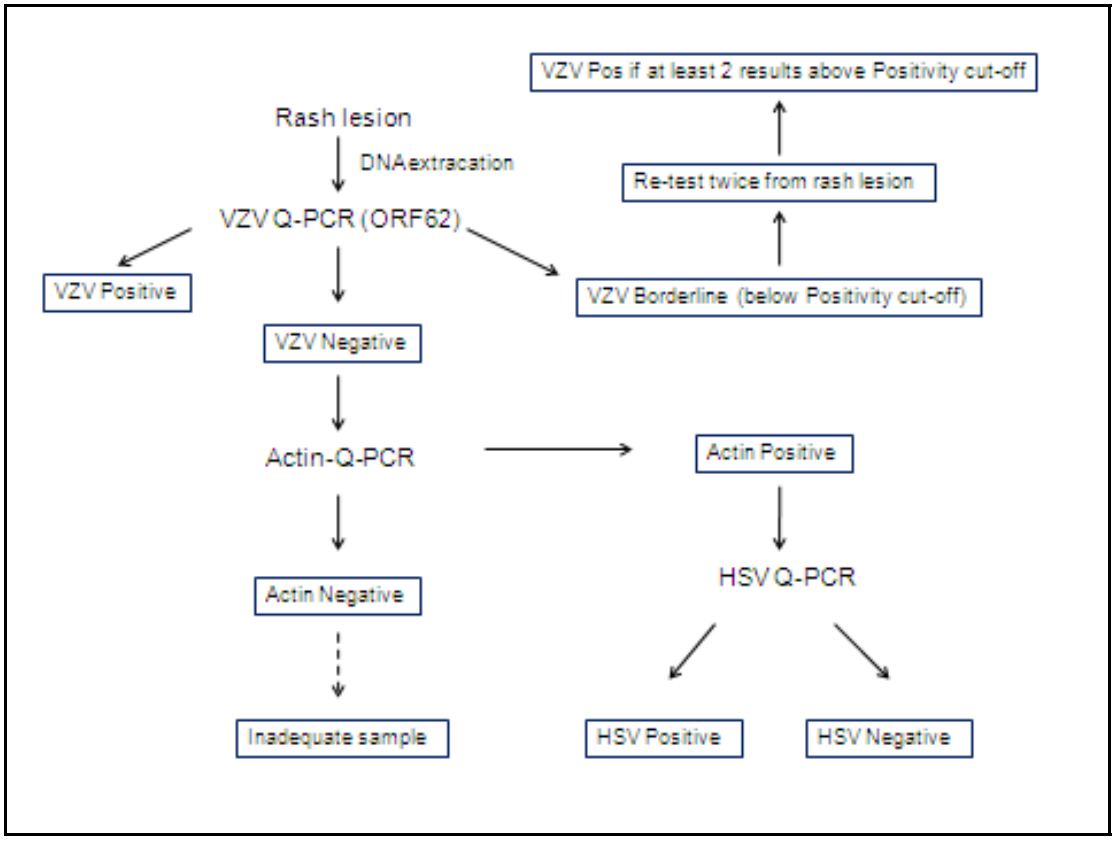
As described ~~here~~ above the HSV qPCR assay ~~will~~ ***may*** be performed ***for exploratory purpose on*** "VZV negative/ β-actin positive samples:

1. If the HSV qPCR signal is below the ***cut-off level*** ~~cut-off of positivity~~ of this assay, the sample will be considered as "HSV negative".
2. If the HSV qPCR signal is ***≥ the cut-off level*** ~~above the cut-off of positivity~~ of this assay, the sample will be considered as "HSV positive".

Note: The cut-off level of the VZV qPCR, β-actin qPCR and HSV qPCR assays is defined as the technical limit of detection of these assays (LOD; i.e. lowest concentration that can be detected by PCR in at least 95% of the tests).

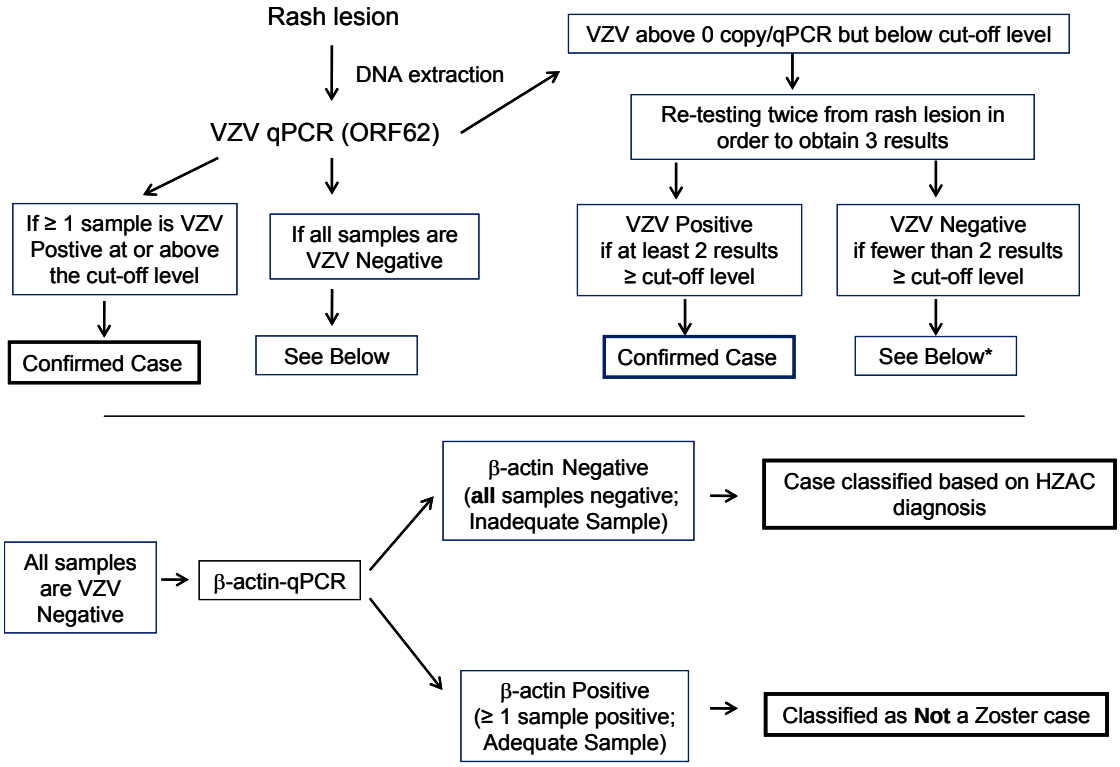
Figure 1 Algorithm for HZ case definition by PCR

ORIGINAL



VZV: Varicella Zoster Virus; Q-PCR: real-time (quantitative) PCR; HSV: Herpes Simplex Virus

UPDATED



VZV: Varicella Zoster Virus; Q-PCR: real-time (quantitative) PCR; HSV: Herpes Simplex Virus

* ***If the VZV qPCR signal is above 0 copy/qPCR but below the cut-off level of the assay, it will be considered as "VZV borderline" and will be re-tested twice in order to obtain 3 results per sample. The sample will be considered as "VZV positive" if at least 2 results out of the three obtained are ≥ the cut-off level of the assay and it will be considered "VZV negative" if fewer than 2 samples are ≥ the cut-off level of the assay. See then below 'All samples are VZV Negative'.***

Note: The cut-off level of the VZV qPCR assay is defined as the technical limit of detection of the assay (LOD of 10 VZV DNA copies; i.e. lowest concentration that can be detected by PCR in at least 95% of the tests)

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Amendment number:	Amendment 2
Amendment date:	16-MAR-2012
Co-ordinating author:	[redacted] Scientific Writer

Rationale/background for changes:

- To provide further guidance and clarification the following updates have been made:
  - In this amendment, the term 'disproved case' has been removed. (Previously, follow-up could be discontinued for disproved cases of HZ.) Currently, standard follow-up is to be conducted for all cases initially clinically diagnosed as suspected HZ, even if the case is subsequently not considered as suspected. Although this situation will be noted in the eCRF. Therefore, all cases initially clinically diagnosed as suspected HZ will be followed for a minimum of 28 days. The term 'clinically diagnosed suspected' has been replaced with 'suspected' where applicable to be in alignment with the aforementioned change. Sections 5.5.1, 5.5.2, 5.5.2.1, 5.5.2.2, 5.5.2.3, 5.5.2.4, 5.5.2.5, 5.6, 5.7.3.10, 5.7.3.11, 5.7.3.16, 7 and 10.7.3 have been updated accordingly.
  - Details have been added regarding follow-up of suspected HZ cases and completion of questionnaires if pain reappears in the same area after a 4-week pain-free period and is not accompanied by a new HZ rash. Sections 5.5.1, 5.6, 5.7.3.11 and 7 have been updated accordingly.
  - Additional photographs of HZ lesions may be taken after Visit HZ-1 to help note the progression of the rash. Sections 5.5.2.2, 5.6 and 5.7.3.11 have been updated accordingly.
  - The circumstances where the investigator has the option to collect up to three additional rash samples after Visit HZ-1 and prior to or at Visit HZ-2 (i.e., <3 lesions present or only papules present) has been clarified in Sections 5.5.2.2, 5.6, 5.7.3.11, 5.8.2 and Appendix B and harmonized with the SPM.
  - The HZ date of onset is not recorded in the eCRF, although date of rash onset and pain are recorded in the eCRF. Sections 5.5.2.1 and 5.5.2.2 have been updated accordingly.
  - Guidance has been provided that HZ complications as defined in Section 5.5.2.5 (including AE/SAE information) should be recorded throughout the duration of the study. Sections 5.5.2.5, 5.6 and 8.3.1 have been updated accordingly.
  - The definition of the end date of a suspected case of HZ has been clarified in

Section 5.5.2.1.

- Clarification has been added that if a 4-week pain free period is achieved, subjects can stop completing questionnaires. If a 4-week pain free period is achieved and additionally the HZ rash resolves, subsequent visit/contacts related to the case of HZ can be cancelled. Sections 5.5.2.2, 5.6, 5.7.3.16 and 10.7.3 have been updated accordingly.
- The definition of pain free period is based upon item 1 of the ZBPI questionnaire and has been updated accordingly in Section 5.5.2.2.
- The ZBPI, EQ-5D and SF-36 questionnaires must be completed until Day HZ-28 at minimum. Sections 5.5.2.2, 5.6 and 5.7.3.11 have been updated accordingly.
- In case questionnaires are completed at the study site, study staff can assist in reading the questions. Questions should be read verbatim to the subject. Family members and care providers who provide assistance should also read questions verbatim. Section 5.5.1 has been updated accordingly.
- The clarification has been added in Section 3 that visit numbers are referred to interchangeably with their month designations throughout the protocol (Month 0 refers to Visit 1, Month 2 refers to Visit 2, etc). For example, all SAEs are to be reported until Visit 4 (Month 14). Visit 4 is used to indicate 12 months post 2nd vaccination. (SAEs related to an HZ complication, related to study participation, related to a concurrent GSK medication/vaccine or any fatal SAE will be reported throughout the study.)
- Zostavax has recently been approved for the prevention of herpes zoster (shingles) in individuals 50 to 59 years of age in the United States. Sections 1.1 and 13 have been updated accordingly.
- Background (Section 1.1) has been updated to reflect that data up to Month 14 is now available from phase II adjuvant dose comparison study Zoster-010.
- Small adjustments in the age ratio of 8:5:3:1 (50-59 YOA; 60-69 YOA; 70-79 YOA and ≥ 80 YOA) and country and subset allocation were necessary to complete enrollment of the study in a timely manner. As a result, text in the synopsis as well as Sections 1.2, 3, 10.4.5, 10.4.5.1, 10.4.5.4, 10.4.5.6.2 and 10.4.5.7.2 were updated accordingly.
- The list of potential immune-mediated diseases (Table 16 in Section 8.3.2.5) has been updated to include narcolepsy.
- Section 10.4.5.3 has been updated to reflect current criteria that are planned to trigger the futility analysis.
- Further information regarding the interim futility analyses will be detailed in the RAP, and Sections 5.5.3, 10.4.5.3 and 10.7.2 have been updated accordingly.
- The list of contributing authors has been updated in the title page.
- The sponsor signatory has been updated in the Protocol Amendment 2 Sponsor Signatory Approval Page.

Amended text has been indicated in *bold italics* and deleted text has been indicated in strikethrough (e.g. ~~text)~~ in the following sections:

Title page

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Protocol Amendment 2 Sponsor Signatory Approval page

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Synopsis

Rationale for the study and study design

This study will enrol subjects in the age ranges 50-59 YOA, 60-69 YOA, 70-79 YOA and ≥ 80 YOA in ***approximately*** an 8:5:3:1 ratio to achieve comparable numbers of HZ in the 3 main age strata (50-59 YOA, 60-69 YOA and ≥ 70 YOA) so that a balanced estimate of the overall VE in persons ≥ 50 YOA can be determined.

Apportionment of ***approximately 20-***25% of the ≥ 70 YOA cohort to persons ≥ 80 YOA ***in both ZOSTER-006 and ZOSTER-022*** ensures that this particularly vulnerable population is adequately represented.

Study design

- Treatment allocation: Eligible subjects will be randomized to investigational vaccine/placebo according to a 1:1 ratio (vaccine:placebo). Subjects will be stratified by age: 50-59 YOA; 60-69 YOA; 70-79 YOA and ≥ 80 YOA in ***approximately*** an 8:5:3:1 ratio**.** The 70-79 YOA and ≥ 80 YOA strata will be combined for primary analyses.

1.1 Background

In the US, *Zostavax* is indicated for prevention of HZ in individuals ≥ ***50*** ~~***60***~~ YOA and older ***[Zostavax Prescribing Information, 2011]*** ~~[CDC, 2008]~~.

Analysis of data obtained up to ***Month 14*** ~~Month 3 (one month after dose 2)~~ is currently available ***for this study***~~, an extended safety follow-up is ongoing~~.

1.2 Rationale for the study and study design

This study will enrol subjects in the age ranges 50-59 YOA, 60-69 YOA, 70-79 YOA and ≥ 80 YOA in ***approximately*** an 8:5:3:1 ratio to achieve comparable numbers of HZ cases in the 3 main age strata (50-59 YOA, 60-69 YOA and ≥ 70 YOA; the 70-79 YOA and ≥ 80 YOA strata will be combined for primary analyses) so that a balanced estimate of the overall VE in persons ≥ 50 YOA can be determined. Apportionment of ***approximately 20-***25% of the ≥ 70 YOA cohort to persons ≥ 80 YOA ensures that this particularly vulnerable population is adequately represented.

3 Study design overview

- Treatment allocation: Eligible subjects will be randomized to investigational vaccine/placebo according to a 1:1 ratio (vaccine:placebo). Subjects will be stratified by age: 50-59 YOA; 60-69 YOA; 70-79 YOA and ≥ 80 YOA in ***approximately*** an 8:5:3:1 ratio. The 70-79 YOA and ≥ 80 YOA strata will be combined for primary analyses.

Throughout the protocol, visit numbers are referred to interchangeably with their month designations (Month 0 refers to Visit 1, Month 2 refers to Visit 2, etc).

5.5.1 Data collection

Also, subjects with ~~clinically diagnosed~~ suspected HZ will be contacted periodically as outlined in Table 3.

In case of difficulty in self-completion of the diary cards or questionnaires, an aide (such as a family member or care provider who is not involved in the study) may provide assistance with reading the questions ***(verbatim)*** and/or transcribing the subject's responses on the questionnaires and/or diary cards.

In case questionnaires are completed at the study site, study staff can assist in reading the questions (verbatim).

For all subjects:

- **EQ-5D and SF-36 questionnaires:** To be completed by all subjects at study entry. Also, to be completed by all subjects at Visits 4, 5 and 6 (subjects with an ongoing ~~clinically diagnosed~~ suspected HZ episode will follow a weekly schedule and do not need to additionally complete the questionnaires at these visits).

EQ-5D and SF-36 will remain as source documents. The information from these questionnaires will only be transcribed into the eCRF for subjects who have ~~clinically diagnosed~~ suspected HZ during the study.

For all subjects in case of a suspected or confirmed case of HZ:

- **Zoster Brief Pain Inventory (ZBPI) questionnaire:** To be completed by subjects with ~~clinically diagnosed~~ suspected HZ on Day HZ-0 (Visit HZ-1) and daily from Day HZ-1 (day after the Visit HZ-1) up to Day HZ-28, and weekly from Day HZ-29 onwards ~~until the case of suspected HZ is disproved, OR~~ until a 4-week pain-free period is documented~~,~~ OR until the cut-off date for final analysis. For all subjects with ongoing HZ-associated pain-at the time of cut-off date for final analysis, ZBPI data will be collected ~~until suspected HZ is disproved, OR~~ until a 4-week pain-free period is documented OR until at least Day HZ-90 (~~see~~***Refer to*** Section 5.5.2.2 for more details).
- **EQ-5D and SF-36 questionnaires:** To be completed weekly by the subjects with ~~clinically diagnosed~~ suspected HZ from Day HZ-0 onwards ~~until the case of clinically diagnosed suspected HZ is disproved, OR~~ until a 4-week pain-free period is documented~~,~~ OR until the cut-off date for final analysis. For all subjects with ongoing HZ-associated pain at the time of the cut-off date for final analysis, EQ-5D and SF-36 data will be collected ~~until suspected HZ is disproved, OR~~ until a 4-week pain-free period is documented OR until at least Day HZ-90 (~~see~~***Refer to*** Section 5.5.2.2 for more details).

5.5.2 Evaluation and confirmation of suspected ~~and confirmed~~ HZ cases

5.5.2.1 Definitions

Subjects clinically diagnosed as having a suspected case of HZ by the investigator will be referred to as a case of '~~clinically diagnosed~~ suspected HZ', and followed up. If a case is not clinically diagnosed as suspected HZ, the investigator should not progress further with evaluation of the case.

The HZ onset date is the earlier of the following two events: 1) the HZ rash start date; or 2) the date on which pain at the site of a subsequent HZ rash is first noted. ~~The HZ onset date will be confirmed by the investigator and recorded in the eCRF.~~

The end date of a HZ episode is defined as the first time at which a subject had no rash (papules, vesicles, ulcers or crusts) ***present***~~and after which he/she did not develop a rash at the same location at any later visit/contact~~. This end date will be recorded in the eCRF.

5.5.2.2 Evaluation of suspected case of HZ

The schedule of visits/contacts that will take place for follow-up of ~~clinically diagnosed~~ suspected HZ cases is presented in Table 3.

- The investigator or his delegate will verify the completed HZ-specific diary card returned by the subject. The information from the diary card will be transcribed into the eCRF. The investigator or his delegate will record relevant information regarding the HZ episode in the eCRF (such as date of onset of pain and rash, date of clinical diagnosis of HZ, location and nature of HZ lesions, HZ-related complications if any)~~. The HZ onset date will be confirmed by the investigator and recorded in the eCRF~~;
- The subject will be asked to complete the ZBPI questionnaires daily from Day HZ-1 (day after the Visit HZ-1) up to Day 28 ***(ZBPI must be completed to Day HZ-28 at minimum)***, and weekly from Day HZ-29 onwards until:

  ~~– The case of clinically diagnosed suspected HZ is disproved; OR~~

  – 28 days after HZ-associated pain ceases. The subject should continue to complete the ZBPI questionnaires weekly until a 28-day (or 4-week) pain free period is documented ~~(i.e., '0' circled for item 3 of the ZBPI questionnaire at each assessment during that entire period~~ ***a 'No' answer to the ZBPI question: 'Have you had any pain caused by your shingles in the last 24 hours' (item 1) at each assessment during that entire period)***; OR

  – The cut-off date for final analysis.

    For all subjects with ongoing HZ-associated pain at the time of cut-off date for final analysis, ~~follow-up for such a subject~~ ***completion of ZBPI questionnaires*** will continue until ~~suspected HZ is disproved, OR until~~ a 4-week pain-free period is documented OR until at least Day HZ-90. ~~The study conclusion contact for such a subject will thus occur after he/she completes follow-up as described above~~.

- The subjects will be asked to complete the EQ-5D and SF-36 questionnaires from Day HZ-0 and continued weekly during the entire period that the ZBPI questionnaires are completed. ***Therefore, these questionnaires should be completed until Day HZ-28 at minimum.***

When a case initially clinically diagnosed as suspected HZ is subsequently not considered anymore by the investigator as suspected HZ, this will be noted in the eCRF. However study procedures to be performed during the follow-up period for a suspected HZ case (seeTable 3)should be continued. ~~If the case of clinically diagnosed suspected HZ is disproved, or i~~

If HZ-associated pain ceases (defined as a 28-day [or 4-week] pain free period), ***the study staff/investigator will inform the subjects to stop completing the ZBPI, EQ-5D and SF-36 questionnaires and will provide instructions for the subject to return the completed questionnaires to the study site. If a 4-week pain-free period is achieved and the HZ rash resolves***, subsequent follow-up visits or contacts related to this case of HZ will be cancelled. ~~The study staff/investigator will inform the subjects to stop completing the~~

~~ZBPI, EQ-5D and SF-36 questionnaires and will provide instructions for the subject to return the completed questionnaires to the study site.~~

- The study staff/investigator will: 1) record relevant information regarding the ~~clinically diagnosed~~ suspected HZ case (such as the location and nature of HZ lesions, the end date of the rash, HZ-related complications, if any); 2) record concomitant medications/vaccinations, including concomitant medication the subject has already received and/or will receive for HZ treatment or treatment of any HZ-related complications (Section 6.6); 3) record intercurrent medical conditions (Section 6.7); and 4) check if the subject received any medical attention [hospitalization, emergency room visit, or a visit to or from medical personnel (medical doctor)] for HZ or any HZ-related complication.
- ***Additional photographs of HZ lesions may be taken after Visit HZ-1 to help note the progression of the rash.***
- ***If the investigator determines that adequate rash samples are not present at Visit HZ-1 (i.e., <3 lesions present or only papules present), the investigator has the option of collecting three additional samples prior to or at Visit HZ-2 (see Section 5.7.3.11).***

5.5.2.3 Confirmation of ~~clinically diagnosed~~ *a* suspected case of HZ

A ~~clinically diagnosed~~ suspected case of HZ can be confirmed in two ways***:***

- By the HZ Ascertainment Committee:

  All ~~clinically diagnosed~~ suspected HZ cases will be referred to the HZ Ascertainment Committee (HZAC). The HZAC will classify all referred cases as either “HZ” or “not HZ”.

  A ~~clinically diagnosed~~ suspected case of HZ will be considered as “HZ” if the HZAC members concur unanimously; otherwise, it will be classified as “not HZ”.

5.5.2.4 Evaluation of severity of HZ-associated pain using the Zoster Brief Pain Inventory

In each case of ~~clinically diagnosed~~ suspected HZ, the subjects will be asked to assess their HZ-associated pain and interference of HZ with their QoL by completing the ZBPI questionnaire either themselves or assisted, by an aide (Section 5.5.1) until ~~the suspected case of HZ diagnosed is disproved,~~ HZ-associated pain ceases (defined as a 28-day [or 4-week] pain free period) or until the cut-off date for final analysis (see further details in Section 5.5.2.2).

5.5.2.5 HZ complications

The presence of HZ complications listed below will be documented in the eCRF, independently from the AE reporting of those HZ complications (***see Section 8.3.1 and*** refer to the SPM for details). Any HZ complications, according to the definitions below, will be recorded by the investigator o~~nly in subjects with clinically diagnosed suspected~~

~~HZ or confirmed HZ~~. ***If a recorded complication is associated with a case of suspected HZ, and that case is finally not considered to be a confirmed case, the associated complication will not be considered a complication of HZ.*** ~~If a recorded complication is associated with a case of clinically diagnosed suspected HZ, and that case of HZ is subsequently disproved, the associated complication will not be considered a complication of HZ.~~

5.5.3 Independent Data Monitoring Committee

Vaccine efficacy for futility analysis, and other analyses described in the protocol to be done in preparation of IDMC review, will be further detailed in the ~~IDMC~~ Reporting and Analysis Plan (RAP).

5.6 Outline of study procedures

Table 2 List of study procedures

Footnote:

[f] EQ-5D and SF-36 will remain as source documents. The information from these questionnaires will only be transcribed in the eCRF for subjects who have a ~~clinically diagnosed~~ suspected HZ event during the study.

Table 3 Study procedures to be performed during the follow-up period for each suspected HZ case

Type of contact	
Timepoints	
Take digital photographs of HZ rash***α***	
Completion† of ZBPI questionnaires by the subjects until ~~HZ is disproved,~~ pain ceases or the cut-off date for final analysis (ZBPI pain data will be collected until at least Day HZ-90)	
Completion‡ of EQ-5D and SF-36 questionnaires by the subjects until ~~HZ is disproved,~~ pain ceases or the cut-off date for final analysis (EQ-5D and SF-36 data will be collected until at least Day HZ-90)	

Note: If ~~the case of clinically diagnosed suspected HZ is disproved, or if~~ HZ-associated pain ceases (defined as a 28 day [or 4-week] pain free period) ***and the HZ rash resolves***, subsequent HZ follow-up visits or contacts will be cancelled. ~~When a case of clinically diagnosed suspected HZ is disproved, collection of HZ related information will be stopped and no further information on that suspected HZ episode will be encoded in the clinical database~~. ***If pain reappears in the same area after a 4-week pain-free period and is not accompanied by a new HZ rash, it will be assigned to the previous HZ-episode. Visits/contacts will restart with Day HZ-0 defined as the first visit of the assigned episode, prior to the pain free period.***

α Additional photographs of HZ lesions may be taken after Visit HZ-1 to help note the progression of the rash.

* If during clinical evaluation at Visit HZ-1, the investigator determines that ~~only papules are present, three samples should be collected (if possible). The investigator has the option of collecting three additional samples if the rash progresses to vesicles or crusts are present prior to or at the Visit HZ-2~~ ***adequate rash samples are not present at Visit HZ-1 (i.e., <3 lesions present or only papules present), the investigator has the option of collecting three additional samples prior to or at Visit HZ-2***.

† Subjects with ~~clinically diagnosed~~ suspected HZ will be asked to complete the ZBPI questionnaire at Day HZ-0 (Visit

HZ-1) to rate HZ-associated pain within the last 24 hours (If the time between the HZ onset and clinical evaluation at Visit HZ-1 is greater than 24 hours, the subject will be asked to complete a second ZBPI also for the elapsed time between the HZ onset and 24 hours before Visit HZ-1); daily from Day HZ- 1 to Day HZ-28, and weekly from Day HZ 29 onwards until ~~suspected HZ is disproved,~~ a 4-week pain-free period is documented or until the cut-off date for final analysis. ***If pain reappears in the same area after a 4-week pain-free period and is not accompanied by a new HZ rash, it will be assigned to the previous HZ-episode. The completion of ZBPI questionnaires will resume based upon the weekly schedule established at the start of the assigned episode***. For all subjects with ongoing HZ-associated pain at the time of cut-off date for final analysis, ZBPI data will be collected ~~until suspected HZ is disproved, OR~~ until a 4-week pain-free period is documented OR until at least Day HZ-90. (See Section 5.5.2.2).
‡Subjects with ~~clinically diagnosed~~ suspected HZ will be asked to complete the EQ-5D and SF-36 questionnaire weekly from Day HZ-0 ***to Day HZ-28, and weekly*** onwards until ~~suspected HZ is disproved,~~ a 4-week pain-free period is documented or until the cut-off date for final analysis. ***If pain reappears in the same area after a 4-week pain-free period and is not accompanied by a new HZ rash, it will be assigned to the previous HZ-episode. The completion of EQ-5D and SF-36 questionnaires will resume based upon the weekly schedule established at the start of the assigned episode.*** For all subjects with ongoing HZ-associated pain at the time of cut-off date for final analysis, EQ-5D and SF-36 data will be collected until ~~suspected HZ is disproved, OR~~ until a 4-week pain-free period is documented OR until at least Day HZ-90. (See Section 5.5.2.2)
Each ~~clinically diagnosed~~ suspected HZ that occurs up to the cut-off date for final analysis will be followed at least until Visit HZ-7 (the study visit at Day HZ-91).

Follow-up for the occurrence of any SAEs will begin at Day 0 and continue until Month 14. Follow-up for the occurrence of SAEs related to ***an HZ complication as defined in Section 5.5.2.5, related to*** study participation, ~~or~~ related to a concurrent GSK medication/vaccine or any fatal SAE~~,~~ will continue until study conclusion.

Table 5 Intervals between contacts with subjects in case of suspected HZ

Footnote:

Note: If ~~a case of clinically diagnosed suspected HZ is disproved or if~~ HZ-associated pain ceases (i.e., after a 4-week pain-free period is documented) ***and the HZ rash resolves***, subsequent follow-up HZ visits or contacts ~~may~~ ***will be*** cancelled (see Section 5.5.2.2).

5.7.3.10 Recording of data from completed EQ-5D and SF-36 questionnaires

- **EQ-5D and SF-36 questionnaires:** To be completed by all subjects at study entry. Also, to be completed by all subjects at Visits 4, 5 and 6 (subjects with an ongoing ~~clinically diagnosed~~ suspected HZ episode will follow a weekly schedule and do not need to additionally complete the questionnaires at these visits).

EQ-5D and SF-36 will remain as source documents. The information from these questionnaires will only be transcribed into the eCRF for subjects who have ~~clinically diagnosed~~ suspected HZ during the study.

5.7.3.11 Follow up of suspected HZ cases and HZ-associated pain

Data will be collected on all ~~clinically diagnosed~~ suspected HZ cases that occur from administration of the first dose of vaccine/placebo until the cut-off date for final analysis (Section 5.7.3.16). For each suspected case of HZ that the investigator concludes is clinically consistent with HZ, data on HZ-associated pain (using ZBPI questionnaires completed by the subject) will be collected until ***Day HZ-28, and from Day HZ-29 until:***1) ~~The case is disproved; 2)~~ the subject has no HZ-associated pain for 4 consecutive weeks; or, ***2***~~3~~) the cut-off date for final analysis. For all subjects with

ongoing HZ-associated pain at the time of cut-off date for final analysis, ZBPI data will be collected ~~until suspected HZ is disproved, OR~~ until a 4-week pain-free period is documented OR until at least Day HZ-90. In addition, subjects with ~~clinically diagnosed~~ suspected HZ will be asked to complete EQ-5D and SF-36 questionnaires weekly. ***If pain reappears in the same area after a 4-week pain-free period and is not accompanied by a new HZ rash, it will be assigned to the previous HZ-episode. The completion of ZBPI, EQ-5D and SF-36 questionnaires will resume based upon the weekly schedule established at the start of the assigned episode. Visits/contacts will also restart according to the schedule in Table 3 with Day HZ-0 defined as the first visit of the assigned episode, prior to the pain free period.*** Refer to Section 5.5.2.2 for more details.

~~If during clinical evaluation at Visit HZ-1, the investigator determines that adequate rash lesion samples cannot be collected, the subject may be asked to return to the study site for collection of suitable HZ lesion samples~~**.** Three replicate rash lesion samples (see Table 6) should be collected on the same day. ~~If during clinical evaluation at Visit HZ-1, the investigator determines that only papules are present, three samples should be collected (if possible). The investigator has the option of collecting three additional samples if the rash progresses to vesicles or crusts are present prior to or at the Visit HZ-2.~~ ***If during clinical evaluation at Visit HZ-1, the investigator determines that adequate rash lesion samples cannot be collected (i.e., less than three lesions present, or if only papules are present), the subject should be asked to return to the study site for collection of additional samples prior to or at the Visit HZ-2 if there is rash progression (i.e., appearance of new/additional lesions if originally less than three lesions present, or appearance of vesicles if originally only papules present). When the subject returns for repeat sample collection, three samples from separate lesions should be collected.***

At Visit HZ-1, the rash will be documented by digital photography. Additional photographs of HZ lesions may be taken after Visit HZ-1 to help note the progression of the rash.

5.7.3.16 Study conclusion

Study end will take place when both conditions for final analysis are met and a minimum 90 days follow-up is completed for each case of ~~confirmed or clinically diagnosed~~ suspected HZ that occurs prior to the cut-off date for final analysis.

When the cut-off date for final analysis is established, the study sites will contact the subjects for the study conclusion contact as soon as possible. If a subject with ~~clinically diagnosed~~ suspected HZ has not completed follow-up until at least Day HZ-90 at the cut-off date for final analysis, follow-up for such a subject will continue until Day HZ-90 (or sooner ~~(1) if the case is disproved or (2)~~ if the subject has no HZ-associated pain for 4 consecutive weeks ***and the HZ rash resolves***).

At the study conclusion contact, the following procedures will take place:

- Follow-up of any cases of ~~confirmed or clinically diagnosed~~ suspected HZ and HZ-associated pain (Sections 5.5.2 and 5.7.3.10);

5.8.2 Biological samples

Table 6 Biological samples

Footnote:

† If during clinical evaluation at Visit HZ-1, the investigator determines that only papules are present, three samples should be collected (if possible). The investigator has the option of collecting three additional samples if the rash progresses to vesicles or crusts are present prior to or at the Visit HZ-2 ***that adequate rash samples are not present at Visit HZ-1 (i.e., <3 lesions present or only papules present), the investigator has the option of collecting three additional samples prior to or at Visit HZ-2***. See the SPM for further details on sample collection.

7 Health economics

For subjects with ~~clinically diagnosed~~ suspected HZ, both questionnaires will be completed weekly from Day HZ-0 onwards ~~until the case of clinically diagnosed suspected HZ is disproved, OR~~ until a 4-week pain-free period is documented~~,~~ OR until the cut-off date for final analysis. For all subjects with ongoing HZ-associated pain at the time of the cut-off date for final analysis, EQ-5D and SF-36 data will be collected ~~until suspected HZ is disproved, OR~~ until a 4-week pain-free period is documented OR until at least Day HZ-90. ***Refer to Section 5.5.2.2 for more details.***

8.3.1 Time period for detecting and recording adverse events, serious adverse events

All HZ complications as defined in Section 5.5.2.5 (including AE/SAE information) will be reported throughout the entire study period.

An overview of the protocol-required reporting periods for AEs and SAEs, pIMDs, medically attended visits ~~and~~, intercurrent medical conditions ***and HZ complications*** in study ZOSTER-022 is shown in Table 14.

Table 14 Reporting periods for AEs, SAEs, pIMDs, medically attended visits ~~and~~, intercurrent medical conditions *and HZ complications* in study ZOSTER-006

									CONTACT (monthly after Visit 3 until study conclusion, except at months that coincide with the subject's scheduled visits)				
Study activity	VISIT 1 DOSE 1				VISIT 2 DOSE 2			VISIT 3	CONTACT	VISIT 4	VISIT 5	VISIT 6	Study conclusion contact
Timing of reporting	Day 0/ Month 0	Day 6 post Dose 1	Day 29 post Dose 1		Day 0/ Month 2	Day 6 post Dose 2	Day 29 post Dose 2	Month 3	Month 8	Month 14	Month 26	Month 38	
Recording of HZ Complications* (including AE/SAE information)													

**** HZ complications are defined in Section 5.5.2.5***

Section 8.3.2.5 AEs of specific interest

Table 16 List of Potential immune-mediated diseases

Neuroinflammatory disorders
Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy), and neuritis (e.g. optic neuritis)
Multiple sclerosis (including variants)
Transverse myelitis
Guillain-Barré syndrome, (including Miller Fisher syndrome and other variants)
Other demyelinating diseases (including acute disseminated encephalomyelitis)
Myasthenia gravis (including Lambert-Eaton myasthenic syndrome)
Non-infectious encephalitis/ encephalomyelitis
Neuritis (including peripheral neuropathies)
Narcolepsy

10.4.5 Sample sizes

The ***provisional*** country allocation and various subsets are also described**.**

10.4.5.1 Primary objective

The final analysis of the ZOSTER-022 study is planned after the accumulation at least 65 PHN cases (expected median are approximately 40 PHN cases in 70-79 YOA and approximately 26 PHN cases in ≥ 80 YOA strata) are accrued from study ZOSTER-022 (primary condition for triggering analysis), and at least 278 confirmed HZ cases (expected median number of cases is 310 HZ cases) across both 70-79 YOA (***expected*** median of 222 HZ cases) and ≥ 80 YOA (***expected*** median of 87 HZ cases) strata**.**

10.4.5.3 Futility analyses and sample size re-assessment

One futility analysis is planned after ~~approximately~~ ***at least*** 25% of the total ***number of*** HZ cases ***anticipated at final analysis*** are observed ***in Zoster-006 (see Table 20),*** and when at least 20% of the total ***number of*** HZ cases ***anticipated at final analysis within each age stratum (50-59 YOA, 60-69 YOA and 70+ YOA) are observed (seeTable 20)*** ~~in each age stratum~~***. Note that HZ cases from ZOSTER-022 may be used to meet the required number of 70+ YOA cases***. The precise timing of that analysis ~~may~~***will*** be ~~triggered~~***determined*** by a blinded review of the HZ **case** accrual in ZOSTER-006 and/or ZOSTER-022. The futility decision rules will be described in the ~~IDMC Charter and statistical analysis plan~~ ***RAP***.

A conservative futility boundary or a predictive power threshold [Proschan, 2006] in the range of ~30% is anticipated but the actual functional form of the beta-spending function or the predictive power threshold used for the trial will be defined in the ~~IDMC Charter/~~IDMC RAP.

10.4.5.4 Provisional region and sub-population allocations

Subjects will be stratified by age: 50-59 YOA; 60-69 YOA; 70-79 YOA and ≥ 80 YOA in ***approximately*** an 8:5:3:1 ratio.

10.4.5.6.2 Humoral immune response vaccine take

Overall, accounting for the same number of subjects to be sampled in vaccine and placebo groups in each of the 15 to 18 countries in order to maintain the blind, and to have a sufficiently large number of evaluable blood samples, the total number of subjects enrolled into the subset should ***approximately*** be 18 x 60 x 2 = ~2160**.**

10.4.5.7.2 Number of subjects in the CMI subset

The CMI analyses will be performed in the Immunogenicity subset in three countries (Czech Republic, Japan and United States) at designated sites that have access to a PBMC processing facility within the acceptable time window from sample collection to PBMC processing. The CMI subset in these countries ~~will~~ ***is expected to*** include 156 subjects to account for anticipated lost or non-evaluable samples, see Table 32.

10.7.2 Statistical considerations for the interim futility analyses

The futility rules will be described in the ~~IDMC Charter/~~IDMC RAP.

10.7.3 Final analysis

When the conditions for triggering the final analysis of efficacy have been reached, the final analysis cut-off date will be defined. Any HZ episode occurring prior to the final analysis cut-off dat***e*** will be followed**,** as described in the RAP, ~~until the case of suspected HZ is disproved, OR~~ until a 4-week pain-free period is documented ***and the HZ rash resolves***, OR until the cut-off date for final analysis. For all subjects with ongoing HZ-associated pain-at the time of cut-off date for final analysis, ~~ZBPI~~ ***questionnaire*** data will be collected ~~until suspected HZ is disproved, OR~~ until a 4-week pain-free period is documented OR until at least Day HZ-90 in order to document potential PHN episodes**.**

13 References

Zostavax (Zoster Vaccine Live) Prescribing Information. June 2011.

Appendix B ASCERTAINMENT OF HZ CASES INCLUDING PCR TESTING ALGORITHM TO CLASSIFY HZ SUSPECTED CASES

To classify the suspected case of HZ, the samples from the rash lesions will be collected for laboratory testing by PCR (3 samples, collected on the same day, per subject). ~~If during clinical evaluation at Visit HZ-1, the investigator determines that only papules are present, three samples should be collected (if possible). The investigator has the option of collecting three additional samples if the rash progresses to vesicles or crust are present prior to or at the Visit HZ-2.~~ ***If during clinical evaluation at Visit HZ-1, the investigator determines that adequate rash lesion samples cannot be collected (i.e., less than three lesions present, or if only papules are present), the subject should be asked to return to the study site for collection of additional samples prior to or at the Visit HZ-2 if there is rash progression (i.e., appearance of new/additional lesions if originally less than three lesions present, or appearance of vesicles if originally only papules present). When the subject returns for repeat sample collection, three samples from separate lesions should be collected.***

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment 3**	
eTrack study number and Abbreviated Title(s)	110390 (ZOSTER-006)
IND number	BB-IND 13857
EudraCT number	2008-000367-42
Amendment number:	Amendment 3
Amendment date:	Final, 28 June 2012
Co-ordinating author:	[redacted], Scientific Writer, [redacted] contractor for GSK Biologicals

Rationale/background for changes:

- At the European Medicines Agency's (EMA) request, GSK Biologicals has updated its procedure for emergency unblinding during the conduct of a clinical study. According to the revised procedure, the responsibility and the decision to break the treatment code in emergency situations resides solely with the investigator and consequently, the investigator will have full authority to break the treatment code.
- To update the list of contributing authors (cover page)

Amended text is indicated in ***bold italics*** and deleted text is shown with ~~strikethrough~~ in the following sections:

Cover page

Contributing authors

- [redacted]***, Health Economics***
- [redacted]***, Project Data Manager***

Section 8.7 Emergency Unblinding

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the study treatment is essential for the clinical management or welfare of the subject, as judged by the investigator.

The emergency unblinding process consists of the automated system (SBIR) that allows the investigator to have unrestricted, immediate and direct access to the subject's individual study treatment.

The investigator has the option of contacting a GSK Biologicals' On-call Central Safety Physician (or Backup) if he/she needs medical advice or needs the support of GSK to perform the unblinding (i.e. he/she cannot access the automated Internet-based system).

Any emergency unblinding must be fully documented by using the Emergency Unblinding Documentation Form, which must be appropriately completed by the investigator and sent within 24 hours to GSK Biologicals.

GSK Biologicals' Contact information for Emergency Unblinding 24/24 hour and 7/7 day availability
GSK Biologicals' Central Safety Physician: ***Outside US/Canada:*** [redacted] ***(GSK Biologicals Central Safety Physician on-call)*** ***US/Canada only:*** [redacted] ***(GSK Biologicals Central Safety Physician on-call)***
GSK Biologicals' Central Safety Physician Back-up: ***Outside US/Canada:*** [redacted] ***US/Canada only:*** [redacted]
Emergency Unblinding Documentation Form transmission: ***Outside US & Canada:*** ***Fax:*** [redacted] ***or*** [redacted] ***US/Canada only:*** ***Fax:*** [redacted]

~~The investigator, or other physician managing the subject, should contact GSK Biologicals' Central Safety Physician to discuss the need for emergency unblinding. Alternatively the investigator may contact the local contact who will contact the GSK Central Safety Physician.~~

~~An investigator should request for unblinding of the subject's treatment code only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the investigational study vaccine(s)/product(s) is essential for the clinical management or welfare of the subject.~~

~~The GSK Biologicals' Central Safety Office will be allowed to access the individual randomisation code. The code will be broken by the GSK Biologicals' Central Safety physician (see below and Study Contact for Emergency Code Break in Sponsor Information) only in the case of medical events that the investigator/physician in charge of the subject feels cannot be treated without knowing the identity of the study vaccine(s)/product(s).~~

~~**GSK Biologicals Central Safety Physician (Study Contact for Emergency Code Break)**~~
~~Phones for 7/7 day availability:~~ ~~Outside US/Canada:~~ [redacted] ~~(GSK Biologicals Central Safety Physician on call)~~ ~~For US/Canada only:~~ [redacted] ~~(GSK Biologicals Central Safety Physician on call)~~
~~Back-up phone contact:~~ ~~Outside US/Canada:~~ [redacted] ~~For US/Canada only:~~ [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 4

eTrack study number and Abbreviated Title(s)	110390 (ZOSTER-006)
IND number	BB-IND 13857
EudraCT number	2008-000367-42
Amendment number:	Amendment 4
Amendment date:	Final, 18 April 2014
Co-ordinating author:	[redacted], Scientific Writer, [redacted] contractor for GSK Biologicals

Rationale/background for changes:

- It is predicted that study ZOSTER-006 will reach the conditions required for triggering final analysis of herpes zoster (HZ) primary endpoint about one year before those conditions being reached for study ZOSTER-022. Therefore GSK decided, as originally planned in these circumstances, to dissociate the two studies in terms of timing of the analysis of each study. Moreover, a two-step approach is allowed for the analysis of each study. Both studies will end concurrently. (Synopsis, Sections 3, 10.4.6)
- In study ZOSTER-022, postherpetic neuralgia (PHN) is demoted from co-primary endpoint to a descriptive secondary endpoint and the overall PHN co-primary endpoint in subjects ≥ 70 YOA for pooled analyses of ZOSTER 006 and ZOSTER-022 will be considered as primary analysis for PHN. Overall PHN in subjects ≥ 50 YOA has become a secondary endpoint for pooled analyses of ZOSTER-006 and ZOSTER-022. The applicable objectives and endpoints have been updated accordingly in the ZOSTER-022 protocol. Pooled analyses of ZOSTER-006 and ZOSTER-022 will only be conducted if the primary objective [HZ vaccine efficacy (VE)] is demonstrated in both ZOSTER-006 and ZOSTER-022 separately. The gatekeeping strategy has been updated accordingly and aligned with the objectives (Synopsis, Sections 1.2, 10.4.2, Table 19, 10.4.3, 10.4.4) ; the gatekeeping strategy diagram has been numbered (Fig. 1).

- The expected number of PHN cases is projected based on current accrual rates. The target number of PHN cases required to trigger pooled PHN analysis has been reduced, while maintaining statistical robustness. A total of at least 35 PHN cases in subjects ≥ 70YOA provides 90% power to demonstrate an overall PHN VE of at least 0% (previously a total of at least 88 PHN cases provided 93% power to demonstrate an overall PHN VE in subjects ≥ 50YOA of at least 25%). In the pooled analysis of studies ZOSTER-006 and ZOSTER-022 clinically meaningful overall PHN VE (PHN VE in ≥ 70 YOA randomized subjects) will be demonstrated if the lower limit of the 95% CI is above 0%. The sample size of the pooled studies ZOSTER-006 and ZOSTER-022 provides 10% chance (previously 22%) to demonstrate statistically significant PHN VE (LL above 0%) in those subjects presenting with a HZ episode. (Sections 10.4.5.1, Table 20, 21, 22, Section 10.4.5.2)
- The analysis steps, i.e. final HZ efficacy analysis (step 1) and end of study analysis (step 2) are defined. The conditions determining the cut-off dates of the 2 analysis steps are detailed.

  The cut-off date for final HZ efficacy analysis will occur given the following conditions:
  - at least 196 confirmed HZ cases are accrued in the primary cohort for analysis of efficacy;
  - approximately 60 HZ cases in subjects 50-59 YOA and approximately 60 HZ cases in subjects 60-69 YOA are accrued in the mTVc;
  - approximately 75% of subjects in each stratum have completed at least 36 months follow-up after Dose 2, and the remaining subjects have completed at least 30 months follow-up after Dose 2.

  The cut-off date for end of study analysis will occur given the following:
  - all previous conditions are met for final HZ analyses in study ZOSTER-022;
  - at least 35 PHN cases in subjects ≥ 70 YOA are accrued in the in the primary cohort for analysis of efficacy when pooling the studies ZOSTER-006 and ZOSTER-022.

  The end of study analysis cannot be performed before the final HZ efficacy analysis. Details regarding study duration are described.
  (Synopsis, Sections 3, 10.4.5.1, 10.4.6)
- An overview of the analyses performed at each analysis step is given. Step 1 will include analyses of the following objectives of ZOSTER-006: all HZ VE objectives and all reactogenicity/safety and immunogenicity objectives. At step 2, all objectives of study ZOSTER-006 will be analyzed. Objectives already analyzed at step 1 will be re-analyzed (confirmatory descriptive in case of inferential analysis at step 1 or descriptive analysis otherwise). At step 2, pooled analyses of studies ZOSTER-006 and ZOSTER-022 are planned; overall PHN VE in subjects ≥ 70 YOA, and other pre-specified endpoints will be analyzed. (Synopsis, Sections 3, 10.4.9, Table 33)

- Each inferential objective in study ZOSTER-006 will be assessed only one time, therefore no alpha adjustment will be applied. For all inferential objectives assessed at first step analysis, a second descriptive analysis will be performed at the end of each study and will serve as confirmatory analysis (Sections 10.4.4, 10.4.7).
- It has been detailed that depending on the further evolution of the case accrual rate, the generated data may be presented in one or more study reports per study (ZOSTER-006 and ZOSTER-022). The final study report for each study will be a comprehensive report containing the results of the two analysis steps (Sections 10.7.4, 10.8.3.2). Wording in Section 10.8.3.4 has been aligned with Section 10.7.4.
- The same blinding level (i.e. observer-blind) remains to be kept throughout the study. Measures taken to ensure the blinding, including the installation of a firewall, are described in a separate charter. Pending the outcome of the final HZ efficacy analysis of studies ZOSTER-006 and ZOSTER-022, a long-term follow-up study might be planned enrolling subjects who participated in the primary studies ZOSTER-006 and ZOSTER-022 and are willing to participate in the follow-up study. The design of the follow-up study remains to be confirmed. (Sections 5.4, 10.4.6, 10.4.8, 10.7.3)
- Given the two-step analyses, in accordance with GSK procedures, in the List of study procedures the final HZ efficacy analysis trigger has been specified, with transcription in the eCRF of the date of the last visit or contact with the subject and addition of the investigator signature (Section 5.6, Table 2). This has also been detailed in a new section 5.7.3.15; the numbering of subsequent sections has been updated accordingly (i.e., Sections 5.7.3.16 and 5.7.3.17).
- It is anticipated that all subjects will have completed Visit 6 at the time of study conclusion; updates have been made accordingly (Sections 3 and 5.6, Table 2 and Table 4).
- Given the two-step analyses, reference is made to the cut-off date for end of study analysis (instead of cut-off date for final analysis) when describing follow-up of HZ up to or close to study end (Sections 5.5.1, 5.5.2.2, 5.5.2.4, 5.6 Table 3, 5.7.3.11, 5.7.3.17, 7, 10.7.3).
- The description of the process for follow up of HZ has been aligned throughout the Table 3 footnotes (Section 5.6) reflecting that if HZ-associated pain ceases (defined as a 28-day [or 4-week] pain free period) and the HZ rash resolves, subsequent HZ follow-up visits or contacts will be cancelled.
- Given the two-step analyses, reference is made to ‘final HZ efficacy analysis’ instead of ‘final analysis’, when applicable (Sections 10.4.5.3, 10.7.1 and 10.7.2, Table 23 and Table 24).
- It has been detailed that in case of unblinding upon the subject’s request to allow the subject to decide if he/ she will consider immunization with a licensed HZ vaccine, the subject will be withdrawn from the study (Sections 5.7.3, 9.2.1).

- The cut-off of the gE-specific ELISA assay has been changed from 18 to 97 mIU/mL. Background signal has been measured with the anti-gE ELISA on samples from Varicella Zoster Virus (VZV) naïve paediatric subjects. This observation of background signal on VZV naïve samples was not part of the original validation of the assay and establishment of the assay cut-off. Background signal measured with the anti-gE ELISA has no impact on Zoster project clinical conclusions as the vast majority of the samples (at all timepoints) have high titerswell above the unspecific response level measured on VZV naïve samples from Measles, Mumps, Rubella and Varicella (MMRV) studies and Zoster vaccine responses are very robust. However this finding triggered re-evaluation of the assay cut-off. Based on complementary validation experiments performed in line with Clinical and Laboratory Standards Institute (CLSI) guidelines and taking into account internal company guidelines the technical and seropositivity cut-off has been set at 97mIU/mL. (Section 5.8.3, Table 7, Appendix A)
- Regarding the reporting of SAEs that are related to study participation (e.g. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine or any fatal SAE, it has been clarified that this includes SAEs that are considered by the investigator to be related to the investigational vaccine and are to be reported until study end (Section 8.3.1; Table 14).
- The section on derived and transformed data for cell-mediated immunogenicity vaccine responses (gE- and VZV-specific) including the definition of vaccine response has been updated in alignment with the harmonised definitions within the ZOSTER project (Section 10.6.4).
- For clarity, the total number of subjects included in the Immunogenicity subset and the CMI subset has been detailed (Section 10.4.5.6.4, Table 30; Section 10.4.5.7.2, Table 32).
- A process related to review of immunogenicity data as described in the protocol is not applicable for the study, therefore any related wording has been removed (Section 10.7.3).
- In accordance with current GSK procedures, where applicable the name of the plan previously referred to as ‘reporting analysis plan’ has been updated to ‘statistical analysis plan’ (List of abbreviations, Sections 10.5.3, 10.7.3, 10.8.2, 10.8.2.3, 10.8.2.4, 10.8.2.5, 10.8.2.6, 10.8.2.7, 10.8.3.4, 10.8.4.1, 10.8.4.2, 10.8.5.2).
- For clarity, it has been detailed that the subject will be reminded that the current study has yearly follow-up visits planned until Month 38 (Visit 6) (Section 5.7.3.14).
- The estimated study period has been updated in the section with country specific requirements for Japan (Section 12.3).
- A reference has been further detailed and references which are not applicable anymore have been removed (Section 13).
- The list of contributing authors and the sponsor signatory have been updated (cover page, sponsor signatory approval page).

Amended text is indicated in ***bold italics*** and deleted text is shown with ~~strikethrough~~ in the following sections:

Cover page

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Protocol Amendment 4 Sponsor signatory approval page

Sponsor signatory

[redacted] ~~Director, Global Clinical Development, Vaccines~~ [redacted] ***Project Level Clinical Research & Development Lead, Director, Global Clinical Development, Vaccines***

Synopsis

Rationale for the study and study design

Study ZOSTER-022 will address VE against ~~PHN~~***HZ*** in subjects ≥ 70 YOA~~, in addition to providing a robust estimate of HZ VE in that age stratum~~. ~~After each study (ZOSTER-006 and ZOSTER-022) is analyzed separately~~ ***At the end of studies ZOSTER-006 and ZOSTER-022***, a pooled analysis of HZ and PHN data from both studies combined is planned and will be described prospectively. ***The analysis of pooled data from both studies for overall PHN in subjects ≥ 70 YOA is positioned as primary analysis for PHN.***

Study design

- ***Planned analysis steps:***

  It is predicted that study ZOSTER-006 will reach the conditions required for triggering final analysis of HZ primary endpoint about one year before those conditions being reached for study ZOSTER-022. Therefore GSK decided, as originally planned in these circumstances, to dissociate the two studies in terms of timing of the analysis of each study. Moreover, a two-step approach is allowed for the analysis of each study. Both studies will end concurrently.

  In study ZOSTER-006, the planned analysis steps are the following:

  1. ***Final HZ efficacy analysis (step 1). Final analysis of HZ primary endpoint:***

  The cut-off date for final HZ efficacy analysis will occur when the following conditions are met:

  – ***at least 196 confirmed HZ cases are accrued in the modified Total Vaccinated cohort (mTVc)*** [(Footnote 1)]***;***

  – ***approximately 60 HZ cases in subjects 50-59 YOA and approximately 60 HZ cases in subjects 60-69 YOA are accrued in the mTVc;***

- ***approximately 75% of subjects in each stratum have completed at least 36 months follow-up after Dose 2, and the remaining subjects have completed at least 30 months follow-up after Dose 2.***

Step 1 will include analyses of the following objectives:

- ***all HZ VE objectives;***
- ***all reactogenicity/safety and immunogenicity objectives.***

2. End of study analysis (step 2).

The cut-off date for end of study analysis will occur given the following:

- ***all conditions (as detailed in ZOSTER-022 protocol) are met for final HZ efficacy analysis in study ZOSTER-022;***
- ***at least 35 PHN cases in subjects ≥ 70YOA are accrued in the mTVc when pooling the studies ZOSTER-006 and ZOSTER-022.***

The end of study analysis (step 2) cannot be performed before the final HZ efficacy analysis (step 1).

At step 2 all objectives of study ZOSTER-006 will be analyzed. Objectives already analyzed at step 1 will be re-analyzed (confirmatory descriptive in case of inferential analysis at step 1 or descriptive analysis otherwise).

Pooled analyses of studies ZOSTER-006 and ZOSTER-022 are planned if the primary objective of study ZOSTER-006 and the primary objective of study ZOSTER-022 are demonstrated. Overall PHN VE in subjects ≥ 70 YOA, and other pre-specified endpoints will be analyzed in the pooled analyses, as specified in ZOSTER-022 protocol.

- Duration of the study: Each subject will be followed for at least 30 months after Dose 2.

~~The cut-off date for final analysis will occur when both of the following conditions are met:~~

- ~~The prespecified number of confirmed HZ and PHN cases in the modified Total Vaccinated cohort (mTVc) required for final analyses of both ZOSTER-006 and ZOSTER-022 are accrued;~~
- ~~75% of subjects (for both ZOSTER-006 and ZOSTER-022) have completed at least 36 months~~

~~follow-up after Dose 2, and the remaining subjects have completed at least 30 months follow-up after Dose 2.~~

All subjects will continue in the study at least until the cut-off date for ~~final~~ ***end of study*** analysis regardless of their date of enrolment. Study end will take place when ***the*** ~~both~~ conditions for ~~final~~ ***end of study*** analysis are met and a minimum 90 days follow-up is completed for each HZ case that occurs up to the cut-off date for ~~final~~ ***end of study*** analysis.

The exact duration of the study for individual subjects will vary. The maximum total study duration for each subject is expected to be ***approximately*** 4 to 5 years.

~~If a delay of approximately 6 months or more is predicted prior to the simultaneous end dates for the two studies based on the rates of accumulation of HZ and PHN cases, then the first study that reaches the criteria for final analysis may be continued until the second study reaches the criteria for final analysis so that the two studies end concurrently.~~

Footnote 1: ***The modified Total Vaccinated cohort (mTVc) is the primary cohort for analysis of efficacy which excludes subjects in the TVc for efficacy analysis who were not administered with the second vaccination or who develop a confirmed case of HZ prior to 1 month after the second vaccination.***

List of abbreviations

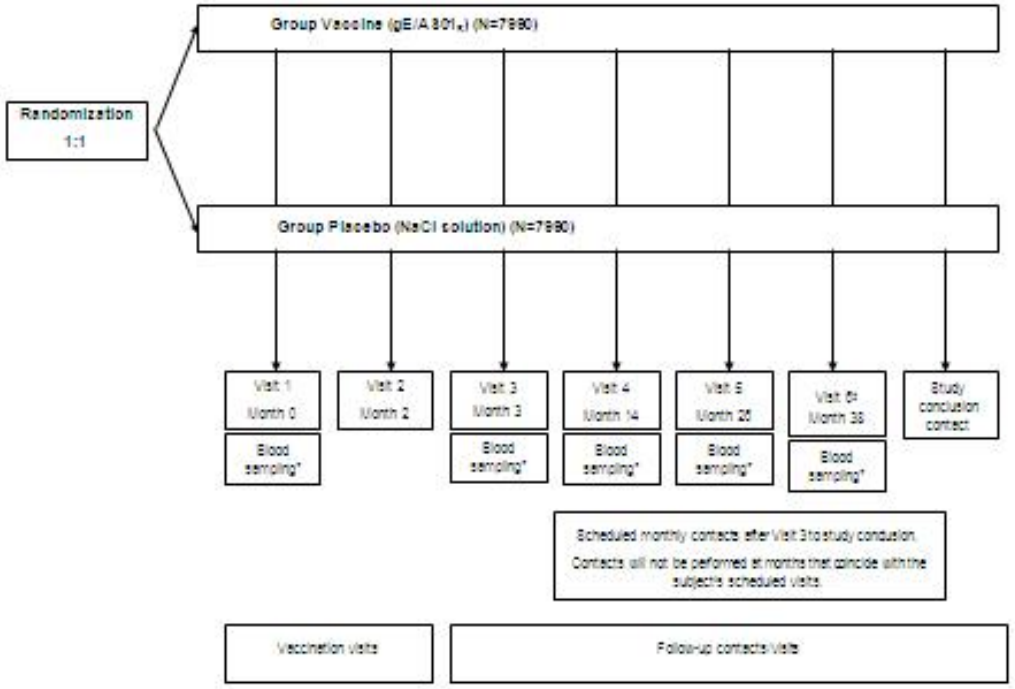
SAP	***Statistical Analysis Plan***

Section 1.2 Rationale for the study and study design

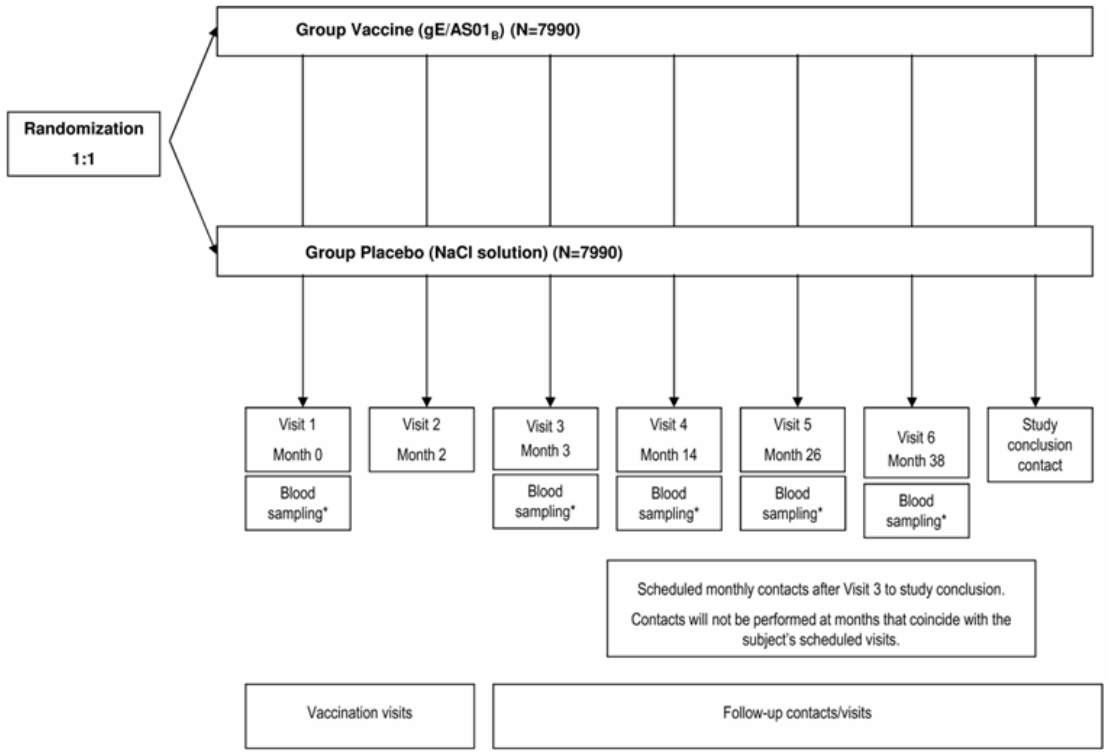
Study ZOSTER-022 will address VE against ~~PHN~~***HZ*** in subjects ≥ 70 YOA~~, in addition to providing a robust estimate of HZ VE in that age stratum~~. **(**~~After each study (ZOSTER-006 and ZOSTER-022) is analyzed separately~~ ***At the end of studies ZOSTER-006 and ZOSTER-022***, a pooled analysis of HZ and PHN data from both studies combined is planned and will be described prospectively. ***The analysis of pooled data from both studies for overall PHN in subjects ≥ 70 YOA is positioned as primary analysis for PHN.***

Section 3 Study design overview

Original figure:



Amended figure:



~~‡ If the conditions for final analysis and study end are met before Visits 6 is completed by all subjects and it is decided to conclude the study, Visit 6 may not take place in some subjects~~.

- ***Planned analysis steps :***

  It is predicted that study ZOSTER-006 will reach the conditions required for triggering final analysis of HZ primary endpoint about one year before those conditions being reached for study ZOSTER-022. Therefore GSK decided, as originally planned in these circumstances, to dissociate the two studies in terms of timing of the analysis of each study. Moreover, a two-step approach is allowed for the analysis of each study. Both studies will end concurrently.

  In study ZOSTER-006, the planned analysis steps are the following:

  1. ***Final HZ efficacy analysis (step 1). Final analysis of HZ primary endpoint:***

     The cut-off date for final HZ efficacy analysis will occur when the following conditions are met:

     - ***at least 196 confirmed HZ cases are accrued in the modified Total Vaccinated cohort (mTVc)*** *(Footnote 3)****;***
     - ***approximately 60 HZ cases in subjects 50-59 YOA and approximately 60 HZ cases in subjects 60-69 YOA are accrued in the mTVc;***
     - ***approximately 75% of subjects in each stratum have completed at least 36 months follow-up after Dose 2, and the remaining subjects have completed at least 30 months follow-up after Dose 2.***

Step 1 will include analyses of the following objectives:

- ***all HZ VE objectives;***
- ***all reactogenicity/safety and immunogenicity objectives.***

2. End of study analysis (step 2).

The cut-off date for end of study analysis will occur given the following:

- ***all conditions (as detailed in ZOSTER-022 protocol) are met for final HZ efficacy analysis in study ZOSTER-022;***
- ***at least 35 PHN cases in subjects ≥ 70 YOA are accrued in the mTVc when pooling the studies ZOSTER-006 and ZOSTER-022.***

The end of study analysis (step 2) cannot be performed before the final HZ efficacy analysis (step 1).

At step 2 all objectives of study ZOSTER-006 will be analyzed. Objectives already analyzed at step 1 will be re-analyzed (confirmatory descriptive in case of inferential analysis at step 1 or descriptive analysis otherwise).

Pooled analyses of studies ZOSTER-006 and ZOSTER-022 are planned if the primary objective of study ZOSTER-006 and the primary objective of study ZOSTER-022 are demonstrated. Overall PHN VE in subjects ≥ 70 YOA, and other pre-specified endpoints will be analyzed in the pooled analyses, as specified in ZOSTER-022 protocol.

- Duration of the study: Each subject will be followed for at least 30 months after Dose 2.

  ~~The cut-off date for final analysis will occur when both of the following conditions are met:~~

  - ~~The prespecified number of confirmed HZ and PHN cases in modified Total Vaccinated cohort (mTVc) required for final analyses of both ZOSTER-006 and ZOSTER-022 are accrued;~~
  - ~~75% of subjects (for both ZOSTER-006 and ZOSTER-022) have completed at least 36 months follow-up after Dose 2, and the remaining subjects have completed at least 30 months follow-up after Dose 2.~~

  All subjects will continue in the study at least until the cut-off date for ~~final~~ ***end of study*** analysis regardless of their date of enrolment. Study end will take place when ***the*** ~~both~~ conditions for ~~final~~ ***end of study*** analysis are met and a minimum 90 days follow-up is completed for each HZ case that occurs up to the cut-off date for ~~final~~ ***end of study*** analysis.

  The exact duration of the study for individual subjects will vary. The maximum total study duration for each subject is expected to be ***approximately*** 4 to 5 years.

  ~~If a delay of approximately 6 months or more is predicted prior to the simultaneous end dates for the two studies based on the rates of accumulation of HZ and PHN cases, then the first study that reaches the criteria for final analysis may be continued~~

~~until the second study reaches the criteria for final analysis so that the two studies end concurrently.~~

Footnote 3: ***The modified Total Vaccinated cohort (mTVc) is the primary cohort for analysis of efficacy which excludes subjects in the TVc for efficacy analysis who were not administered with the second vaccination or who develop a confirmed case of HZ prior to 1 month after the second vaccination.***

Section 5.4 Method of blinding

Immunological data, which could lead to the unblinding of the treatment groups, will not be available during the course of the trial to any investigator or any person involved in the clinical conduct of the study (including data cleaning)~~, until after the database is locked~~.

Refer to Section 10.4.8 for more details regarding aspects of blinding in the study.

Section 5.5.1 Data collection

- **Zoster Brief Pain Inventory (ZBPI) questionnaire**: To be completed by subjects with suspected HZ on Day HZ-0 (Visit HZ-1) and daily from Day HZ-1 (day after the Visit HZ-1) up to Day HZ-28, and weekly from Day HZ-29 onwards until a 4-week pain-free period is documented OR until the cut-off date for ~~final~~ ***end of study*** analysis. For all subjects with ongoing HZ-associated pain-at the time of cut-off date for ~~final~~ ***end of study*** analysis, ZBPI data will be collected until a 4-week pain-free period is documented OR until at least Day HZ-90 (Refer to Section 5.5.2.2 for more details)**.**
- **EQ-5D and SF-36 questionnaires**: To be completed weekly by the subjects with suspected HZ from Day HZ-0 onwards until a 4-week pain-free period is documented OR until the cut-off date for ~~final~~ ***end of study*** analysis. For all subjects with ongoing HZ-associated pain at the time of the cut-off date for ~~final~~ ***end of study*** analysis, EQ-5D and SF-36 data will be collected until a 4-week pain-free period is documented OR until at least Day HZ-90 (Refer to Section 5.5.2.2 for more details).

Section 5.5.2.2 Evaluation of suspected case of HZ

All HZ cases that occur during the study period up to the cut-off date for ~~final~~ ***end of study*** analysis will be followed and evaluated. Please refer to the SPM for information about recording HZ cases that occur after the cut-off date for ~~final~~ ***end of study*** analysis. Such cases will be referred to the local physician for follow-up.

- The subject will be asked to complete the ZBPI questionnaires daily from Day HZ-1 (day after the Visit HZ-1) up to Day 28 (ZBPI must be completed to Day HZ-28 at minimum) and weekly from Day HZ-29 onwards until:

– The cut-off date for ~~final~~ ***end of study*** analysis.

  For all subjects with ongoing HZ-associated pain at the time of cut-off date for ~~final~~ ***end of study*** analysis, completion of ZBPI questionnaires will continue until a 4-week pain-free period is documented OR until at least Day HZ-90.

Section 5.5.2.4 Evaluation of severity of HZ-associated pain using the Zoster Brief Pain Inventory

In each case of suspected HZ, the subjects will be asked to assess their HZ-associated pain and interference of HZ with their QoL by completing the ZBPI questionnaire either themselves or assisted, by an aide (Section 5.5.1) until HZ-associated pain ceases (defined as a 28-day [or 4-week] pain free period) or until the cut-off date for ~~final~~ ***end of study*** analysis (see further details in Section 5.5.2.2).

Section 5.6 Outline of study procedures

Table 2 List of study procedures

Type of contact***/trigger***									VISIT 6[~~f~~]		***Final HZ efficacy analysis trigger***	Study conclusion contact
Timepoints												
Sampling timepoints												
Transcription[~~gf~~] by study staff/investigator of EQ-5D and SF-36 questionnaires completed												
Transcription in eCRF of date of last visit or contact with subject											•	
Investigator signature in eCRF											•	

Note: The double-line border indicates the analyses which will be performed on data (i.e., data that are as clean as possible) obtained at the cut-off date for final HZ efficacy analysis. The possibility of data changes after the final HZ efficacy analysis exists because data collection and data entry may continue until study end. Indicated by the dotted line, pending subjects' advancement in the study, the cut-off date for final HZ efficacy analysis may occur at Visit 6 or some time prior or after this visit.

[~~f~~] ~~If the conditions for final analysis and study end are met before Visit 6 is completed by all subjects and it is decided to conclude the study, Visit 6 may not take place in some subjects~~.

[~~gf~~] EQ-5D and SF-36 will remain as source documents. The information from these questionnaires will only be transcribed in the eCRF for subjects who have a suspected HZ event during the study.

Table 3 Study procedures to be performed during the follow-up period for each suspected HZ case

Type of contact
Timepoints
Completion† of ZBPI questionnaires by the subjects until pain ceases or the cut-off date for ***end of study*** ~~final~~ analysis (ZBPI pain data will be collected until at least Day HZ-90)
Completion‡ of EQ-5D and SF-36 questionnaires by the subjects until pain ceases or the cut-off date for ***end of study*** ~~final~~ analysis (EQ-5D and SF-36 data will be collected until at least Day HZ-90)

† Subjects with suspected HZ will be asked to complete the ZBPI questionnaire at Day HZ-0 (Visit HZ-1) to rate HZ-associated pain within the last 24 hours (If the time between the HZ onset and clinical evaluation at Visit HZ-1 is greater than 24 hours, the subject will be asked to complete a second ZBPI also for the elapsed time between the HZ onset and 24 hours before Visit HZ-1); daily from Day HZ- 1 to Day HZ-28, and weekly from Day HZ-29 onwards until a 4-week pain-free period is documented or until the cut-off date for ~~final~~ ***end of study*** analysis. If pain reappears in the same area after a 4-week pain-free period and is not accompanied by a new HZ rash, it will be assigned to the previous HZ-episode. The completion of ZBPI questionnaires will resume based upon the weekly schedule established at the start of the assigned episode. For all subjects with ongoing HZ-associated pain at the time of cut-off date for ~~final~~ ***end of study*** analysis, ZBPI data will be collected until a 4-week pain-free period is documented OR until at least Day HZ-90 (See Section 5.5.2.2).

‡Subjects with suspected HZ will be asked to complete the EQ-5D and SF-36 questionnaire weekly from Day HZ-0 to Day HZ-28, and weekly onwards until a 4-week pain-free period is documented or until the cut-off date for ~~final~~ ***end of study*** analysis. If pain reappears in the same area after a 4-week pain-free period and is not accompanied by a new HZ rash, it will be assigned to the previous HZ-episode. The completion of EQ-5D and SF-36 questionnaires will resume based upon the weekly schedule established at the start of the assigned episode. For all subjects with ongoing HZ-associated pain at the time of cut-off date for ~~final~~ ***end of study*** analysis, EQ-5D and SF-36 data will be collected until a 4-week pain-free period is documented OR until at least Day HZ-90. Each suspected HZ that occurs up to the cut-off date for ***end of study*** ~~final~~ analysis will be followed at least until Visit HZ-7 (the study visit at Day HZ-91) ***(or sooner if the subject has no HZ-associated pain for 4 consecutive weeks and the HZ rash resolves)***.

Table 4 Intervals between study visits/contacts

Interval
Visit 2 → Visit 6~~*~~

~~* If the conditions for final analysis and study end are met before Visit 6 is completed by all subjects and it is decided to conclude the study, Visit 6 may not take place in some subjects~~.

Section 5.7.3 Procedures during the study

Note that subjects may decide at any time to end their participation in the study or request unblinding of the treatment received. In case of non-emergency unblinding, e.g., to receive a licensed HZ vaccine, subjects will be withdrawn from the study. An

internal operating procedure that describes the process for non-emergency unblinding will be followed.

Section 5.7.3.11 Follow up of suspected HZ cases and HZ-associated pain

Data will be collected on all suspected HZ cases that occur from administration of the first dose of vaccine/placebo until the cut-off date for ~~final~~ ***end of study*** analysis (Section 5.7.3.17). For each suspected case of HZ that the investigator concludes is clinically consistent with HZ, data on HZ-associated pain (using ZBPI questionnaires completed by the subject) will be collected until Day-HZ-28, and from Day HZ-29 until:1) the subject has no HZ-associated pain for 4 consecutive weeks; or, 2) the cut-off date for ~~final~~ ***end of study*** analysis. For all subjects with ongoing HZ-associated pain at the time of cut-off date for ~~final~~ ***end of study*** analysis, ZBPI data will be collected until a 4-week pain-free period is documented OR until at least Day HZ-90.

Section 5.7.3.14 Reminder for monthly follow-up contacts/yearly follow-up visits

The subject will be reminded that the current study still has yearly follow-up visits planned ***until Month 38 (Visit 6).***

Section 5.7.3.15 Final HZ efficacy analysis trigger

When the cut-off date for final HZ efficacy analysis has been reached and communicated to the sites, the following actions need to take place:

- ***Transcription in eCRF of date of last visit or contact with the subject***
- ***Addition of Investigator signature in eCRF (signing of data)***

Section 5.7.3.~~15~~ *16* Invitation for a planned follow-up study

Section 5.7.3.~~16~~ 17 Study conclusion

Study end will take place when ~~both~~ ***the*** conditions for ~~final~~ ***end of study*** analysis are met and a minimum 90 days follow-up is completed for each case of suspected HZ that occurs prior to the cut-off date for ~~final~~ ***end of study*** analysis.

~~If it appears that there will be a large disparity in the study end date for study ZOSTER-006 and ZOSTER-022, respectively, then the first study that meets the criteria for final analysis may be continued until the second study reaches the criteria for final analysis so that the two studies end concurrently.~~***Refer to Section 3 for more details regarding end of study analysis***.

When the cut-off date for ~~final~~ ***end of study*** analysis is established, the study sites will contact the subjects for the study conclusion contact as soon as possible. If a subject with suspected HZ has not completed follow-up until at least Day HZ-90 at the cut-off date for ~~final~~ ***end of study*** analysis, follow-up for such a subject will continue until Day HZ-90

(or sooner if the subject has no HZ-associated pain for 4 consecutive weeks and the HZ rash resolves).

Section 5.8.3 laboratory assays

Table 7 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off	Laboratory
Serum	gE Ab.IgG	ELISA	NA	mIU/mL	~~18~~ ***97***	GSK Biologicals*

Section 7 Health economics

For subjects with suspected HZ, both questionnaires will be completed weekly from Day HZ-0 onwards until a 4-week pain-free period is documented OR until the cut-off date for ~~final~~ ***end of study*** analysis. For all subjects with ongoing HZ-associated pain at the time of the cut-off date for ~~final~~ ***end of study*** analysis, EQ-5D and SF-36 data will be collected until a 4-week pain-free period is documented OR until at least Day HZ-90.

Section 8.3.1 Time period for detecting and recording adverse events, serious adverse events and pregnancies

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (e.g. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine or any fatal SAE will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged. ***This is including SAEs that are considered by the investigator to be related to the investigational vaccine and are to be collected and recorded from the time of the first receipt of study vaccine/placebo until the subject is discharged from the study.***

Table 14 Reporting periods for AEs, SAEs, pIMDs, medically attended visits, pregnancies, intercurrent medical conditions and HZ complications in study ZOSTER-006

Reporting of SAEs related to study participation or GSK concomitant medication/vaccine or any fatal SAE, ***including SAEs that are considered by the investigator to be related to the investigational vaccine,*** after Month 14 until study conclusion

Section 9.2.1 Subject withdrawal from the study

- ***Unblinding upon the subject's request to allow the subject to decide if he/she will consider immunization with a licensed HZ vaccine.***

Section 10.4.2 Significance level

The pooled analysis of studies ZOSTER-006 and ZOSTER-022 is planned provided the following conditions are met, as defined in Section 10.4.4:

1. Clinically meaningful overall HZ VE in subjects ≥ 50 YOA is reached in ZOSTER-006;
2. Clinically meaningful HZ VE is reached in subjects ≥ 70 YOA in ZOSTER-022~~;~~**.**
3. ~~Statistically significant PHN VE is reached in subjects ≥ 70 YOA in ZOSTER-022.~~

The pooled analysis of data in subjects ≥ 50 YOA accrued in study ZOSTER-006 and data in subjects ≥ 70 YOA collected in study ZOSTER-022 allows ***for*** ~~a more robust~~ ***the*** estimation of overall PHN VE ***(subjects ≥ 50 YOA)***, ~~HZ VE in subjects ≥ 70 YOA and~~ PHN VE in subjects ≥ 70 YOA ***and a more robust estimation of HZ VE in subjects ≥ 70 YOA*** ~~. Both objectives,~~ ***(as*** HZ VE in subjects ≥ 70 YOA ~~and PHN VE in subjects ≥ 70 YOA,~~ will be assessed in study ZOSTER-022***)***.

Table 19 Summary of statistical *inferential* evaluations of primary and secondary objectives for studies ZOSTER-006, ZOSTER-022 and the pooled analysis

Analysis	Endpoint	50-59 YOA	60-69 YOA	≥70 YOA	All age strata
ZOSTER-006	HZ VE	S	S	O	P
	PHN VE	-	-	-	-
	PHN VE in HZ subjects	-	-	-	-
ZOSTER-022	HZ VE	-	-	P	-
	PHN VE	-	-	~~P.~~	-
	PHN VE in HZ subjects	-	-	-	-
Pooled analysis	HZ VE	-	-	R	-
	PHN VE	-	-	~~R~~***P***	~~P~~***S***
	PHN VE in HZ subjects	-	-	-	S*

Section 10.4.3 Success criteria

The ***pooled analysis of the ZOSTER-006 and*** ZOSTER-022 ~~study~~***studies*** is ~~also~~ powered to demonstrate statistical***ly*** significant PHN VE ***in subjects ≥ 70 YOA***. Statistical significance of PHN VE in ≥ 70 YOA randomized subjects will be demonstrated if the lower limit of the 95% CI is above 0%. The PHN VE co-primary objective ***of the pooled ZOSTER-006 and ZOSTER-022 studies*** will be tested provided the primary HZ VE is demonstrated ***in each study*** and no adjustment of significance level will be made.

The primary analysis to demonstrate efficacy for overall PHN in subjects ≥ 70 YOA will be performed on the pooled studies ZOSTER-006 and ZOSTER-022. In addition, ~~T~~***t***he pooled analysis of studies ZOSTER-006 and ZOSTER-022 is intended to provide consolidated estimations of the clinically meaningful HZ VE in all subjects ≥ 70 YOA ~~and clinically meaningful overall PHN VE~~ in mTVc subjects randomized to studies ZOSTER-006 and ZOSTER-022. Clinically meaningful HZ VE in subjects ≥ 70 YOA will be demonstrated if the lower limit of the 95% CI is above 10% and clinically meaningful overall PHN VE ***in all subjects ≥ 70 YOA*** will be demonstrated if the lower limit of the 95% CI is above ~~25~~***0***%.

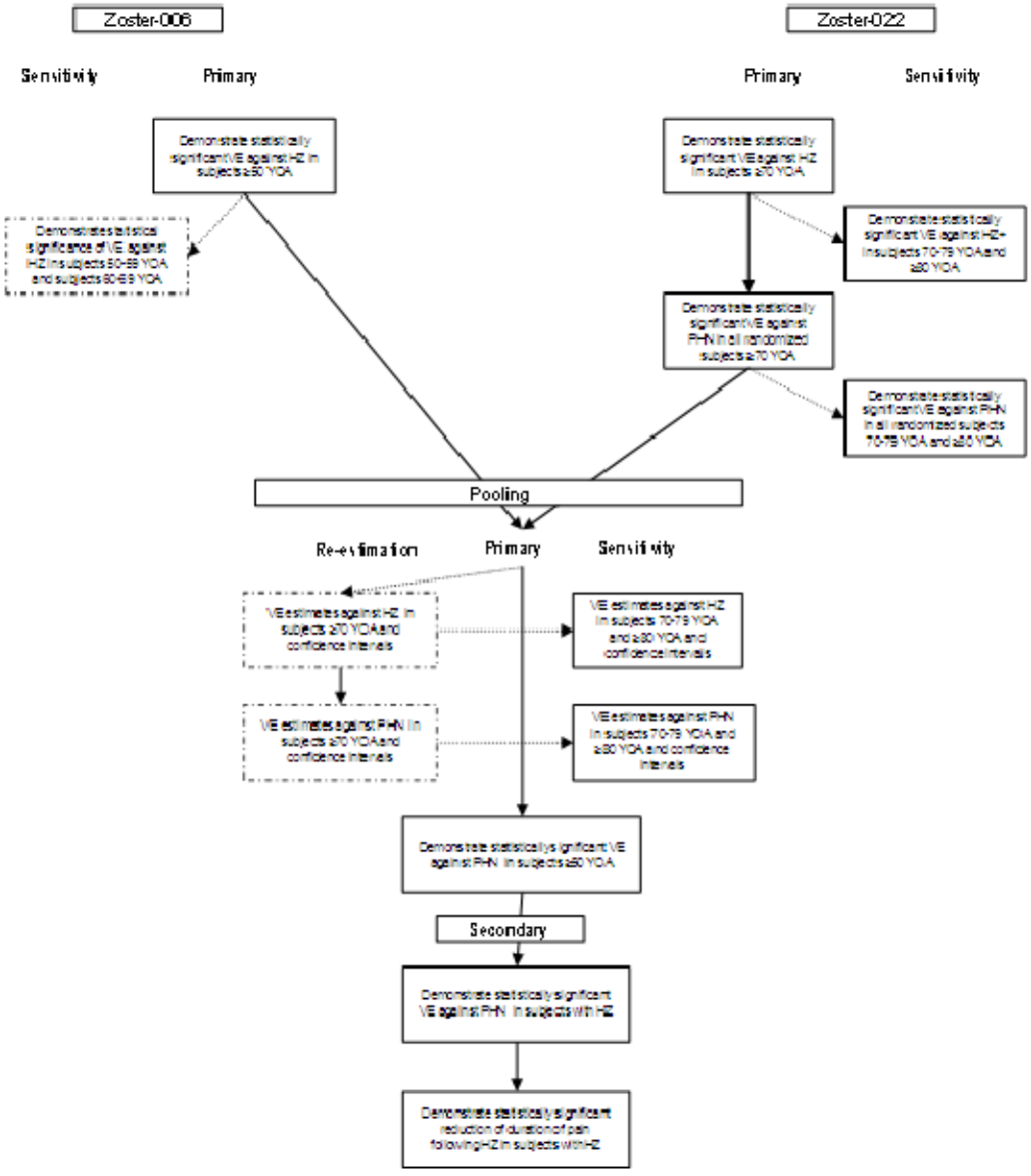
Section 10.4.4 Gatekeeping strategy

The enrolment of subjects ≥ 70 YOA in both studies and the need to provide an estimation of the HZ VE and PHN VE across the two studies, requires the gatekeeping strategy to be defined across the two studies and the pooling ***(see Figure 1)***.

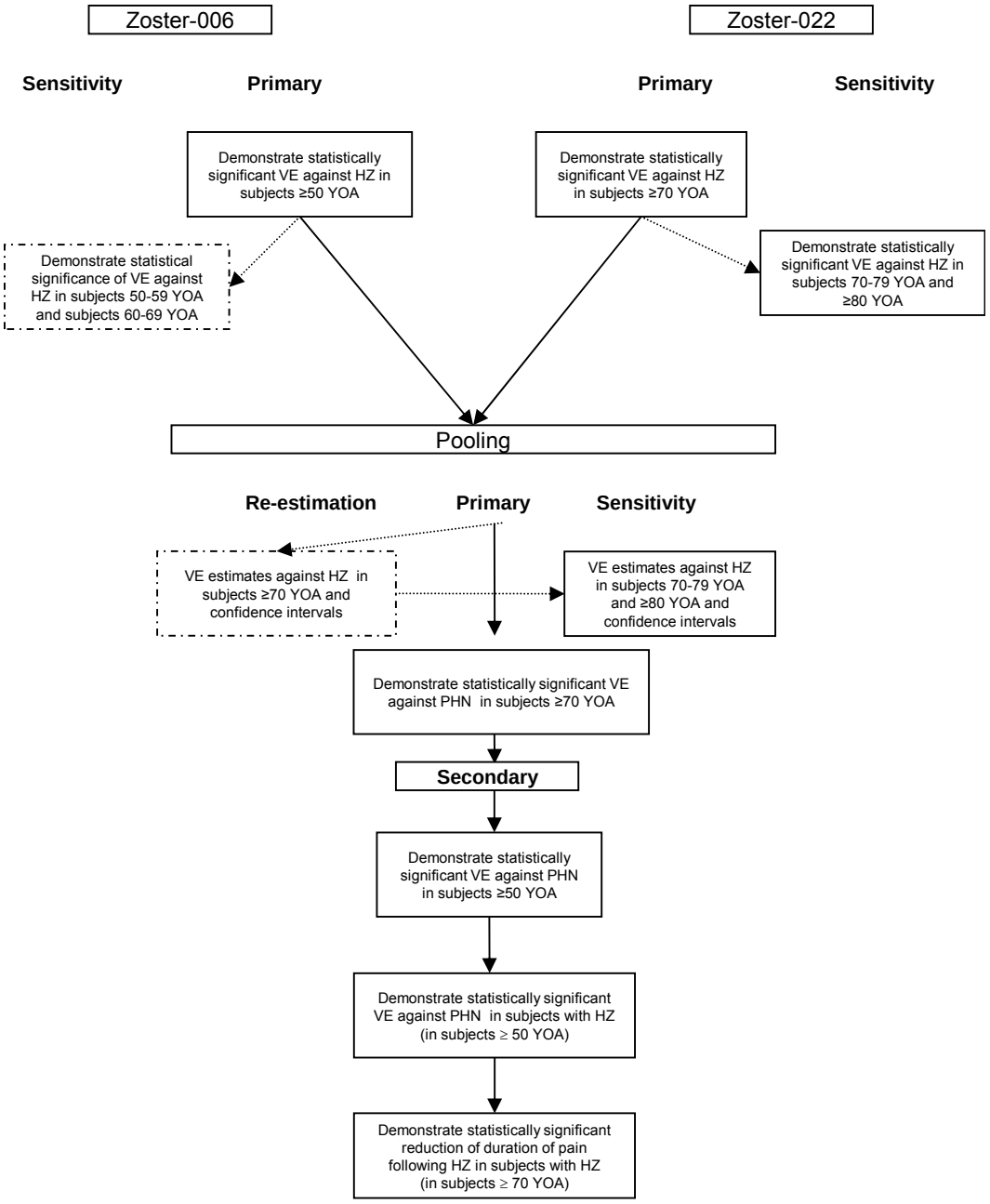
The primary objective of ZOSTER-006 and ***the*** ~~both co~~primary objective~~s~~ of ZOSTER-022 should be demonstrated prior to testing the primary objective of the pooling. ~~The second co-primary of ZOSTER-022 will be tested at 5% 2-sided following demonstration of the first co-primary, also at 5%.~~ Sensitivity analyses will be performed by age strata for each of the primary ~~or co-primary~~ objectives.

Figure 1 Gatekeeping strategy

Original figure:



Amended figure:



The primary objectives of the pooling include the re-estimation of HZ VE ***in subjects ≥ 70 YOA*** and ***estimation of*** PHN VE in subjects ≥ 70 YOA. ~~Both hypotheses are planned to be already demonstrated in ZOSTER-022 and, as a consequence, do not affect the overall type 1 error and are not considered within the main path of the gatekeeping strategy.~~ ***The HZ VE is planned to be already demonstrated in ZOSTER-022 and the pooled PHN VE will be the primary analysis of PHN; as a consequence, they do not affect the overall type 1 error and are not considered within the main path of the gatekeeping strategy.***

The first hypothesis to be tested from the pooled dataset consists in the overall PHN VE in subjects ≥ ~~50~~ ***70*** YOA. Further secondary objectives are then sequentially tested following demonstration of overall PHN VE ***in subjects ≥ 70 YOA*** .

1. ***Demonstrate statistically significant reduction in incidence of PHN (90 days or more) in subjects ≥ 50 YOA***
2. Demonstrate statistically significant reduction in incidence of PHN (90 days or more) in subjects with HZ ***(in subjects ≥ 50 YOA)***
3. Demonstrate statistically significant reduction of duration of severe 'worst' pain following HZ in subjects with HZ ***(in subjects ≥ 70 YOA)***.

Section 10.4.5.1 Primary objective

The final ***HZ efficacy*** analysis of the ZOSTER-006 study is planned after the accumulation of at least 196 confirmed HZ cases across all age strata (primary condition) in the primary cohort for efficacy.

Table 20 Expected ~~median~~ number of HZ and PHN cases in ZOSTER-006

Age strata	Sample size	Median number of HZ cases		Median number of PHN cases ***(initial assumptions)***		***Expected number of PHN cases (projection based on current accrual rates)***	
		Placebo	All	Placebo	All	***Placebo***	***All***
50-59 YOA	7520	48	57	3	3	***4***	***5***
60-69 YOA	4700	48	62	4	6	***5***	***7***
70-79 YOA	2820	40	56	6	8	***4***	***5***
≥ 80 YOA	940	13	22	4	5	***1***	***2***
All	15980	149	196	17	23	***14***	***19***

Median number of cases calculated based on 1000 trial simulations.

The final ***HZ efficacy*** analysis of the ZOSTER-022 study is planned after the accumulation ~~at least 65 PHN cases (expected median are approximately 40 PHN cases in 70-79 YOA and approximately 26 PHN cases in ≥ 80 YOA strata) are accrued from study ZOSTER-022 (primary condition for triggering analysis), and~~ ***of*** at least 278 confirmed HZ cases (expected median number of cases is 310 HZ cases) across both 70-79 YOA (expected median of 222 HZ cases) and ≥ 80 YOA (expected median of 87 HZ cases) strata. All ~~PHN or~~ HZ cases should be accrued in the primary cohort for efficacy.

~~This number of PHN cases would provide ~97% to demonstrate statistically significant PHN VE in all randomized subjects, in addition to the HZ objective above~~.

The end of study analyses of the ZOSTER-006 and the ZOSTER-022 studies are planned after the accumulation at least 35 PHN cases in subjects ≥ 70 YOA in the pooled ZOSTER-006 and ZOSTER-022. All PHN cases should be accrued in the

primary cohort for efficacy. Other conditions for triggering the analyses are described in Section 10.4.5.6. This number of PHN cases would provide ~90% power to demonstrate PHN VE with Lower Limit (LL) above 0%.

Table 21 Expected ~~median~~ number of HZ and PHN cases in ZOSTER-022

Age strata	Sample size	Median number of HZ cases		Median number of PHN cases *(initial assumptions)*		*Expected number of PHN cases (projection based on current accrual rates)*	
		Placebo	All	Placebo	All	***Placebo***	***All***
70-79 YOA	10884	157	222	32	40	***15***	***20***
≥ 80 YOA	3628	54	87	17	26	***5***	***8***
All	14512	210	310	49	65	***20***	***28***

Median number of cases calculated based on 1000 trial simulations.

It is estimated however that the ~~median~~ total number of PHN cases in ≥ 50 YOA subjects is approximately ~~88~~***47***, among which at least ~~79~~ ***35*** PHN cases would be accrued in the ≥ 70 YOA age strata. A total of at least ~~88~~***35*** PHN cases provide ~~93~~***90***% power to demonstrate ***in subjects ≥ 70 YOA*** an overall PHN VE of at least ~~25~~***0***%.

Table 22 Expected ~~median~~ number of HZ and PHN cases in pooled ZOSTER-006 and ZOSTER-022

Age strata	Sample size	Median number of HZ cases		Median number of PHN cases *(initial assumptions)*		*Expected number of PHN cases (projection based on current accrual rates)*	
		Placebo	All	Placebo	All	***Placebo***	***All***
50-59 YOA	7520	48	57	2	3	***4***	***5***
60-69 YOA	4700	48	61	4	6	***5***	***7***
70-79 YOA	13704	196	278	32	48	***19***	***25***
≥ 80 YOA	4568	57	110	17	31	***6***	***10***
All	30492	360	506	57	88	***34***	***47***

Median number of cases calculated based on 1000 trial simulations.

Section 10.4.5.2 Secondary objectives

The sample size of the pooled studies ZOSTER-006 and ZOSTER-022 provide ~~22~~***10***% chance to demonstrate statistically significant PHN VE (LL above 0%) in those subjects presenting with an HZ episode.

Section 10.4.5.3 Futility analyses and sample size re-assessment

The study may involve one (or more) unblinded futility analyses performed by the IDMC. One futility analysis is planned after at least 25% of the total number of HZ cases anticipated at final ***HZ efficacy*** analysis are observed in Zoster-006 (see Table 20), and when at least 20% of the total number of HZ cases anticipated at final ***HZ efficacy*** analysis within each age stratum (50-59 YOA, 60-69 YOA and 70+ YOA) are observed (see Table 20).

Essentially, no increase in the type 1 error of the final ***HZ efficacy*** analysis is incurred as no decision of early termination for efficacy will be made by GSK at any of those analyses.

A more reasonable prediction for the power at the final ***HZ efficacy*** analysis that will be implemented is the expected conditional power or Bayesian predictive power, following integration of the conditional power on the posterior distribution of the VE in each age strata and accounting for the proportion density of each stratum in the total number of HZ cases at the final ***HZ efficacy*** analysis.

Table 23 Observed HZ VE at ZOSTER-006 Interim to trigger futility stopping and conditional power at the final *HZ efficacy* analysis calculated under alternative hypothesis and current observed VE

c: Conditional power at the final HZ efficacy analysis calculated under the sample size (alternative) assumptions
d: Conditional power at the final HZ efficacy analysis calculated under the observed HZ VE at the interim

A more reasonable prediction for the power at the final ***HZ efficacy*** analysis that will be implemented is the expected conditional power or Bayesian predictive power, following integration of the conditional power on the posterior distribution of the VE in each age strata and accounting for the proportion density of each stratum in the total number of HZ cases at the final ***HZ efficacy*** analysis.

Table 24 Observed HZ VE at ZOSTER-022 Interim to trigger futility stopping and conditional power at the final *HZ efficacy* analysis calculated under alternative hypothesis and current observed VE

c.Conditional power at the final ***HZ efficacy*** analysis calculated under the sample size (alternative) assumptions
d.Conditional power at the final ***HZ efficacy*** analysis calculated under the observed HZ VE at the interim

Section 10.4.5.6.4 Number of subjects in the Immunogenicity subset

Table 30 Provisional number of subjects in the Immunogenicity subset in study ZOSTER-006

Age cohort	50-59 YOA		60-69 YOA		≥ 70 YOA		All		
Treatment group	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	***Total***
CMI countries[1]	26	26	26	26	26	26	78	78	***156***
Non-CMI countries[2]	23	23	23	23	23	23	69	69	***138***
All countries [1+2] (Total of 18 countries)							***1269***	***1269***	***2538***

Section 10.4.5.7.2 Number of subjects in the CMI subset

Table 32 Provisional number of subjects in the CMI subset in study ZOSTER-006

Age cohort	50-59 YOA		60-69 YOA		≥ 70 YOA		All		
Treatment group	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	***Total***
Each participating country	26	26	26	26	26	26	78	78	***156***
All countries (Total of 3 countries)							***234***	***234***	***468***

Section 10.4.6 Conditions for triggering analyses

The conditions described below are minimum requirements prior to ***the specified analyses*** ~~unblinding~~.

The following conditions are planned prior to final HZ ***efficacy*** analyses of study ZOSTER-006. The number of HZ and PHN cases mentioned refers to the cases in the primary cohort for efficacy.

~~4. A total of at least 88 PHN cases when pooled with ZOSTER-022 PHN cases accrued.~~

The ZOSTER-006 study will continue until an adequate number of HZ cases will be accrued in ZOSTER-022 and an adequate number of PHN cases will be accrued in both ZOSTER-006 and ZOSTER-022.

The end of study analysis of ZOSTER-006 will occur when the following conditions are met:

1. ***All previous conditions are met for final HZ efficacy analysis in study ZOSTER-022;***
2. ***A total of at least 35 PHN cases in subjects ≥ 70 YOA when pooled with ZOSTER-022 PHN cases are accrued.***

The end of study analysis cannot be performed before the final HZ efficacy analysis.

The following conditions are planned prior to final HZ ***efficacy*** analyses of study ZOSTER-022. The number of HZ and PHN cases mentioned refers to the cases in the primary cohort for efficacy.

~~1. At least 65 PHN cases over both 70-79 and ≥ 80 YOA strata;~~

~~2. A total of at least 88 PHN cases when pooled with ZOSTER-006 PHN cases accrued;~~

The end of study analysis of ZOSTER-022 will occur when the following condition is met:

1. ***A total of at least 35 PHN cases in subjects≥ 70 YOA when pooled with ZOSTER-006 PHN cases are accrued.***

The end of study analysis cannot be performed before the final HZ efficacy analysis.

In study ZOSTER-022, depending on accrual of HZ and PHN cases, final HZ efficacy analysis may occur at the same time as the end of study analysis.

Section 10.4.7 Control of type I error for the two-steps analyses

Although, the analyses of ZOSTER-006 will be performed in two steps. Each objective will be assessed only once. Therefore no adjustment of type I error is needed.

Section 10.4.8 Maintaining the blind

It is planned to maintain the whole team (Central, Local, Investigators) and subjects blinded up to end of study.

A firewall team will be set up in order to allow the planned analyses to be performed and results reported to the relevant authorities while the study blind is maintained to the whole team and subjects. All details of this approach can be found in the firewall charter.

Section 10.4.9 List of objectives assessed at each analysis step

Table 33 ***provides, for studies ZOSTER-006 and ZOSTER-022, an overview of the analyses which will be performed at final HZ efficacy analysis (step 1) and end of study analysis (step 2), respectively.***

For ZOSTER-006, step 1 will include analyses of the following objectives:

- ***all HZ VE objectives;***
- ***all reactogenicity/safety and immunogenicity objectives.***

At step 2 all objectives of study ZOSTER-006 will be analyzed. Objectives already analyzed at step 1 will be re-analyzed (confirmatory descriptive in case of inferential analysis at step 1 or descriptive analysis otherwise).

At step 2, overall PHN VE in subjects ≥ 70 YOA, and other pre-specified endpoints will be analyzed in the pooled analyses of studies ZOSTER-006 and ZOSTER-022.

New table:

Table 33 Overview of analyses performed at each analysis step (ZOSTER-006, ZOSTER-022, pooled analysis of ZOSTER-006 and ZOSTER-022)

			First step* Final HZ efficacy analysis		Second step** End of study analysis	
			Analysis of objective Yes (Y) No (N) Not applicable (NA)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive	Analysis of objective Yes (Y) No (N)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive
ZOSTER-006						
Primary						
	Efficacy					
		To evaluate VE in the prevention of HZ compared to placebo in adults ≥ 50 YOA, as measured by the reduction in HZ risk.	Y	I	Y	CD
Secondary						
	Efficacy					
		To evaluate VE in the prevention of HZ compared to placebo in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, as measured by the reduction in HZ risk;	Y	I	Y	CD
		To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;	N	-	Y	D
		To evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;	N	-	Y	I

			First step* Final HZ efficacy analysis		Second step** End of study analysis	
			Analysis of objective Yes (Y) No (N) Not applicable (NA)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive	Analysis of objective Yes (Y) No (N)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive
		To evaluate VE in the reduction of overall and HZ-related mortality and hospitalizations compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;	N	-	Y	I
		To evaluate VE in the reduction in incidence of HZ-associated complications compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;	N	-	Y	I
		To evaluate VE in the reduction in use of pain medications compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;	N	-	Y	I
	Safety					
		To evaluate vaccine safety and reactogenicity.	Y	D	Y	D
Exploratory						
	Efficacy					
		To evaluate VE in reducing the severity of acute HZ-associated pain compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;	N	-	Y	I
		To evaluate VE in improving Quality of Life (QoL) compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;	N	-	Y	I

			First step* Final HZ efficacy analysis		Second step** End of study analysis	
			Analysis of objective Yes (Y) No (N) Not applicable (NA)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive	Analysis of objective Yes (Y) No (N)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive
		To evaluate VE in the mitigation of Burden-Of-Illness (BOI) caused by HZ compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA.	N	-	Y	I
	Immunogenicity					
		To evaluate vaccine induced cell mediated and humoral immune responses and the persistence of each type of response after two injections of study vaccine in subjects ≥ 50 YOA, and by age strata;	Y	I, D	Y	CD, D
		To evaluate anti-varicella-zoster virus (VZV) neutralizing antibody (Ab) titres in a subset of subjects at Month 0 (pre-vaccination), and at Months 3, 14, 26 and 38, in subjects ≥ 50 YOA, and by age strata.	Y	I, D	Y	CD, D
ZOSTER-022***						
Primary						
	Efficacy					
		To evaluate VE in the prevention of HZ compared to placebo in adults ≥ 70 YOA, as measured by the reduction in HZ risk.	Y	I	Y	CD
Secondary						
	Efficacy					
		To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 70 YOA;	N	-	Y	D
		To evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥ 70 YOA, with confirmed HZ	N	-	Y	I

			First step* Final HZ efficacy analysis		Second step** End of study analysis	
			Analysis of objective Yes (Y) No (N) Not applicable (NA)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive	Analysis of objective Yes (Y) No (N)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive
		To evaluate VE in the reduction of overall and HZ-related mortality and hospitalizations compared to placebo in subjects ≥ 70 YOA	N	-	Y	I
		To evaluate VE in the reduction in incidence of HZ-associated complications compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;	N	-	Y	I
		To evaluate VE in the reduction in use of pain medications compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;	N	-	Y	I
	Safety					
		To evaluate vaccine safety and reactogenicity.	Y	D	Y	D
Exploratory						
	Efficacy					
		To evaluate VE in reducing the severity of acute HZ-associated pain compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;	N	-	Y	I
		To evaluate VE in improving Quality of Life (QoL) compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;	N	-	Y	I
		To evaluate VE in the mitigation of BOI caused by HZ compared to placebo in subjects ≥ 70 YOA;	N	-	Y	I
	Immunogenicity					
		To evaluate vaccine induced humoral immune responses and the persistence of each type of response after two injections of study vaccine in subjects ≥ 70 YOA and by age strata;	Y	I, D	Y	CD, D
		To evaluate anti-varicella-zoster virus (VZV) neutralizing antibody (Ab) titres in a subset of subjects at Month 0 (pre-vaccination), and at Months 3, 14, 26 and 38, in subjects ≥ 70 YOA and by age strata.	Y	I, D	Y	CD, D

			First step* Final HZ efficacy analysis		Second step** End of study analysis	
			Analysis of objective Yes (Y) No (N) Not applicable (NA)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive	Analysis of objective Yes (Y) No (N)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive
Pooled analysis of ZOSTER-006 and ZOSTER-022						
Co-primary						
	Efficacy					
		To evaluate VE in the prevention of PHN compared to placebo in subjects ≥ 70 YOA across both phase III studies.	NA		Y	I
		To consolidate VE estimation in the prevention of HZ compared to placebo in subjects ≥ 70 YOA across both phase III studies;	NA		Y	CD
Secondary						
	Efficacy					
		To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 50 YOA;	NA		Y	I
		To evaluate VE in the prevention of PHN compared to placebo in subjects ≥ 50 YOA with confirmed HZ;	NA		Y	I
		To evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;	NA		Y	CD
	Safety					
		To evaluate vaccine safety and reactogenicity in subjects ≥ 70 YOA.	NA		Y	D

			First step* Final HZ efficacy analysis		Second step** End of study analysis	
			Analysis of objective Yes (Y) No (N) Not applicable (NA)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive	Analysis of objective Yes (Y) No (N)	Type of analysis I: inferential D: descriptive CD; confirmatory descriptive
Exploratory						
	Efficacy					
		To evaluate VE in reducing the severity of acute HZ-associated pain compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;	NA		Y	CD
		To evaluate VE in improving QoL compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;	NA		Y	CD
	Immunogenicity					
		To evaluate vaccine induced humoral immune responses and the persistence of each type of response after two injections of study vaccine in subjects ≥ 50 YOA and by age cohort;	NA		Y	CD
		To evaluate anti-varicella-zoster virus (VZV) neutralizing antibody (Ab) titres in a subset of subjects at Month 0 (pre-vaccination), and at Months 3, 14, 26 and 38, in subjects ≥ 50 YOA and by age strata;	NA		Y	CD
		To assess correlation of the humoral immune responses at Month 3 with protection against HZ.	NA		Y	D

* It is predicted that the first step for Zoster-006 will occur about one year before the first step for Zoster-022.
** The second analysis step for both studies will occur at the same time.
*** Depending on accrual of HZ and PHN cases, in study ZOSTER-022, step 1 may occur at the same time as step 2.

Section 10.5.3 According To Protocol cohort for analysis of efficacy

The list of criteria used to exclude subjects from ATP will be defined prospectively in the ~~Reporting and~~***Statistical*** Analysis Plan (~~R~~***S***AP) prior to database freeze.

Section 10.6.4 Cellular-mediated immune response

- ***For the inferential analysis, T****~~t~~*he frequency of ***CD4 [2+] T cells, i.e.,*** CD4 T cells producing at least 2 activation markers ***among*** ~~(cytokines:~~ IFN-γ, IL-2, TNF-α and/or CD40L, ~~termed "all doubles" or CD4[2+])~~ upon in vitro stimulation with the antigen (induction condition) is calculated by adding an offset of 0.5 to the number of activated CD4***[2+]*** T cells (numerator) divided by the total number of CD4 T cells involved (denominator). A similar calculation will be made for the frequency of CD4 ***[2+]*** T cells ~~producing at least 2 cytokines ("all doubles", CD4[2+])~~ upon in vitro stimulation in medium only (background condition).

Original formula:

$$Freq_{Induction}^{CD4\ 2+} = \frac{n_{Induction}^{2+} + 0.5}{N_{Induction}^{CD4}} \qquad Log_e\left(Freq_{Induction}^{CD4\ 2+}\right) = Log_e\left(\frac{n_{Induction}^{2+} + 0.5}{N_{Induction}^{CD4}}\right)$$

$$Freq_{Background}^{CD4\ 2+} = \frac{n_{Background}^{2+} + 0.5}{N_{Background}^{CD4}} \qquad Log_e\left(Freq_{Background}^{CD4\ 2+}\right) = Log_e\left(\frac{n_{Background}^{2+} + 0.5}{N_{Background}^{CD4}}\right)$$

$n_{Induction}^{2+}$ = Number of antigen - specific CD4 T - cells expressing at least 2 cytokines

$n_{Background}^{2+}$ = Number of CD4 T - cells expressing at least 2 cytokines in the medium only

N^{CD4} = Total number of CD4 involved in the assay (induction or background)

Amended formula:

$$Freq_{Induction}^{CD4[2+]} = \frac{n_{Induction}^{2+} + 0.5}{N_{Induction}^{CD4}} \qquad \log(Freq_{Induction}^{CD4[2+]}) = \log(\frac{n_{Induction}^{2+} + 0.5}{N_{Induction}^{CD4}})$$

$$Freq_{Bachground}^{CD4[2+]} = \frac{n_{Background}^{2+} + 0.5}{N_{Bachground}^{CD4}} \qquad \log(Freq_{Background}^{CD4[2+]}) = \log(\frac{n_{Background}^{2+} + 0.5}{N_{Background}^{CD4}})$$

$n_{Induction}^{2+}$ = number of CD4 T cells secreting at least 2 activation markers after induction with the antigen

$n_{Background}^{2+}$ = number of CD4 T cells secreting at least 2 activation markers in medium condition

N^{CD4} = Total number of CD4 T cells involved in the assay (induction or background)

- ***For the descriptive analyses, the frequency of CD4[2+] T cells upon in vitro stimulation with the antigen (induction condition) is calculated by dividing the number of activated CD4[2+] Tcells (numerator) over the total number of CD4 T cells involved (denominator). The same calculation will be performed for the***

frequency computation for any kinds of cells and for each individual activation marker as appropriate.

New formula

$$Freq_{Induction}^{CD4[2+]} = \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}}$$

$n_{Induction}^{2+}$ = number of CD4 T cells secreting at least 2 activation markers after induction with the antigen

N^{CD4} = Total number of CD4 T cells involved in the assay (induction)

- The frequency of **antigen-specific** (gE or VZV) CD4***[2+]*** T cells for each individual subject is calculated as the difference between the frequency of CD4***[2+]*** T cells ~~producing at least 2 cytokines among IFN-γ, IL-2, TNF-α and/or CD40L, termed "all doubles" or CD4[2+]~~, upon in vitro stimulation with the antigen (induction condition)**,** minus the frequency of CD4***[2+]*** T cells**,** ~~producing at least 2 cytokines ("all doubles", CD4[2+])~~ upon in vitro stimulation in medium only (background condition). ~~When the log-transformation is applied to that variable prior to analysis, differences less or equal to zero (0) are imputed to 1 gE or VZV-specific cytokine secreting CD4 T cell per 10^6 CD4 T cells.~~ ***The differences less or equal to one (1) are imputed to 1 antigen-specific CD4[2+] T cell per 10^6 CD4 T cells. The same calculation will be performed for the frequency computation for any kinds of cells and for each individual activation marker as appropriate.***

Original formula:

$$Freq_{Specific}^{CD4\,2+} = \frac{n_{Induction}^{CD4\,2+} + 0.5}{N_{Induction}^{CD4}} - \frac{n_{Background}^{CD4\,2+} + 0.5}{N_{Background}^{CD4}}$$

$$Log_e\left(Freq_{Specific}^{CD4\,2+}\right) = Log_e\left(\frac{n_{Induction}^{CD4\,2+} + 0.5}{N_{Induction}^{CD4}} - \frac{n_{Background}^{CD4\,2+} + 0.5}{N_{Background}^{CD4}}\right) \quad if \ \frac{n_{Induction}^{CD4\,2+}}{N_{Induction}^{CD4}} > \frac{n_{Background}^{CD4\,2+}}{N_{Background}^{CD4}}$$

$$Log_e\left(Freq_{Specific}^{CD4\,2+}\right) = Log_e\left(\frac{1}{10^6\,cells}\right) \quad if \ \frac{n_{Induction}^{CD4\,2+}}{N_{Induction}^{CD4}} \le \frac{n_{Background}^{CD4\,2+}}{N_{Background}^{CD4}}$$

Amended formula:

$$Freq_{Specific}^{CD4[2+]} = \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} - \frac{n_{Background}^{2+}}{N_{Background}^{CD4}} \quad if \ \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} > 1 + \frac{n_{Background}^{2+}}{N_{Background}^{CD4}}$$

$$Freq_{Specific}^{CD4[2+]} = 1 \quad if \ \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} \le 1 + \frac{n_{Background}^{2+}}{N_{Background}^{CD4}}$$

$n_{Induction}^{2+}$ = number of CD4 T cells secreting at least 2 activation markers after induction with the antigen

$n_{Background}^{2+}$ = number of CD4 T cells secreting at least 2 activation markers in medium condition

N^{CD4} = Total number of CD4 T cells involved in the assay (induction or background)

- The Geometric Mean (GM) frequency calculations are performed by taking the anti-log of the mean of the log frequency transformations;

- ~~The CMI vaccine response against gE is defined for all subjects as a 1.5 to 2-fold increase (see RAP for final threshold) in background-adjusted frequency of CD4 following induction with gE measured at endpoint as compared to pre-vaccination.~~
- ***The CMI vaccine response to gE will be based on the gE-specific data as computed above. The cut-off for the assay (320 positive events/10^6 CD4 T cells) will be used for vaccine response assessment. The vaccine response is defined as the percentage of subjects who have:***
  - ***at least a 2-fold increase as compared to the cut-off, for subjects with pre-vaccination T cell frequencies below the cut-off.***
  - ***at least a 2-fold increase as compared to pre-vaccination T cell frequencies, for subjects with pre-vaccination T cell frequencies above the cut-off.***
- ~~The CMI vaccine response against VZV is defined for all subjects as a 1.5 to 2-fold increase (see RAP for final threshold) in background-adjusted frequency of CD4 following induction with VZV measured at endpoint as compared to pre-vaccination.~~
- ***The CMI vaccine response to VZV will be based on the VZV-specific data as computed above. The cut-off for the assay (320 positive events/10^6 CD4 T cells) will be used for vaccine response assessment. The vaccine response is defined as the percentage of subjects who have:***
  - ***at least a 2-fold increase as compared to the cut-off, for subjects with pre-vaccination T cell frequencies below the cut-off.***
  - ***at least a 2-fold increase as compared to pre-vaccination T cell frequencies, for subjects with pre-vaccination T cell frequencies above the cut-off.***
- A CMI responder is a subject with a CMI response greater than or equal to the cut-off value.

Section 10.7.1 Prior to Final *HZ efficacy* Analysis

Section 10.7.2 Statistical considerations for the interim futility analyses

If a futility analysis occurs and leads to a recommendation by the IDMC to filing prior to study end for ethical reasons, it is mandated that, prior to final ***HZ efficacy*** analysis, the significance level for all primary objectives but also key secondary objectives is set to 0.0001 for both HZ and overall PHN, considering the alternative hypotheses of true vaccine efficacies above 40%. As a consequence, the significance level of the final ***HZ efficacy*** analysis will be adjusted to 4.9998% 2-sided. Practically speaking, however, that adjustment makes no essential difference as using a significance level of 5% 2-sided that will be referred to in other part of this document.

Section 10.7.3 ~~Final~~ *End of study* analysis

When the conditions for triggering the ~~final~~ ***end of*** analysis of efficacy have been reached, the ~~final~~ ***end of study*** analysis cut-off date will be defined. Any HZ episode occurring prior to the ~~final~~ ***end of study*** analysis cut-off date will be followed, as described in the ~~R~~***S***AP, until a 4-week pain-free period is documented and the HZ rash

resolves OR until the cut-off date for ~~final~~ ***end of study*** analysis. For all subjects with ongoing HZ-associated pain at the time of cut-off date for ~~final~~ ***end of study*** analysis, questionnaire data will be collected until a 4-week pain-free period is documented OR until at least Day HZ-90 in order to document potential PHN episodes.

~~Prior to unblinding, the third party responsible for generating immunogenicity data will communicate the results to the SDAC for review and consistency checks with the remaining database. SDAC will make sure than any feedback to that third party does not unblind the laboratory. Data issues on immunogenicity identified by the SDAC and that cannot be resolved beforehand unless unblinding a treatment assignment blind party, will be reviewed after efficacy and safety database lock.~~

Following achievement of criteria triggering analyses, final data collection and data cleaning, the write access to the clinical database will be removed and all eCRF data will become available for ~~final~~ ***end of study*** analysis. The merging of immunogenicity data to the eCRF data will occur after that database lock.

~~A first report will document efficacy and safety results and provide immunogenicity results using descriptive methodology. Analysis of correlate of protection may require extensive exploratory analyses and may be available as an annex report after completion of the primary report. Persistency data may be also provided in annex reports~~.

Section 10.7.4 Study reports

Depending on the further evolution of the case accrual rate, the generated data may be presented in one or more study reports per study (ZOSTER-006 and ZOSTER-022).

- ***The first study report for each study will contain assessment of the HZ VE objectives (ZOSTER-006) or the HZ VE objective (ZOSTER-022) and of safety, reactogenicity and immunogenicity objectives.***
- ***A final study report for each study will contain the assessment of remaining objectives not assessed at the first step, and in addition, but not limited to, the confirmatory descriptive re-analysis of the previously assessed objectives. The final study report for each study will also contain the results presented in the first report (to provide a comprehensive all in one report). Assessment of the objectives of the pooled analyses of both studies will be included in the final ZOSTER-022 study report. Analysis of correlate of protection may require extensive exploratory analyses and therefore may be available as an annex report after completion of this final ZOSTER-022 study report.***

Section 10.8.2 Analysis of efficacy

Additional tables will present the overall VE by region and overall VE by time (e.g., using 1-year interval). The methodology will be described in the ~~R~~***S***AP.

Section 10.8.2.3 Reduction in Burden-of-Illness

That analysis is exploratory and will be described in the ~~R~~***S***AP.

Section 10.8.2.4 Reduction in HZ severity score

Additional implementation details will be provided in the ~~R~~***S***AP.

The statistical methodology for the analysis of HZ severity will be described in the ~~R~~***S***AP and is similar to the methodology described previously for BOI assessment in [Chang, 1994].

Section 10.8.2.5 Reduction in incidence of HZ associated complications

The statistical methodology will be further described in the ~~R~~***S***AP.

Section 10.8.2.6 Reduction of duration of severe 'worst' pain in subjects with an HZ episode

Both methodologies will be further detailed in the ~~R~~***S***AP.

Section 10.8.2.7 Reduction in PHN incidence in subjects with an HZ episode

The statistical methodology will be further described in the ~~R~~***S***AP.

Section 10.8.3.2 Humoral immune response

~~The analysis for immunogenicity will be performed on the pooled data of both ZOSTER-006 and ZOSTER-022 and the results will be provided in an annex report.~~

The analysis for immunogenicity will be performed at final HZ efficacy analysis. A confirmatory descriptive analysis for immunogenicity will be performed at end of study analysis.

An additional humoral immunogenicity analysis will be performed on the pooled data of both ZOSTER-006 and ZOSTER-022 and the results will be provided in the final study report for ZOSTER-022.

Section 10.8.3.4 Correlate of protection

A specific ~~R~~***S***AP will describe the methodologies to be used for that purpose.

The analysis for correlate of protection will be performed on the pooled data of both ZOSTER-006 and ZOSTER-022 and ***may be available as*** ~~provided in~~ an annex report.

Section 10.8.4.1 SF-36 health survey

Details on descriptive statistics and statistical analysis of the effect of the vaccine on the difference over pre-vaccination scores will be provided in the ~~R~~***S***AP.

Section 10.8.4.2 EQ-5D questionnaire

Details on contingency tables for each of the 5-dimension and descriptive statistics for weighted health state index and VAS will be provided in the ~~R~~***S***AP.

Section 10.8.5.2 Additional exploratory safety comparisons

Other exploratory safety analyses may be described in the ~~R~~***S***AP.

Section 12.3 Requirements for Japan

Study Period

June, 2010 ~ ~~August, 2014~~ ***December, 2015 (estimation at the time of protocol amendment 4)***

Section 13 References

Carter WP, Germann CA, Baumann MR. Ophthalmic diagnoses in the ED: herpes zoster ophthamicus. *Am. J. Ophthalmol.* 2008; ***26(5):*** 612– 617.

~~Drummond MF. *Ann. Med.* 2001;33;344–349.~~

~~Walters S, Brazier J. *Quality of Life Research.* 2005 14:1523–1532.~~

Appendix A LABORATORY ASSAYS

Specific Ab (anti-VZV and anti-gE) measurements

Anti-gE ELISA:

The assay cut-off is ~~18~~ ***97*** mIU/mL.

Protocol Amendment 4 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	110390 (ZOSTER-006)
IND number	BB-IND 13857
EudraCT number	2008-000367-42
Date of amendment	Amendment 4 Final: 18 April 2014
Detailed Title	A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' gE/AS01$_B$ vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older.
Sponsor signatory (Amended 18 April 2014)	[redacted] ***Project Level Clinical Research & Development Lead, Director, Global Clinical Development, Vaccines***
Signature	[redacted]
Date	4-25-14

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Statistical Analysis Plan

Study alias & e-track number(s): ZOSTER-006 (110390)

Detailed Title:	A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' gE/AS01$_B$ vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older.
SAP version	1.0
SAP date	05-MAY-2014
Scope:	All Safety and Immuno data pertaining to the above study.
Co-ordinating author:	[redacted]
Other author(s):	[redacted]
Adhoc reviewers:	[redacted]
Approved by:	
Clinical Research and Development Lead	[redacted]
Project CRDL	[redacted]
Project Statistician	[redacted]
Lead Statistician	[redacted]

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LIST OF TABLES

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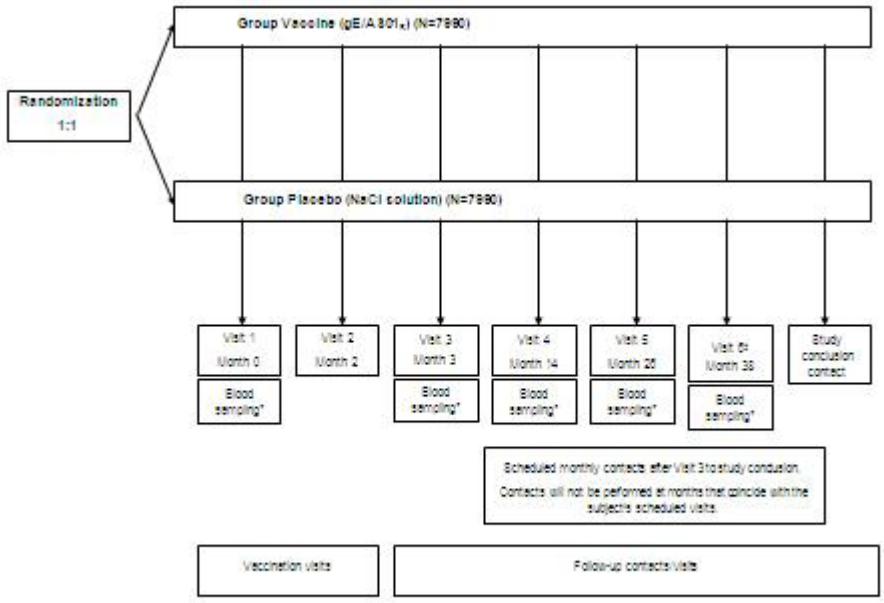
The analysis plan is divided into 2 parts: the first part (called SAP) detailing the analyses to be performed (current document) and a second part, annexes (called TFL) describing the flow and format of tables, figures and listings to be annexed to the SR. two annexes will be prepared, one that describes the TFLs for the step 1 analysis of immunogenicity and safety and a second TFLs for the end of study analysis of immunogenicity and safety. Two separate SAPs and TFLs documents will describe efficacy analysis and Quality of life analysis.

1. DOCUMENT HISTORY

Date	Version	Description	Protocol Version
05-May-2014	First Version	Final analysis for demongraphy, Safety and immunogenicity	Amendment 4 18 Apr 2014

2. STUDY DESIGN



* Blood samples will be collected from all subjects at Visit 1 and Visit 3, and from subsets of subjects additionally at the other visits to assess immune responses.

Note: In case of suspected HZ, the subject will have additional visits and contacts for follow-up of HZ.

The following group names will be used for the statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote
1	Placebo	Placebo
2	HZ/su	Herpes Zoster subunit vaccine

The following sub-group names will be used for the statistical analyses:

Analysis by age group

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote	Pooled Groups 1 label in tables	Pooled Groups 2 label in tables
1	50-59Y	50-59 years old subjects	50-59Y	50-59Y
2	60-69Y	60-69 years old subjects	60-69Y	≥ 60Y
3	70-79Y	70-79 years old subjects	≥ 70Y	≥ 60Y
4	≥ 80Y	≥ 80 years old subjects	≥ 70Y	≥ 60Y

Analysis by region

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote	Pooled Groups label in tables
1	CZ	Czech Republic	Europe
2	EN	Estonia	Europe
3	FI	Finland	Europe
4	FR	France	Europe
5	GE	Germany	Europe
6	IT	Italy	Europe
7	SP	Spain	Europe
8	SW	Sweden	Europe
9	UK	United Kingdom	Europe
10	AS	Australia	Australasia
11	HK	Hong Kong	Australasia
12	JA	Japan	Australasia
13	SK	South Korea	Australasia
14	TW	Taiwan	Australasia
15	BR	Brazil	Latin America
16	MX	Mexico	Latin America
17	US	United States	North America
18	CA	Canada	North America

3. OBJECTIVES

As per protocol.

4. ENDPOINTS

As per protocol.

5. STUDY POPULATION

As per protocol.

5.1. Total Vaccinated cohort

The Total Vaccinated cohort (TVc) will include all vaccinated subjects with respect to the vaccine actually administered.

The TVc for analysis of efficacy will include vaccinated subjects for whom data related to efficacy endpoints are available.

The TVc for analysis of immunogenicity will include vaccinated subjects in the immunogenicity sub-cohort for whom immunogenicity data are available.

The TVc for analysis of safety will include all subjects with at least one vaccine administration documented.

The TVc diary card for analysis of reactogenicity will include all TVC subjects belonging to the diary card subset.

5.2. Modified Total Vaccinated cohort

The mTVc will be the primary population for efficacy analysis, which excludes subjects in the TVc for efficacy analysis who were not administered with the second vaccination or who develop a confirmed case of HZ prior to 1 month after the second vaccination or who received vaccine doses /or replacement not according to their randomized group .

5.3. According To Protocol cohort for analysis of efficacy

The According To Protocol cohort (ATPc) for analysis of efficacy will include all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom efficacy data concerning endpoint measures are available, i.e., excluding all subjects who developed a confirmed case of HZ prior to 1 month after the second vaccination. The list of criteria used to exclude subjects from ATP cohort are:

- Study vaccine dose not administered AT ALL but subject number allocated
- Administration of concomitant vaccine(s) forbidden in the protocol
- Randomisation failure (subject not randomized in the correct group)
- Randomisation code broken at the investigator site or at GSK Safety department
- Side, site or route of study vaccine administration wrong or unknown

  Administration not according to protocol for reason specified by the investigator, other than side, site and route

  Administered study vaccine reported as being the correct one but is not compatible with the vaccine regimen associated to the treatment number
- Wrong replacement or study vaccine administered
- Protocol violation linked to the inclusion/exclusion criteria including age and excluding codes mentioned below
- Subjects not received two doses
- Subjects having an episode of HZ prior than 30 days after the dose 2

The ATPc will be the analysis set for supportive efficacy analysis, only including subjects who developed a confirmed case of HZ during the follow-up period starting from 1 month after the second vaccination (Month 3).

5.4. According To Protocol cohort for analysis of safety

The According To Protocol (ATP) cohort for analysis of safety will include all subjects:

- who have received at least one dose of study vaccine/placebo according to their random assignment;
- ~~with sufficient data to perform an analysis of safety (at least one dose with safety follow-up);~~
- for whom administration site of study vaccine/placebo is known/correct;
- who have not received other medication forbidden in the protocol;
- for whom the randomization code has not been broken.

The ATP safety diary card for analysis of reactogenicity will include all subjects in the ATP safety included in the diary card subset.

5.5. According To Protocol cohort for analysis of immunogenicity

For study ZOSTER-006, the ATPc for analysis of immunogenicity will include all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom immunogenicity results are available at Month 3 for CMI and/or humoral immunogenicity.

The list of applicable elimination codes for each cohort can be found in the study specific form FORM-BIO-CLIN-9004-05 Elim code specifications.

Cohort	Elimination codes	Eli Type
Total vaccinated cohort	900,1030	MA
Total vaccinated cohort diary card	900,1030, 5130	MA
Total vaccinated cohort Humoral	900,1030, 2500	MA
Total vaccinated cohort CMI	900,1030, 2500, 4130	MA
ATP cohort for analysis for safety	900,1030-1500	MA
ATP diary card	900,1030-1500, 5130	MA
mTVC	900,1030,1050,1070, 1500, 2500, 3500	MA
ATP cohort for analysis for immunogenicity-Humoral	900,1030-2500	MA
ATP cohort for analysis for immunogenicity-CMI	900,1030-2500 , 4130	MA
ATP cohort for analysis of efficacy	900, 1030-1070, 1500-2010, 2500,3500	MA

6. STATISTICAL METHODS

All analyses will be presented overall and by age strata. The main age strata for reporting purposes are 50-59, 60-69 and ≥ 70 YOA. Additional analysis will be presented in ≥ 60 YOA.

6.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age at first study vaccination, gender, geographic ancestry, race and ethnicity), cohort description and withdrawal status will be summarized overall and by region.

The mean age (plus range and standard deviation) of the enrolled subjects, as a whole, and per treatment group and stratified by age group will be calculated.

The distribution of subjects enrolled among the study sites will be tabulated as a whole and per vaccine group.

Frequency tables will be generated for categorical variables such as gender.

Mean, median and standard error will be provided for continuous data such as age.

6.2. Analysis of safety

The primary analysis will be based on the Total Vaccinated cohort. A second analysis based on this ATP cohort will be performed to complement the Total Vaccinated Cohort analysis.

When appropriate, tabulations will be presented overall and by time of occurrence relative to last vaccination (e.g., using windows such as Days 0-6, Days 0-29 and more than 30 days post-vaccination).

6.2.1. Within groups assessment

For each treatment group, the following results will be tabulated overall and by age strata.

The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general adverse event (solicited and unsolicited) and with any AE during the solicited follow-up period, i.e., the day of vaccination and six subsequent days after each vaccination will be tabulated with exact 95% CI after each vaccine dose and overall.

The percentage of doses followed by at least one local AE (solicited and unsolicited), by at least one general AE (solicited and unsolicited) and by any AE will be tabulated, overall vaccination course, with exact 95% CI. The same tabulation will be done for grade 3 AEs, related AEs and grade 3 related AEs.

The percentage of subjects reporting each individual solicited local and general AE during the solicited 7-day (Days 0-6) follow-up period will be tabulated with exact 95% CI.

The percentage of doses followed by each individual solicited local and general AE during the solicited 7 day (Days 0-6) follow-up period will be tabulated, overall vaccination course, with exact 95% CI.

For all solicited symptoms, the same tabulation will be performed for grade 3 solicited AEs and for solicited general AEs with relationship to vaccination.

The number and percentage of subjects with at least one local solicited AE, with at least one general solicited AEand with any solicited AE during the 7-day follow-up period with exact 95% CIs after each vaccine dose and overall by vaccination group will be provided

Duration ~~and prevalence~~ of fever will be presented, analyses will be broken down by route.

The proportion of subjects with at least one report of unsolicited AE during the 30-day (Days 0 29) follow-up period after each vaccination classified according to the MedDRA System Organ Class and Preferred Terms will be tabulated, with exact 95% CI.

The distribution of the number of unsolicited AEs per subject will be tabulated.

The same tabulation will be performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination. The proportion of AEs resulting in a medically attended visit (other than routine health maintenance visits) will also be tabulated.

Incidences of SAEs during the 30-day (Days 0 - 29) follow-up period after each vaccination, and during any time during the study classified according to the MedDRA System Organ Class and Preferred Terms will be tabulated, with exact 95% CI.

A separate tabulation will report some of the major categories of SAEs that occur with higher frequencies in elderly subjects including: cardiac, vascular, respiratory, neurological, congestive heart failure, myocardial infarction, varicella or HZ-like rash, cerebral or vascular events.

Incidences of SAEs by major categories including: cardiac, vascular, respiratory, neurological, congestive heart failure, myocardial infarction, varicella or HZ-like rash, cerebral vascular. Listing will also be provided, sorted by patients and sorted by preferred term.

Incidence of withdrawal due to AEs will be tabulated. Listing will also be provided, sorted by subjects and sorted by MedDRA Preferred Term.

The proportion of subjects with at least one report of pIMDs during the entire study period will be tabulated overall and by time window (eg 0-6 month, 6-12 month and more than 12 month). Listing will also be provided, sorted by subjects and sorted by MedDRA Preferred Term.

The proportion of subjects with concomitant medication will be tabulated, until 30 days after each vaccine dose and overall, with exact 95% CI.

Proportion and incidence rate of subjects with fatal outcome will be tabulated overall and by time window (0-~~2~~3 months, ~~2~~3-6 months, 6-12 months and more then 12 months after dose 1.

Proportion of subjects experiencing an HZ episode using pain medications by type (opioids, non-narcotics, antidepressants, miscellaneous) will be tabulated.

6.2.2. Additional exploratory safety comparisons

The standardized asymptotic 95% CI for the difference between the two groups and the associated 2-sided p-value to detect group difference will be computed for the following endpoints:

- The proportion of subjects with at least one report of unsolicited AE classified by the MedDRA presented by System Organ Class.The proportion of subjects with at least one report of unsolicited AE classified by the MedDRA presented by System Organ Class and Preferred Term.
- Incidences of SAEs classified according to the MedDRA System Organ Class and Preferred Terms.

The objective of these analyses is to identify a safety signal as defined by the Council for the International Organization of Medical Sciences (CIOMS) VI working group, i.e., a report or reports of an event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continues surveillance. It is recognized that the use of any method to identify safety signals has the potential to identify a large number of events which may or may not have a causal relationship to drug treatment due to multiplicity of endpoints. In order to put any safety signal in perspective a permutation test will be conducted to quantify the probability to observe at least one false safety signal according to the threshold p-value defining a signal. In addition, clinical significance and biological plausibility will need to be accounted before establishing causality.

In the following section, we will describe a proposed approach to help detection of SAE signal

6.2.3. AE signal method

6.2.3.1. Analysis by System Organ Class (SOC)

Three summary tables and one plot of probability of false signal will be provided:

1. The first summary table will be the complete table with SOC only with ratio of proportion between both groups and exact non adjusted p-values. The second table will be a subset of the first with only SOC of interest.
2. The plot of probability of false signal will be built on the whole data set used to produce the summary of the first table. The plot will be zoomed to have in Y-axis adjusted p-values between 0 and 0.15. An additional table of correspondence between unadjusted p-values and the adjusted p-value (i.e. probability of false signal) will be provided as annotation for the plot provided. SOC with adjusted p-value below 15% will be considered to identify SOC of interest for further review.
3. The third summary table will be a subset of the first table containing the PT associated to SOC of interest for further review. This table will be sorted by p-values (lowest to highest) within each SOC.

6.2.3.2. Analysis by SOC & PT

Two summary tables and one plot of probability of false signal will be provided:

1. The first summary table will be the complete table with SOC and PT with ratio of proportion between both groups and exact non adjusted p-values. This table will be sorted by SOC and PT.
2. The second summary table will be a subset of the first containing only SOC & PT when the adjusted p-values are below 15%. This table will be sorted by p-values (lowest to highest).
3. The plot of probability of false signal will be built on the whole data set used to produce the summary of the first table. The plot will be zoomed to have in Y-axis adjusted p-values between 0 and 0.15. An additional table of correspondence between unadjusted p-values and the adjusted p-value (i.e. probability of false signal) will be provided as annotation for the plot provided.

6.3. Analysis of immunogenicity

The primary analysis will be based on the ATP cohort for analysis of immunogenicity. If the percentage of subjects excluded from this ATPc is more than 5%, a second analysis based on the Total vaccinated cohort will be performed to complement the ATP analysis.

The analysis for immunogenicity will be performed by treatment group, by age strata and by region/country.

6.3.1. Cell-mediated immune response

CMI response will only be assessed and analyzed in the CMI component of the Immunogenicity subset as defined in Section 4.1 in the protocol.

6.3.1.1. Descriptive statistics

For CMI response, the following parameters (for gE and VZV specific CD4[2+] frequency and CD4[+2] T-cell following induction with gE and VZV) will be tabulated by treatment group, overall and by age group at Months 0, 3, 14, 26 and 38:

- descriptive statistics of the frequency of CD4 T cell secreting at least two different cytokines (IFN-γ, IL-2, TNF-α,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least IFN-γ and another cytokine (IL-2, TNF-α,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least IL-2 and another cytokine (IFN-γ, TNF-α,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least TNF-α and another cytokine (IFN-γ, IL-2,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least CD40L and another cytokine (IFN-γ, IL-2, TNF-α) to both VZV and gE antigens;
- descriptive statistics on the fold over pre-vaccination at months 3, 14, 26 and 38.
- Vaccine response rate with exact 95% CI at Months 3, 14, 26 and 38 (only in the gE-specific CD4[2+] T-cell frequency at Month 3, 14, 26 and 38)

6.3.1.2. Inferential Analyses

The inferential analysis on CMI endpoint is performed using ‘a’ Treatment comparison of the Frequency of CD4[2+]” following induction and ‘b’ Treatment comparison of the Frequency of gE-specific CD4[2+]”. Analysis described in ‘b’ involves derivations of confidence intervals using the theorem of propagation of error (or delta-method) from estimates of means and variances calculated according to the methodology described in ‘a’.

a. The Frequency of CD4[2+] following gE-induction

If the data allows, inferential analysis on the log-transformed frequency of CD4 T cells producing at least two different cytokines following induction with antigen will be performed overall and by age strata, in subjects with HZ and healthy subjects.

A simple Analysis of Covariance (ANCOVA) model will be used to analyze the post-vaccination (Month 3) log-transformed frequency of CD4 T cells secreting at least 2 cytokines following induction with gE antigen.

The fixed-effect model will include the means for all levels of the treatment effect, all levels of age strata and interactions levels. Covariates will include the log-transformed pre-vaccination frequency following induction with the antigen and the non-specific background log-transformed frequency. Least-squares means and 95% CI are back-transformed to provide geometric means and ratios.

Sensitivity analyses will include additional effects for regions and appropriate interactions in the model in order to provide estimations and 95% CI by region. The same ANCOVA model as described above will be used for the sensitivity analyses. The fixed-effect model will include the means for all levels of the treatment effect, all levels of age strata and all levels of region and interactions levels. The effects that are not significant at the 5% level will be removed from the model.

Geometric means (GMs) of post-vaccination CD4[2+] T cell frequency following induction with gE, will be calculated conditionally to the means of the pre-vaccination log-transformed CD4[2+] T cell frequency following induction with gE and the post-vaccination log-transformed CD4[2+] T cell frequency under background conditions. Difference of means between vaccines will be calculated together with 95% CIs and back-transformed to the original units to provide frequency GMs and frequency GM ratios. For each stratum, estimation of the fold-increase in frequencies following induction will be presented together with confidence intervals.

b. Treatment comparison of the Frequency of gE-specific CD4[2+]

The same ANCOVA model as described above will be used to analyze the log-transformed ratio between induction frequency and background frequency of CD4[2+]. Least-square means and difference of least-squares means will then be back-transformed and used to provide estimates for the frequency difference divided by background ([induction – background] / background). The log-transformed ratios of these estimates between treatments will be calculated together with confidence intervals according to the delta-method (error propagation method). These estimates better represent the net effect of the vaccines over the frequency of CD4[2+]as the nuisance background mean frequency is subtracted from the mean induction frequency.

6.3.2. Humoral immune response

Humoral immune response will be assessed and analyzed in the Humoral Immunogenicity subset as defined in Section 4.1 in the protocol.

Descriptive statistics

For the humoral immune response, at each timepoint that a blood sample is available (Month 0, Month 3, Month 14, Month 26 and Month 38), the following parameters (with 95% CIs) will be tabulated for each treatment group, by age group and by region/country:

- Geometric mean concentrations (GMCs) of anti-gE Ab with 95% confidence interval (CIs);
- Humoral seropositivity rates with exact 95% confidence interval (CIs);
- Vaccine response rates with 95% confidence interval (CIs);
- Descriptive statistics of the fold over pre-vaccination at months 3, 14, 26 and 38 (Mean, Standard deviation, Min, Q1, Median, Q3, Max).

Inferential Analyses

If the data allows, inferential analysis on the log-transformed Antibody concentrations will be performed overall and by age strata or sub-strata, in subjects infected with HZ and healthy subjects.

A simple ANCOVA model will be used to analyze post-vaccination (Month 3) log-transformed anti-gE and anti-VZV ELISA antibody concentrations. The fixed-effect model will include the means for all levels of treatment effect and all levels of age strata. The pre-vaccination log-transformed antibody concentrations (Month 0) will be included as continuous covariate.

Least-squares means and 95% CI are back-transformed to provide geometric means and ratios. Sensitivity analyses will include additional effects for regions and appropriate interactions in the model in order to provide estimations and 95% CI by region. The fixed-effect model will include the means for all levels of the treatment effect, all levels of age strata and all levels of region and interactions levels. The effects that are not significant at the 5% level will be removed from the final model.

Geometric means of post-vaccination Ab concentrations will be calculated for month 3 conditionally to the means of the log-transformed concentrations at pre-vaccination calculated across the treatment groups. The difference of means between vaccine and placebo will be calculated together with 95% CIs (2-sided) and back-transformed to the original units to provide GMCs and GM ratios

6.3.3. VZV neutralizing antibody response

Descriptive statistics

The following parameters will be tabulated by treatment group, overall and by age group at Month 0, Month 3, Month 14, Month 26 and Month 38:

- Geometric mean titres (GMTs) of anti-VZV neutralizing Abs with 95% CIs;
- Descriptive statistics on the fold over pre-vaccination;
- Tabulations will be presented overall and by region.

6.3.4. Correlate of protection

An exploratory analysis will be implemented in an attempt to correlate humoral immune responses to vaccination and subsequent HZ risk [Dunning, 2006]. More details of the methodologies will be included in SAP of study Zoster-022.

Serum blood samples have been collected from all subjects at Month 0 (pre-vaccination) and Month 3, and may be used for correlate of protection analysis. Additional subject samples may be retrieved and analyzed based on some demographics and baseline characteristics to match more exactly with characteristics of those who developed HZ.

The analysis for correlate of protection will be performed on the pooled data of both ZOSTER-006 and ZOSTER-022 and may be provided in an annex report. Further details will be provided in SAP of ZOSTER-022.

6.4. Quality of life

A specific SAP will describe the methodologies to be used for the quality of life analysis.

7. STATISTICAL CALCULATIONS

7.1. Derived and transformed data

7.1.1. Demography

Age: Age at the reference activity, computed as the number of units between the date of birth and the reference activity. In case of partialcompletion of any of these 2 dates:

15th of month, If only the day is missing

30th of June, if day and months are missing.

7.1.2. Immunogenicity

7.1.2.1. Humoral immune response

The current cut-off values that apply for gE and VZV Ab responses are described in Table 7 of Section 5.8.3 in the protocol. Those values may changes as improvements are introduced to the analytical methods. The final cut-off values that are used for the analyses will be stated in the study report.

- A seronegative subject is a subject whose Ab concentration is below the cut-off value.
- A seropositive subject is a subject whose Ab concentration is greater than or equal to the cut-off value.
- The seropositivity rate is defined as the percentage of seropositive subjects.
- The anti-gE humoral immune response to vaccine for subjects who are seropositive at baseline is defined as at least 4-fold increase in the anti-gE Ab concentration at the endpoint as compared to the pre-vaccination anti-gE antibody concentration. The anti-gE humoral immune response to vaccine for subjects who are seronegative at baseline is defined as at least 4-fold increase in the antigE Ab concentration at the endpoint as compared to the anti-gE Ab cut-off value for seropositivity.
- The anti-VZV humoral immune response to vaccine for subjects who are seropositive at baseline is defined as at least 4-fold increase in the anti-VZV Ab concentration at the endpoint as compared to the pre-vaccination anti-VZV Ab concentration. The anti-VZV humoral immune response to vaccine for subjects who are seronegative at baseline is defined as at least 4-fold increase in the anti-VZV Ab concentration at the endpoint as compared to the anti-VZV Ab cut-off value for seropositivity.
- The Geometric Mean Concentrations (GMCs) calculations are performed by taking the anti-log of the mean of the log concentration transformations. For descriptive statistics only, Ab concentrations below the cut-off of the assay will be given an arbitrary value equal to half the cut-off for the purpose of GMC calculation. For inferential analyses, those concentrations below the cut-off will be considered as missing to avoid potential influential data.

7.1.2.2. Cellular-mediated immune (CMI) response

- For the inferential analysis, the frequency of CD4 [2+] T cells, i.e., CD4 T cells producing at least 2 activation markers among IFN-γ, IL-2, TNF-α and/or CD40L, upon in vitro stimulation with the antigen (induction condition) is calculated by adding an offset of 0.5 to the number of activated CD4[2+] T cells (numerator) divided by the total number of CD4 T cells involved (denominator). A similar calculation will be made for the frequency of CD4 [2+] T cells upon in vitro stimulation in medium only (background condition).

$$Freq_{Induction}^{CD4[2+]} = \frac{n_{Induction}^{2+} + 0.5}{N_{Induction}^{CD4}} \qquad \log(Freq_{Induction}^{CD4[2+]}) = \log(\frac{n_{Induction}^{2+} + 0.5}{N_{Induction}^{CD4}})$$

$$Freq_{Bachground}^{CD4[2+]} = \frac{n_{Background}^{2+} + 0.5}{N_{Bachground}^{CD4}} \qquad \log(Freq_{Background}^{CD4[2+]}) = \log(\frac{n_{Background}^{2+} + 0.5}{N_{Background}^{CD4}})$$

$n_{Induction}^{2+}$ = number of CD4 T cells secreting at least 2 activation markers after induction with the antigen

$n_{Background}^{2+}$ = number of CD4 T cells secreting at least 2 activation markers in medium condition

N^{CD4} = Total number of CD4 T cells involved in the assay (induction or background)

- For the descriptive analyses, the frequency of CD4[2+] T cells upon in vitro stimulation with the antigen (induction condition) is calculated by dividing the number of activated CD4[2+] Tcells (numerator) over the total number of CD4 T cells involved (denominator). The same calculation will be performed for the frequency computation for any kinds of cells and for each individual activation marker as appropriate. (Amended 18 April 2014)

$$Freq_{Induction}^{CD4[2+]} = \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}}$$

$n_{Induction}^{2+}$ = number of CD4 T cells secreting at least 2 activation markers after induction with the antigen

N^{CD4} = Total number of CD4 T cells involved in the assay (induction)

- The frequency of antigen-specific (gE or VZV) CD4[2+] T cells for each individual subject is calculated as the difference between the frequency of CD4[2+] T cells, upon in vitro stimulation with the antigen (induction condition), minus the frequency of CD4[2+] T cells, upon in vitro stimulation in medium only (background condition). The differences less or equal to one (1) are imputed to 1 antigen-specific CD4[2+] T cell per 10^6 CD4 T cells. The same calculation will be performed for the frequency computation for any kinds of cells and for each individual activation marker as appropriate. (Amended 18 April 2014)

$$Freq_{Specific}^{CD4[2+]} = \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} - \frac{n_{Background}^{2+}}{N_{Background}^{CD4}} \quad if \quad \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} > 1 + \frac{n_{Background}^{2+}}{N_{Background}^{CD4}}$$

$$Freq_{Specific}^{CD4[2+]} = 1 \quad if \quad \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} \leq 1 + \frac{n_{Background}^{2+}}{N_{Background}^{CD4}}$$

$n_{Induction}^{2+}$ = number of CD4 T cells secreting at least 2 activation markers after induction with the antigen

$n_{Background}^{2+}$ = number of CD4 T cells secreting at least 2 activation markers in medium condition

N^{CD4} = Total number of CD4 T cells involved in the assay (induction or background)

- The Geometric Mean (GM) frequency calculations are performed by taking the anti-log of the mean of the log frequency transformations;
- The CMI vaccine response to gE will be based on the gE-specific data as computed above. The cut-off for the assay (320 positive events/10^6 CD4 T cells) will be used for vaccine response assessment. The vaccine response is defined as the percentage of subjects who have:
  - at least a 2-fold increase as compared to the cut-off, for subjects with pre-vaccination T cell frequencies below the cut-off.
  - at least a 2-fold increase as compared to pre-vaccination T cell frequencies, for subjects with pre-vaccination T cell frequencies above the cut-off.
- The CMI vaccine response to VZV will be based on the VZV-specific data as computed above. The lower limit of linearity (LLL) for the assay (320 positive events/10^6 CD4 T cells) will be used for vaccine response assessment. The vaccine response is defined as the percentage of subjects who have:
  - at least a 2-fold increase as compared to the cut-off, for subjects with pre-vaccination T cell frequencies below the LLL.
  - at least a 2-fold increase as compared to pre-vaccination T cell frequencies, for subjects with pre-vaccination T cell frequencies above the LLL.
- A CMI responder is a subject with a CMI response greater than or equal to the LLL value.

Table 1 Cell-Mediated Immunogenicity (CMI)

System	Component	Challenge	Method	Unit	LLL	Laboratory
Peripheral Blood Mononuclear Cells	Cells CD4.All double CD40 Ligand or Interleukin-2 or Tumor Necrosis Factor alpha or Interferon gamma Background Reduced	gE	ICS	Events/10E6 CD4+ T-cells	320**	CEVAC*

* University of Gent, Belgium or another validated laboratory designated by GSK Biologicals.

** Corresponding to the lower limit of linearity.

ICS = Intracellular cytokine staining

7.1.3. Number of decimals

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/ reactogenicity.

Display Table	Parameters	Number of decimal digits
Demographic characteristics	Mean, median age	1
Demographic characteristics	SD (age)	2
Immunogenicity	Ratio of GMT/C	2
Reactogenicity	Mean, Min, Q1, Median, Q3, Max for duration	1
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2
All summaries	p-value	4

7.2. Handling of missing data

For the analysis of solicited symptoms, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVc will include only subjects/doses with documented safety data (i.e., symptom screen/sheet completed).

For the analysis of unsolicited AEs/SAEs/concomitant medication, all vaccinated subjects will be considered and subjects who did not report an event will be considered as subjects without an event.

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

The reasons for and timings of missing data will be reviewed and discussed. The likely patterns for missing data will be assessed and compared with the actual missing data pattern in light of CHMP /EWP/1776/99 and implementation recommendations.

7.3. Methodology for computing CI

Unless otherwise mentioned, the confidence intervals will be 2 sided 95% CI and calculated according to the following methods:

7.3.1. Binomial Data

The exact 95% CIs for a proportion within a group will be calculated according to Clopper & al. (1934).

7.3.2. Continuous Data

The 95% CI for geometric mean titres/concentrations (GMTs/GMCs) in non-inferential analyses will be obtained within each group separately. The 95% CI for the mean of log-transformed titre/concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMCs will be then obtained by exponential-transformation of the 95% CI for the mean of log-transformed titre/concentration.

Refer to dedicated methods for inferential methods.

7.4. Inferential analysis and statistical models

7.4.1. Cellular-mediated immune response

See section 6.3.1 for statistical method.

A similar analysis as describe in section 6.3.1 and 7.1.2.1will be implemented on the post-vaccination frequency of CD4 T cells producing at least two different cytokines following induction.

The model is defined as follow:

$$y_{ijk3} = \gamma_j + \mu_k + \alpha.x_{ijk} + \beta.y_{ijk0} + \varepsilon_{ijk}$$

$$\hat{y}_j \,|\, \bar{y}_0, \bar{x} = \gamma_j + \mu_k + \alpha.\bar{x} + \beta.\bar{y}_0$$

$$\varepsilon_{ijk} \approx N(0, \sigma),$$

y_{ijk3} = log-*transformed frequency following induction with antigen for subject* i,*treatment* j *and age cohort* k *at month* 3

y_{ijk0} = log-*transformed frequency following induction with antigen for subject* i,*treatment* j *and age cohort* k *at pre-vaccination*

x_{ijk} = log-*transformed frequency following induction with medium only (background)*

$\bar{y}_0$ = *mean of* log-*transformed frequency following induction at pre-vaccination*

$\bar{x}_0$ = *mean of* log-*transformed frequency following induction at pre-vaccination*

Example of SAS code

1 - Overall analysis

```
PROC GLM DATA=file;
  BY    v_id;
  CLASS pid treatment agecat;
  MODEL Log(frequency of induction at month 3)] = agecat
                                                  treatment
              Log(frequency of induction at pre-vaccination)]
              Log(frequency of background)] ;

  LSMEANS treatment / AT MEANS CL DIFF=CONTROL("Placebo") ALPHA=0.05
  ;

  ODS OUTPUT LSMEANS=lsm;
  ODS OUTPUT DIFFS=dif;
RUN;
```

2- By subgroup analysis

The same model will be applied for each age strata and for each region

7.4.2. Humoral immune response

See section 6.3.2 for statistical method.

A similar analysis as describe in section 6.3.2 and 7.1.2.1will be implemented on the post-vaccination anti-gE ELISA titers.

The following SAS code will be used to perform this analysis.

1 - Overall analysis

```
PROC GLM DATA=file ;
      CLASS pid treatment agecat;
      MODEL log(antibody concentrations) = agecat treatment
            Log(antibody concentration at pre-vaccination) ;
  LSMEANS treatment / AT MEANS CL DIFF=CONTROL(“Placebo”) ALPHA=0.05
  ;
 ODS OUTPUT LSMEANS=lsm;
 ODS OUTPUT DIFFS=diff;
RUN;
```

2- By subgroup analysis

For each age strata and each region, a similar model will be used.

7.5. Sensitivity analyses

Sensitivity analyses will include additional effects for region levels and appropriate interactions in the model in order to provide estimations and 95% CI by region.

The following interactions below will be implemented. The effects that are not significant at the 5 % level will then be removed, provided it does not change the conclusion.

```
MODEL Log(frequency of induction at month 3)]  =
treatment
agecat agecat*treatment
region region*treatment
region*agecat*treatment
Log(frequency of induction at pre-vaccination)
agecat*Log(frequency of induction at pre-vaccination)
region*Log(frequency of induction at pre-vaccination)
Log(frequency of background)
agecat*Log(frequency of background)
region*Log(frequency of background)
```

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in the protocol will be described and justified in the final study report.

Description	Analysis ID (SDD sub-folder)
Final HZ efficacy Analysis	Analysis_E1_35
End-of-study Analysis	Analysis_E1_XX

8.2. Statistical considerations for interim analyses

Not applicable.

8.3. Final HZ efficacy and end-of-study analysis

Two analyses are planned, in each analysis all objectives will be assessed. The first analysis (final HZ efficacy analysis) will be considered as primary analysis for any inferential analysis. The end-of-study analysis will provided the complete analysis of the full data available at the end of study and serve as confirmatory analysis for the objectives demonstrated at previous steps.

Blind will be maintained through the end-of-study analysis. Individual listings will only be provided to the Firewall Team / added to an unblinded report version if applicable

9. CHANGES FROM PLANNED ANALYSES

The following criterion is not used to eliminate subjects from the ATP cohort for safety **"with sufficient data to perform an analysis of safety (at least one dose with safety follow-up)**. The reactogenicity analyses will be performed on the subjects with diary cards returned, therefore the subjects without diary cards will not be included in the analysis. In the analysis of AEs, the subjects who did not report any event will be considered without event.

The first time window (0-23 months) used for safety analyses (SAEs, PIMDs and fatal events) have been modified according to standard time window used in Zoster program (from dose 1 to one month post dose 2).

The vaccine response rate (VRR) in CMI have been modified and adapted with the new definition included on protocol amendment.

Additional descriptive immunogenicity analysis will be also provided by country.

10. REFERENCES

- Dunning A. A model for immunological correlates of protection. Statist. Med. 2006, 25:1485–1497.
- Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika,* 1934; 26: 404-413.

11. ABBREVIATIONS

AE	Adverse event
ATP	According-To-Protocol
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry
EL.U/ml	ELISA unit per milliliter
ELISA	Enzyme-linked immunosorbent assay
Eli_type	Internal GSK database code for type of elimination code
GMC	Geometric mean antibody concentration
GSK	GlaxoSmithKline
IU/ml	International units per milliliter
MedDRA	Medical Dictionary for Regulatory Activities
N.A.	Not Applicable
OTH	Other
RDE	Remote Data Entry
pIMD	potential Immune Mediated Disease
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SR	Study Report
SYN	Synopsis
TFL	Tables Figures and Listing template annexed to SAP
LLL	Lowe Limit of linearity

Statistical Analysis Plan

Study alias & e-track number(s): ZOSTER-006 (110390)

Detailed Title:	A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' gE/AS01$_B$ vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older.
SAP version	***2***.0
SAP date	***20-OCT-2014***
Scope:	All Safety and Immuno data pertaining to the above study.
Co-ordinating author:	[redacted]
Other author(s):	[redacted]
Adhoc reviewers:	[redacted]
Approved by:	
Clinical Research and Development Lead	[redacted]
Project CRDL	[redacted]
Project Statistician	[redacted]
Lead Statistician	[redacted]

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Abbreviations

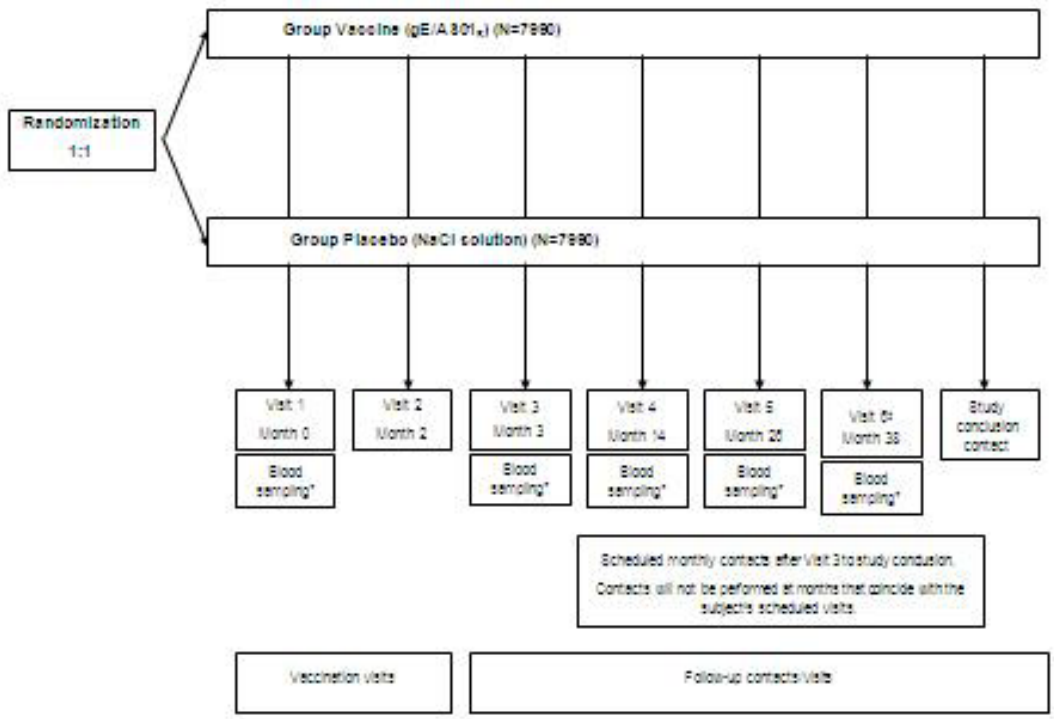
AE	Adverse event
ATP	According-To-Protocol
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry
EL.U/ml	ELISA unit per milliliter
ELISA	Enzyme-linked immunosorbent assay
Eli_type	Internal GSK database code for type of elimination code
GMC	Geometric mean antibody concentration
GSK	GlaxoSmithKline
IU/ml	International units per milliliter
MedDRA	Medical Dictionary for Regulatory Activities
N.A.	Not Applicable
OTH	Other
RDE	Remote Data Entry
pIMD	potential Immune Mediated Disease
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SR	Study Report
SYN	Synopsis
TFL	Tables Figures and Listing template annexed to SAP
LLL	Lowe Limit of linearity

The analysis plan is divided into 2 parts: the first part called statistical analysis plan (SAP) detailing the analyses to be performed (current document) and a second part, annexes (called TFL) describing the flow and format of tables, figures and listings to be annexed to the study report (SR). Two annexes will be prepared, one that describes the TFLs for the step 1 analysis of immunogenicity and safety and a second one that describes the TFLs for the analysis of end-of-study analysis of immunogenicity and safety. ***Each of the following analysis efficacy analysis, correlate of protection and Quality of Life analysis will be described in a Separate SAPs and TFLs documents.***

1. DOCUMENT HISTORY

Date	Version	Description	Protocol Version
05-May-2014	First Version	Final analysis for demongraphy, Safety and immunogenicity	Amendment 4 18 Apr 2014
20-October-2014	2.0	Amendment	Amendment 4 18 Apr 2014

2. STUDY DESIGN



* Blood samples will be collected from all subjects at Visit 1 and Visit 3, and from subsets of subjects additionally at the other visits to assess immune responses.

Note: In case of suspected HZ, the subject will have additional visits and contacts for follow-up of HZ.

The following group names will be used for the statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote
1	HZ/su	Herpes Zoster subunit vaccine
2	Placebo	Placebo

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The following sub-group names will be used for the statistical analyses:

Analysis by age group

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote	Pooled Groups 1 label in tables	Pooled Groups 2 label in tables
1	50-59Y	50-59 years old subjects	50-59Y	50-59Y
2	60-69Y	60-69 years old subjects	60-69Y	≥ 60Y
3	70-79Y	70-79 years old subjects	≥ 70Y	≥ 60Y
4	≥ 80Y	≥ 80 years old subjects	≥ 70Y	≥ 60Y

Analysis by region

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote	Pooled Groups label in tables
1	CZ	Czech Republic	Europe
2	EN	Estonia	Europe
3	FI	Finland	Europe
4	FR	France	Europe
5	GE	Germany	Europe
6	IT	Italy	Europe
7	SP	Spain	Europe
8	SW	Sweden	Europe
9	UK	United Kingdom	Europe
10	AS	Australia	Australasia
11	HK	Hong Kong	Australasia
12	JA	Japan	Australasia
13	SK	South Korea	Australasia
14	TW	Taiwan	Australasia
15	BR	Brazil	Latin America
16	MX	Mexico	Latin America
17	US	United States	North America
18	CA	Canada	North America

3. OBJECTIVES

As per protocol.

4. ENDPOINTS

As per protocol.

5. STUDY POPULATION

As per protocol.

5.1. Total Vaccinated cohort

The Total Vaccinated Cohort (TVC) will include all vaccinated subjects with respect to the vaccine actually administered.

The TVC for analysis of efficacy will include vaccinated subjects for whom data related to efficacy endpoints are available.

The TVC for analysis of immunogenicity will include vaccinated subjects in the immunogenicity sub-cohort for whom immunogenicity data are available.

The TVC for analysis of safety will include all subjects with at least one vaccine administration documented.

The TVC diary card for analysis of reactogenicity will include all TVC subjects belonging to the diary card subset.

The subjects from closed sites will be excluded from the TVC.

5.2. Modified Total Vaccinated cohort

The mTVC will be the primary population for efficacy analysis, which excludes subjects in the TVC for efficacy analysis who were not administered with the second vaccination or who developed a confirmed case of HZ prior to 1 month after the second vaccination or who received vaccine doses /or replacement not according to their randomized group .

5.3. According To Protocol cohort for analysis of efficacy

The According To Protocol cohort (ATP) for analysis of efficacy will include all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom efficacy data concerning endpoint measures are available, i.e., excluding all subjects who developed a confirmed case of HZ prior to 1 month after the second vaccination. The list of criteria used to exclude subjects from ATP cohort are:

- Study vaccine dose not administered AT ALL but subject number allocated
- Administration of concomitant vaccine(s) forbidden in the protocol
- Randomisation failure (subject not randomized in the correct group)
- Randomisation code broken at the investigator site or at GSK Safety department
- Site or route of study vaccine administration wrong or unknown

  Administration not according to protocol for reason specified by the investigator, other than side, site and route

  Administered study vaccine reported as being the correct one but is not compatible with the vaccine regimen associated to the treatment number
- Wrong replacement or study vaccine administered ***(not compatible with the vaccine regimen associated to the treatment number).***
- Protocol violation linked to the inclusion/exclusion criteria including age and excluding codes mentioned below
- Subjects who did not received two doses
- Subjects having an episode of HZ prior than 30 days after the dose 2

The ATP ***cohort for efficacy*** will be the analysis set for supportive efficacy analysis.

5.4. According To Protocol cohort for analysis of safety

The According To Protocol (ATP) cohort for analysis of safety will include all subjects ***from TVC cohort***:

- ***who meet all eligibility criteria***
- who have received at least one dose of study vaccine/placebo according to their random assignment;
- for whom administration site of study vaccine/placebo is known/correct;
- ***who have not received other vaccine forbidden in the protocol (Section 6.6.1 from protocol);***
- for whom the randomization code has not been broken.

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The ATP safety diary card for analysis of reactogenicity will include all subjects in the ATP safety included in the diary card subset.

5.5. According To Protocol cohort for analysis of immunogenicity

For study ZOSTER-006, the ATPc for analysis of immunogenicity will include all evaluable subjects ***from the According To Protocol (ATP) cohort for analysis of safety*** (i.e., those meeting all eligibility criteria, complying with the procedures and intervals ***allowed for the analysis***, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom immunogenicity results are available at Month 3 for CMI and/or humoral immunogenicity.

The intervals allowed for the inclusion in the ATP cohort for analysis of immunogenicity are defined as follow

	Group	*Interval*	*Allowed interval for ATP cohort analysis of immunogenicity*
Interval between vaccinations	***HZ/su***	***HZ/su (Dose 1) – HZ/su (Dose 2)***	***49-83 Days***
	Placebo	***Placebo (Dose 1) – Placebo (Dose 2)***	***49-83 Days***
Interval between vaccination and blood sample taken	***HZ/su***	***HZ/su (Dose 2) – Visit Visit Month 3 for BS***	***28-48 days***
	Placebo	***HZ/su (Dose 2) – Visit Month 3 for BS***	***28-48 days***

BS= blood sampling taken

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The list of applicable elimination codes for each cohort can be found in the study specific form FORM-BIO-CLIN-9004-05 Elim code specifications.

Cohort	Elimination codes	Eli Type
Total vaccinated cohort	900,1030	MA
Total vaccinated cohort diary card	900,1030, 5130	MA
Total vaccinated cohort Humoral	900,1030, 2500	MA
Total vaccinated cohort CMI	900,1030, 2500, 4130	MA
ATP cohort for analysis for safety	900,1030-1500	MA
ATP diary card	900,1030-1500, 5130	MA
mTVC	900,1030,1050,1070, 1500, 2500, 3500	MA
ATP cohort for analysis for immunogenicity-Humoral	900,1030-2500	MA
ATP cohort for analysis for immunogenicity-CMI	900,1030-2500 , 4130	MA
ATP cohort for analysis of efficacy	900, 1030-1070, 1500-2010, 2500,3500	MA

6. STATISTICAL METHODS

All analyses will be presented overall and by age strata. The main age strata for reporting purposes are 50-59, 60-69 and ≥ 70 YOA. Additional analysis will be presented in ≥ 60 YOA.

6.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age at first study vaccination, gender, geographic ancestry, race and ethnicity), cohort description and withdrawal status will be summarized overall and by region.

The mean age (plus range and standard deviation) of the enrolled subjects, as a whole, and per treatment group and stratified by age group will be calculated.

The distribution of subjects enrolled among the study sites will be tabulated as a whole and per vaccine group.

Frequency tables will be generated for categorical variables such as gender.

Mean, median and standard error will be provided for continuous data such as age.

In addition, the following table will be performed for CTRS posting:

- ***Percentage of Enrolled subjects by country will be tabulated by group,***
- ***Percentage of Enrolled subjects in the following age categories ≤64, 65-84, ≥85 will be tabulated by group.***

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6.2. Analysis of safety

The primary analysis will be based on the Total Vaccinated cohort. A second analysis based on the ATP cohort for safety will be performed to complement the Total Vaccinated Cohort analysis.

When appropriate, tabulations will be presented overall and by time of occurrence relative to last vaccination (e.g., using windows such as Days 0-6, Days 0-29 and more than 30 days post-vaccination).

6.2.1. Within groups assessment

For each treatment group, the following results will be tabulated overall and by age strata.

The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general adverse event (solicited and unsolicited) and with any AE during the solicited follow-up period, i.e., the day of vaccination and six subsequent days after each vaccination will be tabulated with exact 95% CI after each vaccine dose and overall.

The percentage of doses followed by at least one local AE (solicited and unsolicited), by at least one general AE (solicited and unsolicited) and by any AE will be tabulated, overall vaccination course, with exact 95% CI. The same tabulation will be done for grade 3 AEs, related AEs and grade 3 related AEs.

The number and percentage of subjects with at least one local solicited AE, with at least one general solicited AE and with any solicited AE during the 7-day follow-up period with exact 95% CIs after each vaccine dose and overall by vaccination group will be provided

The percentage of subjects reporting each individual solicited local and general AE during the solicited 7-day (Days 0-6) follow-up period will be tabulated with exact 95% CI.

The percentage of doses followed by each individual solicited local and general AE during the solicited 7 day (Days 0-6) follow-up period will be tabulated, overall vaccination course, with exact 95% CI.

For all solicited symptoms, the same tabulation will be performed for grade 3 solicited AEs and for solicited general AEs with relationship to vaccination. ***For fever, the summary will be presented by half cumulative degree increment.***

Duration of fever will be presented, analyses will be done ***overall and*** broken down by route.

The proportion of subjects with at least one report of unsolicited AE during the 30-day (Days 0-29) follow-up period after each vaccination classified according to the MedDRA System Organ Class and Preferred Terms will be tabulated, with exact 95% CI.

The distribution of the number of unsolicited AEs per subject will be tabulated.

The same tabulation will be performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination. The proportion of AEs resulting in a medically attended visit (other than routine health maintenance visits) will also be tabulated.

Proportion of subjects reporting at least one serious adverse events classified by MedDRA Primary System Organ Class and Preferred Term by time window and overall (eg 0-29 days, 0-3 months, 0-8 Months ,3-8 month, 8-14 month and more than 14 month) will be tabulated, with exact 95% CI.

A separate tabulation will report some of the major categories of SAEs that occur with higher frequencies in elderly subjects including: cardiac, vascular, respiratory, neurological, congestive heart failure, myocardial infarction, varicella or HZ-like rash, cerebral or vascular events, stroke. Listing will also be provided, sorted by patients and sorted by preferred term.

The proportion of subjects with at least one report of pIMDs during the entire study period will be tabulated overall and by time window (eg 0-3 month, 3-8 month, 8-14 month and more than 14 month) will be tabulated, with exact 95% CI. Listing will also be provided, sorted by subjects and sorted by MedDRA Preferred Term.

The proportion of subjects with fatal outcome during the entire study period will be tabulated overall and by time window (eg 0-29 days, 0-3 month, 3-8 month, 8-14 month and more than 14 month) will be tabulated, with exact 95% CI.

Proportion of subjects of subjects with, HZ-related complications and HZ-related hospitalizations, will be tabulated overall and by time window. (eg 0-29 days, 0-3 month, 3-8 month, 8-14 month and more than 14 month)

Incidence of withdrawal due to AEs will be tabulated. Listing will also be provided, sorted by subjects and sorted by MedDRA Preferred Term.

The proportion of subjects with concomitant medication will be tabulated, until 30 days after each vaccine dose and overall, with exact 95% CI.

Proportion of subjects experiencing an HZ episode using pain medications by type ***(Aspirin, Paracetamol, NSAIDs, Opioids, Topicals, Others (antiepileptics, antidepressants …))*** will be tabulated.

SAEs and pIMD for subjects from the closed centers will be described separately

The following additional analysis will be performed

- ***Summary of temperature value by half degree cumulative increment taken reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall doses and subjects with no conversion rule***
- ***For each specified route of temperature measurement***

  Number and percentage of subjects who reported fever (by half degree cumulative increment) measured via each route during the 7-day (Days 0-6) post-vaccination period following each dose and overall with no conversion rule.

The following additional analysis will be performed for CTRS

- ***The number of occurrence of the 5% most frequent non-serious unsolicited AE classified by the MedDRA Preferred Terms and reported up to 30 days after each vaccination will be tabulated***
- ***The number of occurrence of SAE classified by the MedDRA Preferred Terms and reported up to 30 days after each vaccination will be tabulated***

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6.2.2. Additional exploratory safety comparisons

The ***exact*** 95% CI for ***the relative risk*** between the two groups and the associated 2-sided p-value to detect group difference will be computed for the following endpoints:

- The proportion of subjects with at least one report of unsolicited AE classified by the MedDRA presented by System Organ Class.The proportion of subjects with at least one report of unsolicited AE classified by the MedDRA presented by System Organ Class and Preferred Term.
- Incidences of SAEs classified according to the MedDRA System Organ Class and Preferred Terms.

The objective of these analyses is to identify a safety signal as defined by the Council for the International Organization of Medical Sciences (CIOMS) VI working group, i.e., a report or reports of an event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continues surveillance. It is recognized that the use of any method to identify safety signals has the potential to identify a large number of events which may or may not have a causal relationship to drug treatment due to multiplicity of endpoints. In order to put any safety signal in perspective a permutation test will be conducted to quantify the probability to observe at least one false safety signal according to the threshold p-value defining a signal. In addition, clinical significance and biological plausibility will need to be accounted before establishing causality.

In the following section, we will describe a proposed approach to help detection of SAE signal

6.2.3. AE signal method

6.2.3.1. Analysis by System Organ Class (SOC)

Three summary tables and one plot of probability of false signal will be provided:

1. The first summary table will be the complete table with SOC only with ratio of proportion between both groups and exact non adjusted p-values. The second table will be a subset of the first with only SOC of interest.
2. The plot of probability of false signal will be built on the whole data set used to produce the summary of the first table. The plot will be zoomed to have in Y-axis adjusted p-values between 0 and 0.15. An additional table of correspondence between unadjusted p-values and the adjusted p-value (i.e. probability of false signal) will be provided as annotation for the plot provided. SOC with adjusted p-value below 15% will be considered to identify SOC of interest for further review.
3. The third summary table will be a subset of the first table containing the PT associated to SOC of interest for further review. This table will be sorted by p-values (lowest to highest) within each SOC.

6.2.3.2. Analysis by SOC & PT

Two summary tables and one plot of probability of false signal will be provided:

1. The first summary table will be the complete table with SOC and PT with ratio of proportion between both groups and exact non adjusted p-values. This table will be sorted by SOC and PT.
2. The second summary table will be a subset of the first containing only SOC & PT when the adjusted p-values are below 15%. This table will be sorted by p-values (lowest to highest).
3. The plot of probability of false signal will be built on the whole data set used to produce the summary of the first table. The plot will be zoomed to have in Y-axis adjusted p-values between 0 and 0.15. An additional table of correspondence between unadjusted p-values and the adjusted p-value (i.e. probability of false signal) will be provided as annotation for the plot provided.

6.3. Analysis of immunogenicity

The primary analysis will be based on the ATP cohort for analysis of immunogenicity. If the percentage of subjects excluded from this ATP cohort is more than 5%, a second analysis based on the Total vaccinated cohort will be performed to complement the ATP analysis.

The analysis for immunogenicity will be performed by treatment group, by age strata and by region/country.

6.3.1. Cell-mediated immune response

CMI response will only be assessed and analyzed in the CMI component of the Immunogenicity subset as defined in Section 4.1 in the protocol.

6.3.1.1. Descriptive statistics

For CMI response, the following parameters (for gE and VZV specific CD4[2+] frequency and CD4[+2] T-cell following induction with gE and VZV) will be tabulated by treatment group, overall and by age group at Months 0, 3, 14, 26 and 38:

- descriptive statistics of the frequency of CD4 T cell secreting at least two different cytokines (IFN-γ, IL-2, TNF-α,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least IFN-γ and another cytokine (IL-2, TNF-α,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least IL-2 and another cytokine (IFN-γ, TNF-α,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least TNF-α and another cytokine (IFN-γ, IL-2,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least CD40L and another cytokine (IFN-γ, IL-2, TNF-α) to both VZV and gE antigens;
- descriptive statistics on the fold over pre-vaccination at months 3, 14, 26 and 38.
- Vaccine response rate with exact 95% CI at Months 3, 14, 26 and 38 (only in the gE-specific CD4[2+] T-cell frequency at Month 3, 14, 26 and 38)

6.3.1.2. Inferential Analyses

The inferential analysis on CMI endpoint is performed using ‘a’ Treatment comparison of the Frequency of CD4[2+]” following induction and ‘b’ Treatment comparison of the Frequency of gE-specific CD4[2+]”. Analysis described in ‘b’ involves derivations of confidence intervals using the theorem of propagation of error (or delta-method) from estimates of means and variances calculated according to the methodology described in ‘a’.

a. The Frequency of CD4[2+] following gE-induction

If the data allows, inferential analysis on the log-transformed frequency of CD4 T cells producing at least two different cytokines following induction with antigen will be performed overall and by age strata, in subjects with HZ and healthy subjects.

A simple Analysis of Covariance (ANCOVA) model will be used to analyze the post-vaccination (Month 3) log-transformed frequency of CD4 T cells secreting at least 2 cytokines following induction with gE antigen.

The fixed-effect model will include the means for all levels of the treatment effect, all levels of age strata and interactions levels. Covariates will include the log-transformed pre-vaccination frequency following induction with the antigen and the non-specific background log-transformed frequency. Least-squares means and 95% CI are back-transformed to provide geometric means and ratios.

Sensitivity analyses will include additional effects for regions and appropriate interactions in the model in order to provide estimations and 95% CI by region. The same ANCOVA model as described above will be used for the sensitivity analyses. The fixed-effect model will include the means for all levels of the treatment effect, all levels of age strata and all levels of region and interactions levels. The effects that are not significant at the 5% level will be removed from the model.

Geometric means (GMs) of post-vaccination CD4[2+] T cell frequency following induction with gE, will be calculated conditionally to the means of the pre-vaccination log-transformed CD4[2+] T cell frequency following induction with gE and the post-vaccination log-transformed CD4[2+] T cell frequency under background conditions. Difference of means between vaccines will be calculated together with 95% CIs and back-transformed to the original units to provide frequency GMs and frequency GM ratios. For each stratum, estimation of the fold-increase in frequencies following induction will be presented together with confidence intervals.

b. Treatment comparison of the Frequency of gE-specific CD4[2+]

The same ANCOVA model as described above will be used to analyze the log-transformed ratio between induction frequency and background frequency of CD4[2+]. Least-square means and difference of least-squares means will then be back-transformed and used to provide estimates for the frequency difference divided by background ([induction – background] / background). The log-transformed ratios of these estimates between treatments will be calculated together with confidence intervals according to the delta-method (error propagation method). These estimates better represent the net effect of the vaccines over the frequency of CD4[2+]as the nuisance background mean frequency is subtracted from the mean induction frequency.

6.3.2. Humoral immune response

Humoral immune response will be assessed and analyzed in the Humoral Immunogenicity subset as defined in Section 4.1 in the protocol.

Descriptive statistics

For the humoral immune response, at each timepoint that a blood sample is available (Month 0, Month 3, Month 14, Month 26 and Month 38), the following parameters (with 95% CIs) will be tabulated for each treatment group, by age group and by region/country:

- Geometric mean concentrations (GMCs) of anti-gE Ab with 95% confidence interval (CIs);
- Humoral seropositivity rates with exact 95% confidence interval (CIs);
- Vaccine response rates with 95% confidence interval (CIs);
- Descriptive statistics of the fold over pre-vaccination at months 3, 14, 26 and 38 (Mean, Standard deviation, Min, Q1, Median, Q3, Max).

In addition, the following analysis will be done

Mean Geometric Increase (MGI) with exact 95% CI for anti-gE

Distribution of the fold increase i.e Percentage of subjects with a more than X-fold (e.g. >2, >4, >6,..-fold) increase will be tabulated per group with 95%CI.

Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max) of fold increase over pre-vaccination for anti-gE

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Inferential Analyses

If the data allows, inferential analysis on the log-transformed Antibody concentrations will be performed overall and by age strata or sub-strata, in subjects infected with HZ and healthy subjects.

A simple ANCOVA model will be used to analyze post-vaccination (Month 3) log-transformed anti-gE and anti-VZV ELISA antibody concentrations. The fixed-effect model will include the treatment and age strata ***as fixed effect***. The pre-vaccination log-transformed antibody concentrations (Month 0) will be included as continuous covariate.

Least-squares means and 95% CI are back-transformed to provide geometric means and ratios. Sensitivity analyses will include additional effects for regions and appropriate interactions in the model in order to provide estimations and 95% CI by region. The fixed-effect model will include the means for all levels of the treatment effect, all levels of age strata and all levels of region and interactions levels. The effects that are not significant at the 5% level will be removed from the final model.

Geometric means of post-vaccination Ab concentrations will be calculated for month 3 conditionally to the means of the log-transformed concentrations at pre-vaccination calculated across the treatment groups. The difference of means between vaccine and placebo will be calculated together with 95% CIs (2-sided) and back-transformed to the original units to provide GMCs and GM ratios

6.3.3. VZV neutralizing antibody response

Descriptive statistics

The following parameters will be tabulated by treatment group, overall and by age group at Month 0, Month 3, Month 14, Month 26 and Month 38:

- Geometric mean titres (GMTs) of anti-VZV neutralizing Abs with 95% CIs;
- Descriptive statistics on the fold over pre-vaccination;
- Tabulations will be presented overall and by region.

In addition, the following analysis will be done

- ***Mean Geometric Increase (MGI) with exact 95% CI for anti-gE***
- ***Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max) of fold increase over pre-vaccination for anti-gE***
- ***Distribution of the fold increase i.e Percentage of subjects with a more than X-fold (e.g. >2, >4, >6,..-fold) increase will be tabulated per group with 95%CI.***

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6.3.4. Correlate of protection

An exploratory analysis will be implemented in an attempt to correlate humoral immune responses to vaccination and subsequent HZ risk [Dunning, 2006]. ***A specific SAP will describe the methodologies to be used for that purpose.***

Serum blood samples have been collected from all subjects at Month 0 (pre-vaccination) and Month 3, and may be used for correlate of protection analysis. Additional subject samples may be retrieved and analyzed based on some demographics and baseline characteristics to match more exactly with characteristics of those who developed HZ.

The analysis for correlate of protection will be performed on the pooled data of both ZOSTER-006 and ZOSTER-022 and may be provided in an annex report.

6.4. Quality of life

A specific SAP will describe the methodologies to be used for the quality of life analysis.

7. STATISTICAL CALCULATIONS

7.1. Derived and transformed data

7.1.1. Demography

Age: Age at the reference activity, computed as the number of units between the date of birth and the reference activity. In case of partialcompletion of any of these 2 dates:

15th of month, If only the day is missing

30th of June, if day and months are missing.

7.1.2. Immunogenicity

7.1.2.1. Humoral immune response

The current cut-off values that apply for gE and VZV Ab responses are described in Table 7 of Section 5.8.3 in the protocol. Those values may changes as improvements are introduced to the analytical methods. The final cut-off values that are used for the analyses will be stated in the study report.

- A seronegative subject is a subject whose Ab concentration is below the cut-off value.
- A seropositive subject is a subject whose Ab concentration is greater than or equal to the cut-off value.
- The seropositivity rate is defined as the percentage of seropositive subjects.
- The anti-gE humoral immune response to vaccine for subjects who are seropositive at baseline is defined as at least 4-fold increase in the anti-gE Ab concentration at the endpoint as compared to the pre-vaccination anti-gE antibody concentration. The anti-gE humoral immune response to vaccine for subjects who are seronegative at baseline is defined as at least 4-fold increase in the antigE Ab concentration at the endpoint as compared to the anti-gE Ab cut-off value for seropositivity.
- The anti-VZV humoral immune response to vaccine for subjects who are seropositive at baseline is defined as at least 4-fold increase in the anti-VZV Ab concentration at the endpoint as compared to the pre-vaccination anti-VZV Ab concentration. The anti-VZV humoral immune response to vaccine for subjects who are seronegative at baseline is defined as at least 4-fold increase in the anti-VZV Ab concentration at the endpoint as compared to the anti-VZV Ab cut-off value for seropositivity.

- The Geometric Mean Concentrations (GMCs) calculations are performed by taking the anti-log of the mean of the log concentration transformations. For descriptive statistics only, Ab concentrations below the cut-off of the assay will be given an arbitrary value equal to half the cut-off for the purpose of GMC calculation.

7.1.2.2. Cellular-mediated immune (CMI) response

For the inferential analysis, the frequency of CD4 [2+] T cells, i.e., CD4 T cells producing at least 2 activation markers among IFN-γ, IL-2, TNF-α and/or CD40L, upon in vitro stimulation with the antigen (induction condition) is calculated by adding an offset of 0.5 to the number of activated CD4[2+] T cells (numerator) divided by the total number of CD4 T cells involved (denominator). A similar calculation will be made for the frequency of CD4 [2+] T cells upon in vitro stimulation in medium only (background condition).

$$Freq^{CD4[2+]}_{Induction} = \frac{n^{2+}_{Induction} + 0.5}{N^{CD4}_{Induction}} \qquad \log(Freq^{CD4[2+]}_{Induction}) = \log(\frac{n^{2+}_{Induction} + 0.5}{N^{CD4}_{Induction}})$$

$$Freq^{CD4[2+]}_{Bachground} = \frac{n^{2+}_{Background} + 0.5}{N^{CD4}_{Bachground}} \qquad \log(Freq^{CD4[2+]}_{Background}) = \log(\frac{n^{2+}_{Background} + 0.5}{N^{CD4}_{Background}})$$

$n^{2+}_{Induction}$ = number of CD4 T cells secreting at least 2 activation markers after induction with the antigen

$n^{2+}_{Background}$ = number of CD4 T cells secreting at least 2 activation markers in medium condition

N^{CD4} = Total number of CD4 T cells involved in the assay (induction or background)

For the descriptive analyses, the frequency of CD4[2+] T cells upon in vitro stimulation with the antigen (induction condition) is calculated by dividing the number of activated CD4[2+] Tcells (numerator) over the total number of CD4 T cells involved (denominator). The same calculation will be performed for the frequency computation for any kinds of cells and for each individual activation marker as appropriate. (Amended 18 April 2014)

$$Freq^{CD4[2+]}_{Induction} = \frac{n^{2+}_{Induction}}{N^{CD4}_{Induction}}$$

$n^{2+}_{Induction}$ = number of CD4 T cells secreting at least 2 activation markers after induction with the antigen

N^{CD4} = Total number of CD4 T cells involved in the assay (induction)

The frequency of antigen-specific (gE or VZV) CD4[2+] T cells for each individual subject is calculated as the difference between the frequency of CD4[2+] T cells, upon in vitro stimulation with the antigen (induction condition), minus the frequency of CD4[2+] T cells, upon in vitro stimulation in medium only (background condition). The differences less or equal to one (1) are imputed to 1 antigen-specific CD4[2+] T cell per 10^6 CD4 T cells. The same calculation will be performed for the frequency computation for any kinds of cells and for each individual activation marker as appropriate. (Amended 18 April 2014)

$$Freq^{CD4[2+]}_{Specific} = \frac{n^{2+}_{Induction}}{N^{CD4}_{Induction}} - \frac{n^{2+}_{Background}}{N^{CD4}_{Background}} \quad if \quad \frac{n^{2+}_{Induction}}{N^{CD4}_{Induction}} > 1 + \frac{n^{2+}_{Background}}{N^{CD4}_{Background}}$$

$$Freq^{CD4[2+]}_{Specific} = 1 \quad if \quad \frac{n^{2+}_{Induction}}{N^{CD4}_{Induction}} \leq 1 + \frac{n^{2+}_{Background}}{N^{CD4}_{Background}}$$

$n^{2+}_{Induction}$ = number of CD4 T cells secreting at least 2 activation markers after induction with the antigen

$n^{2+}_{Background}$ = number of CD4 T cells secreting at least 2 activation markers in medium condition

N^{CD4} = Total number of CD4 T cells involved in the assay (induction or background)

The Geometric Mean (GM) frequency calculations are performed by taking the anti-log of the mean of the log frequency transformations;

The CMI vaccine response to gE will be based on the gE-specific data as computed above. The cut-off for the assay (320 positive events/10^6 CD4 T cells) will be used for vaccine response assessment. The vaccine response is defined as the percentage of subjects who have:

- at least a 2-fold increase as compared to the cut-off, for subjects with pre-vaccination T cell frequencies below the cut-off.
- at least a 2-fold increase as compared to pre-vaccination T cell frequencies, for subjects with pre-vaccination T cell frequencies above the cut-off.

The CMI vaccine response to VZV will be based on the VZV-specific data as computed above. The lower limit of linearity (LLL) for the assay (320 positive events/10^6 CD4 T cells) will be used for vaccine response assessment. The vaccine response is defined as the percentage of subjects who have:

- at least a 2-fold increase as compared to the cut-off, for subjects with pre-vaccination T cell frequencies below the LLL.
- at least a 2-fold increase as compared to pre-vaccination T cell frequencies, for subjects with pre-vaccination T cell frequencies above the LLL.

A CMI responder is a subject with a CMI response greater than or equal to the LLL value.

Table 1 Cell-Mediated Immunogenicity (CMI)

System	Component	Challenge	Method	Unit	LLL	Laboratory
Peripheral Blood Mononuclear Cells	Cells CD4.All double CD40 Ligand or Interleukin-2 or Tumor Necrosis Factor alpha or Interferon gamma Background Reduced	gE	ICS	Events/10E6 CD4+ T-cells	320**	CEVAC*

* University of Gent, Belgium or another validated laboratory designated by GSK Biologicals.
** Corresponding to the lower limit of linearity.
ICS = Intracellular cytokine staining

7.1.3. Number of decimals

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/ reactogenicity.

Display Table	Parameters	Number of decimal digits
Demographic characteristics	Mean, median age	1
Demographic characteristics	SD (age)	2
Immunogenicity	Ratio of GMT/C	2
Reactogenicity	Mean, Min, Q1, Median, Q3, Max for duration	1
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2
All summaries	p-value	4

7.2. Handling of missing data

For the analysis of solicited symptoms, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVc will include only subjects/doses with documented safety data (i.e., symptom screen/sheet completed).

For the analysis of unsolicited AEs/SAEs/concomitant medication, all vaccinated subjects will be considered and subjects who did not report an event will be considered as subjects without an event.

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

The reasons for and timings of missing data will be reviewed and discussed. The likely patterns for missing data will be assessed and compared with the actual missing data pattern in light of CHMP /EWP/1776/99 and implementation recommendations.

7.3. Methodology for computing CI

Unless otherwise mentioned, the confidence intervals will be 2 sided 95% CI and calculated according to the following methods:

7.3.1. Binomial Data

The exact 95% CIs for a proportion within a group will be calculated according to Clopper & al. (1934).

7.3.2. Continuous Data

The 95% CI for geometric mean titres/concentrations (GMTs/GMCs) in non-inferential analyses will be obtained within each group separately. The 95% CI for the mean of log-transformed titre/concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMCs will be then obtained by exponential-transformation of the 95% CI for the mean of log-transformed titre/concentration.

Refer to dedicated methods for inferential methods.

7.4. Inferential analysis and statistical models

7.4.1. Cellular-mediated immune response

See section 6.3.1 for statistical method.

A similar analysis as describe in section 6.3.1 and 7.1.2.1will be implemented on the post-vaccination frequency of CD4 T cells producing at least two different cytokines following induction.

The model is defined as follow:

$$y_{ijk3} = \gamma_j + \mu_k + \alpha.x_{ijk} + \beta.y_{ijk0} + \varepsilon_{ijk}$$

$$\hat{y}_j \left| \bar{y}_0, \bar{x} \right. = \gamma_j + \mu_k + \alpha.\bar{x} + \beta.\bar{y}_0$$

$$\varepsilon_{ijk} \approx N(0, \sigma),$$

y_{ijk3} = log-*transformed frequency following induction with antigen for subject* i,*treatment* j *and age cohort* k *at month* 3

y_{ijk0} = log-*transformed frequency following induction with antigen for subject* i,*treatment* j *and age cohort* k *at pre-vaccination*

x_{ijk} = log-*transformed frequency following induction with medium only (background)*

$\bar{y}_0$ = *mean of* log-*transformed frequency following induction at pre-vaccination*

$\bar{x}_0$ = *mean of* log-*transformed frequency following induction at pre-vaccination*

Example of SAS code

1 - Overall analysis

```
PROC GLM DATA=file;
  BY    v_id;
  CLASS pid treatment agecat;
  MODEL Log(frequency of induction at month 3)] = agecat
                                                  treatment
              Log(frequency of induction at pre-vaccination)]
              Log(frequency of background)] ;

  LSMEANS treatment / AT MEANS CL DIFF=CONTROL("Placebo") ALPHA=0.05
  ;

  ODS OUTPUT LSMEANS=lsm;
  ODS OUTPUT DIFFS=dif;
RUN;
```

2- By subgroup analysis

The same model will be applied for each age strata and for each region

7.4.2. Humoral immune response

See section 6.3.2 for statistical method.

A similar analysis as describe in section 6.3.2 and 7.1.2.1will be implemented on the post-vaccination anti-gE ELISA titers.

The following SAS code will be used to perform this analysis.

1 - Overall analysis

```
PROC GLM DATA=file ;
      CLASS pid treatment agecat;
      MODEL log(antibody concentrations) = agecat treatment
            Log(antibody concentration at pre-vaccination) ;
  LSMEANS treatment / AT MEANS CL DIFF=CONTROL(“Placebo”) ALPHA=0.05
  ;
 ODS OUTPUT LSMEANS=lsm;
 ODS OUTPUT DIFFS=diff;
RUN;
```

2- By subgroup analysis

For each age strata and each region, a similar model will be used.

7.5. Sensitivity analyses

Sensitivity analyses will include additional effects for region levels and appropriate interactions in the model in order to provide estimations and 95% CI by region.

The following interactions below will be implemented. The effects that are not significant at the 5 % level will then be removed, provided it does not change the conclusion.

```
MODEL Log(frequency of induction at month 3)]  =
treatment
agecat agecat*treatment
region region*treatment
region*agecat*treatment
Log(frequency of induction at pre-vaccination)
agecat*Log(frequency of induction at pre-vaccination)
region*Log(frequency of induction at pre-vaccination)
Log(frequency of background)
agecat*Log(frequency of background)
region*Log(frequency of background)
```

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in the protocol will be described and justified in the final study report.

Description	Analysis ID (SDD sub-folder)
Final HZ efficacy Analysis	Analysis_E1_35
End-of-study Analysis	Analysis_E1_XX

8.2. Statistical considerations for interim analyses

Not applicable.

8.3. Final HZ efficacy and end-of-study analysis

Two analyses are planned, in each analysis all objectives will be assessed. The first analysis (final HZ efficacy analysis) will be considered as primary analysis for any inferential analysis. The end-of-study analysis will provided the complete analysis of the full data available at the end of study and serve as confirmatory analysis for the objectives demonstrated at previous steps.

Blind will be maintained through the end-of-study analysis. Individual listings will only be provided to the Firewall Team / added to an unblinded report version if applicable

9. CHANGES FROM PLANNED ANALYSES

The following criterion is added to eliminate subjects from the ATP cohort for safety

- Who meet all eligibility criteria
- for whom administration site of study vaccine/placebo is known***/correct***;
- who have not received other vaccine forbidden in the protocol (Section 6.6.1 from protocol);

In addition, subjects who received medication forbidden in the protocol will be only excluded from the ATP cohort for immunogenicity but included in the ATP cohort for safety

The following criterion is not used to eliminate subjects from the ATP cohort for safety **"with sufficient data to perform an analysis of safety (at least one dose with safety follow-up)**. The reactogenicity analyses will be performed on the subjects with diary cards returned, therefore the subjects without diary cards will not be included in the analysis. In the analysis of AEs, the subjects who did not report any event will be considered without event.

For the purpose of the ATP analysis of immunogenicity, the specific interval for blood sampling taken after the second dose of HZ/su has been set at 28-48 days instead the protocol-defined interval between study visits of 30-48 days.

The first time window (0-3 months) used for safety analyses (SAEs, PIMDs and fatal events) have been modified according to standard time window used in Zoster program (from dose 1 to one month post dose 2).

The vaccine response rate (VRR) in CMI have been modified and adapted with the new definition included on protocol amendment.

Additional descriptive immunogenicity analysis will be also provided by country.

10. AMENDMENT

A separate SAP will be written for the analysis of the correlate of protection.

Section 2

The order of the group in the table has been switch; the vaccine group will be first and placebo group at second position.

Section 5.1

The subjects from the closed site Genova will be excluded from the TVC.

Section 5.3

Wrong administration side is allowed

And clarification has been made on the following bullet

- Wrong replacement or study vaccine administered ***(not compatible with the vaccine regimen associated to the treatment number).***

Section 5.4

The following criterion is added to eliminate subjects from the ATP cohort for safety

- Who meet all eligibility criteria
- who have not received other vaccine forbidden in the protocol (Section 6.6.1 from protocol);

In addition, subjects who received medication forbidden in the protocol will be only excluded from the ATP cohort for immunogenicity but included in the ATP cohort for safety. Also, the administration site of the study vaccine/placebo should be correct.

Section 5.5

Interval allowed for the analysis has been enlarged as compared to the protocol defined interval and wording has been adjusted.

Section 6.1

Analysis for CTRS posting have been added

Section 6.2.1

For fever analysis, the summary will be presented by half cumulative degree increment.

For SAE analysis, the following analysis has been added

Proportion of subjects reporting at least one serious adverse events classified by MedDRA Primary System Organ Class and Preferred Term by time window and overall (eg 0-29 days, 0-3 months, 0-8 Months ,3-8 month, 8-14 month and more than 14 month) will be tabulated, with exact 95% CI.

For pIMD analysis, different time windows have been revised to summarize the proportion of subjects with pIMDs. The following analysis

The proportion of subjects with at least one report of pIMDs during the entire study period will be tabulated overall and by time window (eg 0-6 month, 6-12 month and more than 12 month).

Has been replaced by

The proportion of subjects with at least one report of pIMDs during the entire study period will be tabulated overall and by time window (eg 0-3 month, 3-8 month, 8-14 month and more than 14 month) will be tabulated, with exact 95% CI.

For fatal outcome analysis, different time windows have been revised to summarize the proportion of subjects with fatal outcome. The following analysis

Proportion and incidence rate of subjects with fatal outcome will be tabulated overall and by time window (0-3 months, 3-6 months, 6-12 months and more then 12 months after dose 1.

Has been replaced by

The proportion of subjects with fatal outcome during the entire study period will be tabulated overall and by time window (eg 0-29 days, 0-3 month, 3-8 month, 8-14 month and more than 14 month) will be tabulated, with exact 95% CI.

Proportion of subjects experiencing an HZ episode using pain medications by type (opioids, non-narcotics, antidepressants, miscellaneous) will be tabulated.

Has been replaced by

Proportion of subjects experiencing an HZ episode using pain medications by type (Aspirin, Paracetamol, NSAIDs, Opioids, Topicals, Others (antiepileptics, antidepressants, …)) will be tabulated.

The following analysis has been added

Proportion of subjects of subjects with, HZ-related complications and overall and HZ-related hospitalizations, will be tabulated overall and by time window. (eg 0-29 days, 0-3 month, 3-8 month, 8-14 month and more than 14 month)

Analysis for CTRS posting have been added

Additional analysis on fever by route have been proposed

SAEs and pIMD for subjects from the closed centers will be described in details

Section 6.2.2

The exact confidence interval for the relative risk between the two groups will be displayed instead of the standardized asymptotic confidence interval of the difference.

Section 6.3.2

The following analysis have been added

Mean Geometric Increase (MGI) with exact 95% CI for anti-gE

Distribution of the fold increase i.e Percentage of subjects with a more than X-fold (e.g. >2, >4, >6,..-fold) increase will be tabulated per group with 95%CI.

Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max) of Mean Geometric Increase (MGI) for anti-gE

Section 6.3.3

The following analysis have been added

Mean Geometric Increase (MGI) with exact 95% CI for anti-gE

Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max) of Mean Geometric Increase (MGI) for anti-gE

Distribution of the fold increase i.e Percentage of subjects with a more than X-fold (e.g. >2, >4, >6,..-fold) increase will be tabulated per group with 95%CI.

Section 6.3.4

Specific SAP will describe the methodologies will be used for the analysis of the correlate of protection

And so, Further details will be provided in SAP of ZOSTER-022 has been removed from the text

Section 7.2.1.2

For the inference analysis, no data will be removed even for concentration below the cut off. And so, the following statement has been removed :

For inferential analyses, those concentrations below the cut-off will be considered as missing to avoid potential influential data.

11. REFERENCES

Dunning A. A model for immunological correlates of protection. Statist. Med. 2006, 25:1485–1497.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika, 1934; 26: 404-413.

Statistical Analysis Plan Approval

Protocol Title:	Efficacy, safety, and immunogenicity study of GSK Biologicals' Herpes Zoster vaccine GSK1437173A in adults aged above 50 years.
eTrack study number	110390
eTrack abbreviated title	ZOSTER-006
Protocol version/date	Amendment 2 (16 March 2012)
Scope:	All efficacy data pertaining to the above study
Version:	Version 1
Date:	23-Mar-2012
Co-ordinating author:	[redacted]
Other author(s):	

Approved by:

Lead Clinical Development Director	[redacted]		
	Name	Signature	dd-mmm-yyyy
Clinical Development Director	[redacted]		
	Name	Signature	dd-mmm-yyyy
Lead Statistician	[redacted]		
	Name	Signature	dd-mmm-yyyy

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The SAP is divided into 2 parts: the first part details the analyses to be performed (current document) and the second part, annex (-es) (called TFL) describes the flow and format of tables, figures and listings to be annexed to the SR.

1. DOCUMENT HISTORY

Date	Version	Description
23-Mar-2012	First Version	Futility analysis and Efficacy objectives

2. STUDY DESIGN

The following group names will be used for the statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote	Pooled Groups label in tables
1	gEAS01B	gE/AS01B	NA
2	Placebo	Placebo	NA

3. OBJECTIVES

As per protocol

4. ENDPOINTS

As per protocol

5. STUDY POPULATION

5.1. Total Vaccinated cohort

The Total Vaccinated cohort (TVc) will include all vaccinated subjects (at least one dose) with respect to the vaccine actually administered.

5.2. Modified Total Vaccinated cohort

The mTVc will be the primary population for efficacy analysis, which excludes subjects in the TVc from efficacy analysis who did not receive two doses of the planned vaccine or who develop a confirmed case of herpes zoster (HZ) prior to 1 month (30 days) after the second vaccination.

5.3. According To Protocol cohort for analysis of efficacy

The According To Protocol cohort (ATPc) for analysis of efficacy will include all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom efficacy data concerning endpoint measures are available, but excluding all subjects who developed a confirmed case of HZ prior to 1 month (30 days) after the second vaccination. The list of criteria used to exclude subjects from ATPc will be defined prospectively prior to database freeze.

The ATPc will be the analysis set for supportive efficacy analysis, only including subjects who developed a confirmed case of HZ during the follow-up period starting from 1 month after the second vaccination (Month 3).

Cohort	Elimination codes	Eli Type
ATP cohort for analysis of efficacy	[3010 to 3500]	MA
mTVC	1050-1070-1500-1510	FU/MA
TVC cohort	1030 (subjects not vaccinated)	MA

6. STATISTICAL METHODS

6.1. Interim analysis for futility

One futility analysis is planned. The following conditions are planned prior to futility analyses of vaccine efficacy against HZ in study ZOSTER-006. The number of HZ cases mentioned refers to the cases in the primary cohort for efficacy (mTVC).

1. At least 49 HZ cases across all age group in ZOSTER-006;
2. At least :
    a. 11 HZ cases in subjects in the 50-59 years of age (YOA) stratum in ZOSTER-006;
    b. 12 HZ cases in subjects in the 60-69 YOA stratum in ZOSTER-006;
    c. 15 HZ cases in subjects in the 70+ YOA strata in both ZOSTER-006 and ZOSTER-022.

6.1.1. Futility rules agreed by GSK Management

The following futility rule has been agreed by GSK management (ref Futility rules document):

A predictive power of 10% was selected as the threshold below which the ZOSTER-006 study would be declared futile.

6.1.2. Statistical methodology for analysis of futility

Two different approaches are proposed to evaluate futility, based on all observed HZ cases from ZOSTER-006 and ZOSTER-022 at futility analysis. The first approach will use a Frequentist approach. The second one will use a Bayesian approach. The primary method will be the Frequentist approach.

6.1.2.1. Frequentist approach

This approach has three steps:

1. Vaccine efficacy (VE) and relative risk (RR) for HZ will be tabulated for each age stratum (50-59, 60-69 and 70+ YOA);
2. An N-weighted VE, using expected numbers of cases in each age stratum at final analysis in ZOSTER-006 as weight, will be calculated;
3. Calculate the predictive power based on the calculated N-weighted VE and other parameters used when setting up the futility criteria (O'Brian-Fleming boundaries, assumed VE and criteria of success at final analysis).

6.1.2.2. Bayesian approach

Using all HZ cases accrued from ZOSTER-006 and ZOSTER-022, we will predict the accrual of further HZ cases using interim VE and incidence estimates (or distribution) and analyse both interim and predicted data with the planned method for Final analysis (stratified Poisson). A non-informative Bayesian Poisson ratio model will be built for each of the 3 age-strata, and interim data will be used to estimate the posterior distribution of VE and incidence. The accrual of further HZ cases up to the final analysis will be simulated, using posterior predictive distribution, and the analysis of interim and simulated cases analysed.

The proportion of simulated trials leading to success would be used as a proxy of the predictive power (probability of success) at final analysis.

6.1.2.3. Testing the futility rule

The predictive powers calculated by both the Frequentist and the Bayesian approachs will be compared to the futility rule.

- If the calculated Predictive power is less than the futility boundary, the study will be declared futile, and the IDMC will provide this statement to the team.
- If the calculated Predictive power is greater than the futility boundary, the study will be declared not futile, and the IDMC will provide this statement to the team.

In case of disagreement between the Frequentist the Bayesian approaches, the Frequentist approach will be considered as primary.

6.2. Final analysis for Efficacy

The primary analysis will be based on the mTVC cohort for analysis of efficacy. A secondary analysis based on the Total Vaccinated Cohort (TVC) and the ATPc for efficacy will be performed to complement the mTVC analysis.

When overall VE is presented, the age stratification factor will include the 3 main age strata. When VE by age is presented, the same model will be run using only the data pertaining to the strata under consideration.

Additional tables will present the overall VE by region and overall VE by time (e.g., using 1-year intervals).

All p-values reported are related to the null hypothesis test VE = 0, or absence of effect of the vaccine, and will account for p-value adjustment for multiple testing scheme when applicable.

6.2.1. Reduction of HZ

The following conditions are planned prior to final HZ analyses of study ZOSTER-006. The number of HZ and PHN cases mentioned refers to the cases in the primary cohort for efficacy.

1. At least 196 HZ cases across all age groups for the overall HZ efficacy analysis;
2. ~75% of the initial sample size (not accounting for any sample-size reassessment) in each strata with at least 36 months follow-up and the remaining subjects having completed at least 30 months follow-up after Dose 2 in order to ensure enough safety data;
3. Approximately 60 HZ cases in subjects 50-59 YOA and approximately 60 HZ cases in subjects 60-69 YOA for the HZ analysis by age in the 50-59 and 60-69 YOA age strata, respectively;
4. A total of at least 88 PHN cases when pooled with ZOSTER-022 PHN cases accrued.

Primary Inferential Analyses

The primary analysis method of the vaccine VE will consider the exact inference on the relative risk stratified for age strata and regions conditionally to the total number of HZ cases observed and time at risk. The method is implemented in the Poisson procedure of the StatXact package provided by Cytel. Relative risks will be calculated overall and by age-strata. Stratification will include age and regions for the overall analysis and region alone when analysis by age strata.

Incidence rates and VE with 95% CI will be tabulated for primary efficacy endpoint. P-value (to test H0 = [VE≤25%]) will be tabulated for the primary endpoint.

The efficacy of ZOSTER vaccine against HZ will be demonstrated if the LL of the two-sided 95% CI of VE is above 25%.

Secondary Inferential Analyses

The elapsed time following the HZ-case exclusion period after the second vaccination to the first HZ episode may be analyzed using Cox's proportional hazard regression stratified for age strata and region with vaccine groups as covariates. Wald test and CIs will be produced.

Ties will be handled using the Efron method. Cox adjusted survival curves will be produced for each combination of vaccine group and age category.

Descriptive statistics

For each treatment group, the number of subjects at risk, person-time, number of confirmed events (HZ) and incidence rate, and incidence of confirmed HZ cases will be tabulated overall and by age strata. The results will be presented over the whole study and by visit interval. Similar tables will describe the median time-to-event and hazard rate.

Survival curves for each vaccine group will be calculated non-parametrically, tabulated and presented graphically overall and by age strata using the Kaplan-Meier (i.e., Product-Limit) method.

Sensitivity analysis of the overall VE after each multiple of 12 months following last vaccination will be provided in order to assess consistency of VE over time.

6.2.2. Secondary objectives

6.2.2.1. Reduction in overall PHN risk

The overall reduction in PHN risk will be evaluated similarly to the HZ risk using the exact inference on the relative risk stratified for age strata and regions conditionally to the total number of HZ cases observed and time at risk. Similarly to the HZ VE, a Poisson distribution for the number of PHN cases under placebo and vaccine groups is assumed.

The efficacy of ZOSTER vaccine against PHN will be demonstrated if the LL of the two-sided 95% CI of VE is above 0%.

6.2.2.2. Reduction of duration of severe 'worst' pain in subjects with an HZ episode

The time-to-cessation of severe 'worst' pain will be analyzed using a survival methodology. The primary analysis will consist in a Cox-proportional model to assess the hazard rate reduction in ZBPI worst pain duration due to the vaccine in those subjects that presented HZ.

The efficacy of ZOSTER vaccine against duration of several worst pain will be demonstrated if the LL of the two-sided 95% CI of VE derived from the Hasard ratio is above 0%.

A change-point piecewise exponential model [Arani, 2001; Desmond, 2002] may be used as sensitivity analysis to compare hazard rates related to acute (0-30 days), sub-acute (30-120 days) and chronic (120+ days) pain between vaccine group and placebo. The cut-off points 30 days and 120 days were suggested according to Desmond [Desmond, 2002]. Those cut-off points may additionally be estimated using the data. The comparisons across both sub-acute pain and chronic pain will be combined using a likelihood-ratio test.

For each treatment group, the number of subjects at risk (with confirmed HZ), number of subjects with severe "worst" pain and incidence rate will be tabulated overall and by age strata. Similar tables will describe the median, median, minimum and maximum duration of severe "worst" pain.

Survival curves for each vaccine group will be calculated non-parametrically and presented graphically overall and by age strata using the Kaplan-Meier (i.e., Product-Limit) method.

6.2.2.3. Reduction of HZ-related mortality and hospitalizations

The reduction of HZ-related mortality and hospitalizations will be evaluated through;

- The vaccine VE will consider the exact inference on the relative risk stratified for age strata and regions conditionally to the total number of HZ cases observed and time at risk. The method is implemented in the Poisson procedure of the StatXact package provided by Cytel. Relative risks will be calculated overall and by age-strata. Stratification will include age and regions for the overall analysis and region alone when analysis by age strata.

The efficacy of ZOSTER vaccine against HZ-related mortality and hospitalizations will be demonstrated if the LL of the two-sided 95% CI of VE is above 0%.

6.2.2.4. Reduction in incidence of HZ associated complications

The overall incidence of HZ associated complications, in subjects with an HZ episode, overall and by age group will be presented and compared with placebo using asymptotic standardized unconditional binomial test [Miettinen, 1985]. The analysis will be stratified by age group and weights associated to each stratum will be pre-specified.

The efficacy of ZOSTER vaccine against HZ associated complications will be demonstrated if the LL of the VE is above 0%.

6.2.2.5. Reduction in use of pain medications

The reduction in use of pain medication will be evaluated through;

- The vaccine VE will consider the exact inference on the relative risk stratified for age strata and regions conditionally to the total number of HZ cases observed and time at risk. The method is implemented in the Poisson procedure of the StatXact

package provided by Cytel. Relative risks will be calculated overall and by age-strata. Stratification will include age and regions for the overall analysis and region alone when analysis by age strata.

The efficacy of ZOSTER vaccine in reduction in use of pain medications will be demonstrated if the LL of the two-sided 95% CI of VE is above 0%.

All analyses will be presented overall and by age strata. The main age strata for reporting purposes are 50-59, 60-69 and ≥70 YOA. In addition, the results for the ≥ 70 YOA stratum will also be presented separately for 70-79 and ≥ 80 YOA subjects. The study is not powered prospectively to demonstrate efficacy in these 2 sub-strata taken separately. Another set of analyses in subjects ≥ 60 YOA will also be presented.

Any exploratory or sensitivity analysis may be performed in addition to the analyses described below on an ad-hoc basis. The significance level of those analyses may not however be fully controlled.

6.2.3. Exploratory objectives

6.2.3.1. Reduction in Burden-of-Illness

The overall reduction in Burden-of-Illness will be evaluated through:

- The "Chop-lump" test [Follmann, 2009] for the overall reduction in Burden-of-Illness scores in all subjects between vaccine and placebo will be implemented and compared to the original analysis of the Burden-of-Illness proposed by Chang, 1994;
- VE with respect to the BOI due to HZ (VE BOI) is defined as the relative reduction in the BOI score in the vaccine group as compared with that in the placebo group and calculated as 1 - relative risk (i.e., 1- the HZ BOI score in the vaccine group divided by the HZ BOI score in the placebo group).

6.2.3.2. Reduction in HZ severity score

The reduction in HZ severity score will be evaluated through:

- The "Chop-lump" test [Chang, 1994] for the reduction in HZ severity scores in subjects with HZ between vaccine and placebo will be implemented.

The HZ severity analysis applies to subjects with HZ and includes the first 4 weeks following the HZ episode.

Additional analyses may be performed using partial AUC, calculated from 0 to specific elapsed time after HZ onset. That approach accounts partially for any difference in pain score profiles or pattern (e.g., long duration with low scores versus short score with high scores) even though subjects may have the same overall AUC.

6.2.3.3. Reduction in PHN incidence in subjects with an HZ episode

The reduction in PHN incidence in subjects with an HZ episode will be evaluated through:

- The incidence of PHN in subjects with an HZ episode, overall and by age group will be presented and compared with placebo using asymptotic standardized unconditional binomial test [Miettinen, 1985]. The analysis will be stratified by age group and weights associated to each stratum will be pre-specified.

6.2.3.4. Improvement of subject's quality of life by ZBPI

Descriptive statistics and inferential analysis of QoL subscale of ZBPI (item 9: questions A to G) total scores and scores per item over time will be provided overall and by age group.

7. STATISTICAL CALCULATIONS

7.1. Derived and transformed data

7.1.1. Handling of missing data

For a given subject and a given efficacy measurement, missing or non-evaluable measurements will not be imputed for the primary analysis. The missing endpoint and censoring are supposed to occur independently, and the pattern of the missingness being either Completely At Random (MCAR) or Missing At Random (MAR) only.

Sensitivity analyses will be pre-specified prior to unblinding for each main efficacy endpoint in order to assess the sensitivity of the conclusions to missing-data pattern. When repeated measurements are planned, primary methodology will include mixed effect model for repeated measurement analysis [Mallinckrodt, 2008].

7.1.2. Efficacy data

The HZ incidence rate is determined with reference to the first confirmed HZ case observed in the patient, should several HZ cases occur in the same subject.

The HZ-free period for a subject is calculated from HZ onset to time zero relative to the cohort considered: first vaccination for TVc and beyond the HZ-case exclusion period following the second injection for mTVc and ATP.

The number of Person-Years at risk over an interval of time is the sum of the confirmed HZ-free episodes over all subjects at risk during that interval, either up to the cut-off date for the analysis, the censoring date or the occurrence of the first HZ case for a subject.

RR is defined as the ratio of the incidence rates of the vaccine group over the placebo group.

VE is defined as the 1 – RR.

The following outputs will be derived from the efficacy data recorded using the ZBPI:

Duration of severe worst pain

For each confirmed HZ cases the follow up time is considered as starting from the date of HZ episode and ending the last day of ZBPI questionnaire period. The confirmed HZ cases without severe "worst" pain are considered as non-event cases. The cases with severe "worst" pain are considered as an event cases, their time to event is calculated as being the difference between their follow up time period and duration of pain. Those transformations allow computing vaccine efficacy in term of severe "worst" pain-free period.

HZ burden-of-illness score

For each confirmed case of HZ, responses to the "worst pain" question in the ZBPI are used to calculate a "HZ severity-of-illness" score, defined as the area under the curve (AUC) of HZ-associated pain plotted against time during the 182-day period after the onset of the case. Subjects developing HZ will present "severity-of-illness" scores ranging from 0 up to, theoretically, 1820. A score of 0 is recorded for subjects in whom HZ did not develop during the study period.

HZ severity score

The methodology described for the HZ burden-of-illness score will be applied to the 4 weeks during which a daily measure is taken and provide the HZ severity score. The HZ severity score will apply only to subjects with HZ. Subjects not infected with HZ will not take part in this analysis.

7.2. Number of decimals

The following decimal description will be used for the efficacy analyses.

Display Table	Parameters	Number of decimal digits
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2
All summaries	p-value	3
Efficacy	VE, including LL & UL of CI	2
	IR	2
	T, T/N	1
	p-value	3

7.3. Primary method for Vaccine Efficacy:

VE will consider the exact inference on the relative risk stratified for age strata and regions conditionally to the total number of HZ cases observed and time at risk. Stratification will include age and regions for the overall analysis and region alone when analysis by age strata.

This method computes an exact confidence interval (CI) around the rate ratio (ratio of the event rates in the vaccinated versus control group) and takes into account the follow-up time of the subjects within each group. VE is then defined as 1 minus the rate ratio.

The follow-up time for each subject will start

- at the day after first vaccination (Month 0) if analyses are done on the Total vaccinated cohort for efficacy, or
- at 30 days after second vaccination (Month 3) if analyses are done on the mTVC or ATP cohort for efficacy.

The follow-up time for each subject will end

- at the time of the event; or,
- at date of last visitfor subjects who completed the study and did not have an event; or,
- at the latest visit for which data is available for subjects who did not yet complete the study at the time of the interim analysis or final analysis (if criteria to reach final analyses are met before all subjects complete their last visit) and did not have an event:
    - For HZ endpoints, we take the minimum date of the start of the rash or start of the pain to assess the HZ, whichever comes first.

The follow-up time will be calculated in days as Date of end of follow-up period – Date of vaccination, and expressed in person-years at risk (number of days/365.25).

7.4. Vaccine Efficacy using Cox regression model

In addition to the primary analysis, VE and its CI will also be calculated using a Cox regression model. This methodology can take into account specific risk factors which might have been imbalanced, by chance, at the beginning of the trial between the vaccinated and control group. Risk factors that will be investigated are age strata and country. VE is then calculated as 1 minus the hazard ratio.

Cox regression assumes proportional hazards throughout the follow-up period. This assumption will be checked by a test based on the Schoenfeld residuals.

If there is strong evidence that the hazard rate is not constant over the surveillance period, then a non-parametric analysis will be performed.

7.5. Time-to-first event methodology: follow-up time and status

The study participants will be actively followed for the occurrence of HZ, PHN and use of pain medications during entire study follow up. The events linked to primary and secondary efficacy outcomes (with onset time) will be identified and in case multiple events are observed for the same subject, only the first event will be considered.

For **primary and secondary endpoints**, the follow-up time and the status will be recorded as follows:

- If the subject gets his/her first event of corresponding primary or secondary endpoints during the study follow up period, the status will be 1 and the associated time will be the number of days between start date of the considered period (30 days after last study vaccination) and the date of the appearance of the event. If he/she gets the same event afterwards, it will not be considered in the analysis.
- If a subject does not get the event of corresponding endpoint during the study follow up, the status will be 0 and the associated time will be the number of days the subject is followed (if a subject is dropped-out from the study, his/her date of last contact will be taken into account).
- Subjects meeting censoring criteria will be included in the analysis.

7.6. Methods for Confidence Intervals (CIs)

7.6.1. CIs for Vaccine Efficacy

7.6.1.1. Poisson distribution

The CI for vaccine efficacy can then be derived from the exact CI from RR (Miettinen, 1985). This method is implemented in the Poisson procedure of the StatXact package provided by Cytel.

7.6.1.2. Binomial distribution

The Vaccine Efficacy (VE) can be estimated by:

$$VE = 1 - \frac{n1/N1}{n2/N2} = 1 - \frac{n1}{r * n2}$$

where n1 = number of cases in the vaccinated group

N1 = follow-up time the vaccinated group

n2 = number of cases in the control group

N2 = follow-up time in the control group

$$r = \frac{N1}{N2}$$

Conditionally to the total number of cases n = n1+ n2 and r, let p denote the proportion of cases in the vaccine group,

$$VE = 1 - \frac{n1}{n} * \frac{n}{r*(n-n1)} = 1 - p * \frac{1}{r*(1-p)} = 1 - \frac{p}{r*(1-p)}$$

where p = n1/n is binomially distributed.

Therefore, there is a monotonic link between VE, the true vaccine efficacy, and p, the true proportion of subjects in the vaccine group among the total cases in the two groups.

The CI for vaccine efficacy can then be derived from the exact CI from p (Dragalin, Fedorov and Cheuvart, 2002). This method is implemented in the Binomial procedure of the StatXact package provided by Cytel.

7.6.1.3. Cox regression

The CI for vaccine efficacy can then be derived from the Wald CI from Hazard Ratio. This method is implemented in the PHREG procedure of the SAS/STAT package (SAS V9.2).

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Description	Analysis ID (SDD sub-folder)	TFL short title
Futility analysis at 25% of HZ accrual	2	Interim
Final Analysis	1	Final
End of study analysis	EOS	EOS

8.2. Prior to Final Analysis

Blinded review of efficacy data will be performed in order to anticipate rate of accrual of HZ events within each age strata.

Unblinded evaluation of futility efficacy will be performed by the IDMC.

8.3. Statistical considerations for interim analysis

When 49 confirmed HZ cases have accrued in ZOSTER-006 and at least 20% of HZ cases are observed in each age strata [50-59 years], [60-69 years] and [70+ years] (see section 6.1), an interim analysis for futility will be performed.

8.3.1. Interim analysis for Benefit

GSK has no plan to proceed with early registration for efficacy (i.e., following the interim analysis) due to the following reasons:

- The expected low accrual rate of PHN cases and the need to collect a sufficient number of events to achieve a robust estimate of PHN VE;
- The duration of protection conferred by the vaccine is an important characteristic and because this futility analysis occurs at an early stage of the trial it will not be able to provide the required data if the study is stopped prematurely;
- Accumulation of longer term safety data than will be available at the interim analysis.

If the futility analysis occurs and leads to a recommendation by the IDMC to file prior to study end for ethical reasons, it is mandated that, prior to final analysis, the significance level for all primary objectives, and also key secondary objectives, is set to 0.0001 for both HZ and overall PHN, considering the alternative hypotheses of true vaccine efficacies above 40%. As a consequence, the significance level of the final analysis will be adjusted to 4.9998% 2-sided.

8.3.2. Interim analysis for Futility

Two different approaches are proposed, based on all observed cases in both ZOSTER-006 and ZOSTER-022 at interim. The first approach will calculate the predictive power using a Frequentist approach. The second one will evaluate the predictive power using a Bayesian approach.

8.3.2.1. Frequentist approach

This approach has three steps:

1. VE and RR for HZ will be tabulated in each age stratum (50-59, 60-69 and 70+ YOA);
2. An N-weighted VE, using as weight the expected number of HZ cases in each age stratum at final analysis in ZOSTER-006, will be calculated;
3. Calculate the predictive power based on the calculated N-weighted VE and other parameters used when setting up the futility criteria (O'Brian-Fleming boundaries, assumed VE and Criteria of success at final analysis).

Evaluate Vaccine efficacy in each strata

Using all cases retrieved in both ZOSTER-006 and ZOSTER-022, we will evaluate VE in each of the three following age strata (50-59, 60-69 and 70+ YOA).

The method used will be similar to the method described in section 7.1.2. VE and 95% CI will be tabulated.

Evaluate N-Weighted Vaccine efficacy

Using details given in Appendix 1:

1. Calculate RR (as 1-VE) and Loge (RR) of each of the three age strata;
2. Calculate the Weight of each age stratum as expected number of cases at final analysis (using incidence rates of the interim analysis) (noted wi; i = 1 to 3);
3. Calculate the sum of weighted Loge(RR) of the three age strata and divide by the sum of weights;
4. Use the back transformation (1-exp(.)) to retrieve the correspondent weighted VE.

The 95% CI is approximated from the Asymptotic normality of the Loge(RR) and the associated variance of the Loge(RR) from Agresti (1990):

1. Calculate the Standard Error (SE) of RR in each of the three age strata by
   SE = sqrt((1/(nv+0.5))-(1/(Nv+0.5))+(1/(np+0.5))-(1/(Np+0.5)));
2. Calculate the global SE using the Variance properties by
   SE = sqrt((Sum wi^2 SE^2) / (sum wi)^2);
3. Calculate 95% CI as Loge(RR)± 1.96 SE and deduce by back transformation the 95% CI of weighted VE.

The weighted VE calculated is noted as N-weighted VE, more details are provided in Appendix 1.

Calculate predictive power

The two following SAS procedures will be used to calculate the predictive power. The SEQDESIGN procedure used to evaluate designs interim analyses and the SEQTEST procedure performs the interim analyses based on the sample sizes and boundary values produced by the SEQDESIGN procedure.

1. Based on the O'Brian-Fleming Method, evaluation of the boundary values using the PROC SEQDESIGN:

   The SEQDESIGN procedure designs interim analyses for clinical trials. PROC SEQDESIGN computes the boundary values for the trial. The boundary values are derived in such a way that the overall Type I and Type II error probability levels are maintained at the levels specified in the design. Method chosen is the O'Brian-Fleming method. The SEQDESIGN procedure computes the boundary values. The following parameters have been fixed (during the determination of the futility rules) : Assumed VE = 69% , Criteria of success LL > 25%, Gamma = -5 (Gamma family sepnding function linked to O'Brian-Fleming boundaries), Beta = 0.0031 (Type II error), Alpha = 0.025 (Type one error)

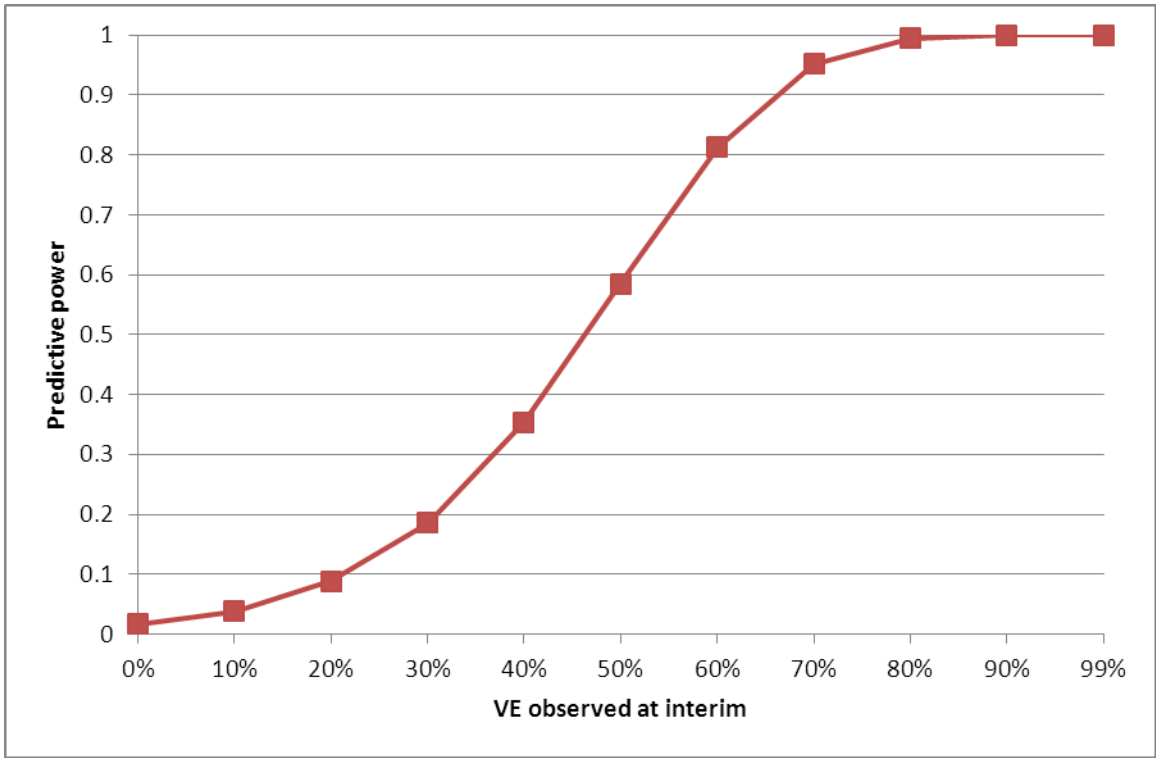
2. Calculate the Predictive power using the PROC SEQTEST:

Based on the weighted VE calculated at interim, the SEQTEST procedure compare the test statistic on interim data with the corresponding boundary values computed by the SEQDESIGN procedure and provide the predictive power.

The predictive power calculated is the posterior probability that the test statistic at the final stage would exceed the rejection critical value given the observed statistic and a prior distribution of the hypothetical reference. A non-informative prior is used in the procedure.

Illustration of the predictive power for different VE observed at interim is given in the figure 2.

Figure 1 Predictive power to demonstrate the primary objective with lower limit of 95% CI ≥ 25% for different observed VEs with 49 cases



8.3.2.2. Bayesian approach

All HZ cases accrued from ZOSTER-006 and ZOSTER-022 will be used.

A Bayesian framework is used to simulate accrual of HZ cases in each age stratum under vaccine and placebo over the period of time between interim and final analysis.

The duration of accrual is determined in order for the median number of HZ cases to reach between 196 and 200 over the 3 age strata. The joint posterior distribution of placebo incidence and vaccine efficacy is calculated separately for each age stratum using unblinded interim data and non-informative priors.

The joint distribution of the number of HZ cases under placebo and vaccine is simulated based on the joint posterior distribution of placebo incidence and vaccine efficacy and assuming (conditionally) independent Poisson distribution for the number of HZ cases.

Provided that the sum of simulated HZ cases across the 3 age strata is between 196 and 200, the simulations are analysed using the frequentist methodology planned for the final analysis.

A success is considered when the LL of the 95% confidence interval for VE is above 25%.

The probability of success of the final analysis given the interim data is estimated as the ratio of successes over the total number of simulations presented a total of 196 to 200 HZ cases.

Details on the Bayesian framework is described in Laurent & Legrand (2011).

8.3.2.3. Testing the futility rule

Both predictive powers calculated by the frequentist approach will be compared to the futility rule.

- If the Predictive power calculated is less than the futility boundary, the study will be declared futile, and the IDMC will provide this statement to the team.
- If the Predictive power calculated is greater than the futility boundary, the study will be declared not futile, and the IDMC will provide this statement to the team.

The IDMC will have access to the full analysis results and will provide GSK the applicable statement.

8.4. Final analysis

When the conditions for triggering the final analysis of efficacy have been reached, the final analysis cut-off date will be defined. Any HZ episode occurring prior to the final analysis cut-off date will be followed**,** as described in the protocol, until the case of suspected HZ is disproved, OR until a 4-week pain-free period is documented, OR until the cut-off date for final analysis. For all subjects with ongoing HZ-associated pain-at the time of cut-off date for final analysis, ZBPI data will be collected until suspected HZ is disproved, OR until a 4-week pain-free period is documented OR until at least Day HZ-90 in order to document potential PHN episodes**.**

Following achievement of criteria triggering analyses, final data collection and data cleaning, the write access to the clinical database will be removed and all eCRF data will become available for final analysis. A first report will document efficacy and safety results and provide immunogenicity results using descriptive methodology.

Analysis of correlate of protection may require extensive exploratory analyses and may be available as an annex report after completion of the primary report. Persistency data may be also provided in annex reports.

9. CHANGES FROM PLANNED ANALYSES

No changes from protocol planned analyses.

10. REFERENCES

[Alan] Alan Agresti. Introduction to categorical analysis. 1990.

Arani RB., Soong S-J, Weiss HL, et al. Phase specific analysis of herpes zoster associated pain data: a new statistical approach. *Statist., Med.* 2001;20:2429–2439.

Chan ISF, Wang WWB, Heyse J. Encyclopedia of Biopharmaceutical Statistics. *Vaccine Clinical Trials*. 2003;1005–1022.

Chang MN, Guess HA, Heyse JF. Reduction in burden of illness: a new efficacy measure for prevention trials. *Stat Med.*1994;13:1807–1814.

Cohen JI, Straus SE, Arvin AM. Varicella zoster virus and its replication. 2007; p. 2774-2818. In D. M. Knipe and P. M. Howley (ed.), *Fields virology*, 5th ed. Lippincott/The Williams & Wilkins Co., Philadelphia, PA.

Coplan PM, Schmader K, Nikas A, et al. Development of a measure of the burden of pain due to herpes zoster and postherpetic neuralgia for prevention trials: adaptation of the brief pain inventory. *J Pain*. 2004;5(6):344–356.

Desmond Renee A, Weiss Heidi L, Arani Ramin B, Soong Seng-jaw, Wood Martin J, Fiddian Paul A, Gnann John W, Whitley Richard J. Clinical Applications for Change-Point Analysis of Herpes Zoster Pain. *Journal of Pain and Symptom Management.* 2002, 23:510–516.

Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis.* 2007;44 Suppl 1:S1–26.

Dworkin et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. *The Journal of Pain*. 2008;9(2):105–121.

Farrar JT, Young JP Jr, LaMoreau L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on a 11-point numerical pain rating scale. *Pain*. 2001;94:149–158.

Follmann DA, Fay MP, Proschan, MA. Chop-lump tests for Vaccine trials. *Biometrics.* 2009;65: 885–893.

Hanley and Lippman-Hand. If nothing goes wrong, is everything all right? Interpreting zero numerators. *JAMA.* 1983;249:1743–1745.

Laurent S, Legrand C., 2011, A Bayesian framework for the ratio of two Poisson rates in the context of vaccine efficacy trials. ESAIM: Probability and Statistics, doi:10.1051/ps/2010018

Mallinckrodt C, Lane P, Schnell D, Peng Y, Mancuso J. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials, *DIJ*. 2008;42:303–319.

Miettinen OS, Nurminen M. Comparative analysis of two rates. *Statistics in Medicine*. 1985; 4:213–226.

Oxman MN, Levin MJ, Johnson GR, et al. Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352:2271–2284.

Rowbotham MC. What is a “Clinically meaningful” reduction in pain? *Pain*. 2001;94:131–132.

11. ABBREVIATIONS

ATP	According-To-Protocol
AUC	Area Under Curve
BOI	Burden-Of-Illness
CI	Confidence Interval
Eli_type	Internal GSK database code for type of elimination code
eCRF	Electronic Case Report Form
HZ	Herpes ZOSTER
GSK	GlaxoSmithKline
IDMC	Independent Data Monitoring Committee
IR	Incidence Rates
LL	Lower limit
MAR	Missing At Random
MCAR	Missing Completely At Random
mTVc	Modified Total Vaccinated Cohort
N.A.	Not Applicable
OTH	Other
PHN	Postherpetic Neuralgia
QoL	Quality of Life
R	R free software from free fondation software
RDE	Remote Data Entry
RR	Relative Risk
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBIR	GSK Biological's Internet Randomization System
SE	Standard Error
sqrt	Square root
SR	Study Report
SYN	Synopsis
TFL	Tables Figures and Listing template annexed to SAP
TVc	Total Vaccinated Cohort
UL	Upper Limit

VE	Vaccine Efficacy
YOA	Years Of Age
ZBPI	Zoster Brief Pain Inventory

APPENDIX 1 N-Weighted Vaccine efficacy

The N-weighted estimate of vaccine efficacy is used to yield a single estimate of efficacy across the different age strata. At time of futility analysis, all cases accrued in ZOSTER-022 will be also used in the evaluation of the futility rule in order to account for all information available at this time.

The Stratified Poisson analysis planned for the final analysis use implicitely the number of cases accrued in each strata as weight. In order to correct the bias made by including the cases from ZOSTER-022 (only in the [70+ years] strata, we propose to use the weighted VE (using number of cases by strata expected at final analysis as weight) as estimation of the vaccine efficacy at futility analysis.

Expected value of VE : The mean (or expected value of) VE across the three strata can be computed and be used as a measure of central tendency, to characterize the average VE that can be expected in the ZOSTER-006.

Definition of Expected value: For a random variable X with two possible values (x1, x2) with corresponding probabilities (p, q), the mean (or expected value) of the random variable X is defined as:

Expected value = mean =E(X) =x1.p = x2.p (13.1)

The expected value of VE across the three strata that can be computed and used to characterize the average VE that can be expected from the FAS may be obtained analogously using the computations shown in Equation 13.1 as follows.

Calculation of Expected values of VE: Let the expected value of VE be denoted by E(VE). Then E(VE) cane be computed as

E(VE) = 100% x (1-exp(Expected value of loge [relative risk])) (13.2)

The rationale for such a computation is that the estimate of loge[relative risk] that is asymptotically normally distributed.. The asymptotic normal distribution property of the estimate of loge[relative risk] can be used to obtain a 95% confidence interval corresponding to the estimate of E (VE). The N-weighted average estimate of vaccine efficacy in the FAS were computed based on the calculations given in Equation 13.2. The use of the term "N-weighted" arises from the calculation of the expected value of loge[relative risk].

Statistical Analysis Plan Approval

Protocol Title:	Efficacy, safety, and immunogenicity study of GSK Biologicals' Herpes Zoster vaccine GSK1437173A in adults aged above 50 years.
eTrack study number	110390
eTrack abbreviated title	ZOSTER-006
Protocol version/date	Amendment 2 (16 March 2012) ***Amendment 4 (18 Apr 2014)***
Scope:	All efficacy data pertaining to the above study
Version:	Version ***2***
Date:	***05 May 2014***
Co-ordinating author:	[redacted]
Other author(s):	

Approved by:

Lead Clinical Development Director	[redacted]		
	Name	Signature	dd-mmm-yyyy
Clinical Development Director	[redacted]		
	Name	Signature	dd-mmm-yyyy
Lead Statistician	[redacted]		
	Name	Signature	dd-mmm-yyyy

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The SAP is divided into 2 parts: the first part details the analyses to be performed (current document) and the second part, annex (-es) (called TFL) describes the flow and format of tables, figures and listings to be annexed to the SR.

1. DOCUMENT HISTORY

Date	Version	Description
23-Mar-2012	First Version	Futility analysis and Efficacy objectives
05-May-2014	*Second Version*	*Futility analysis and Efficacy objectives (adaptation to amendment 4 and small corrections)*

2. STUDY DESIGN

The following group names will be used for the statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote	Pooled Groups label in tables
1	***HZ/su***	***Herpes Zoster subunit vaccine***	NA
2	Placebo	Placebo	NA

3. OBJECTIVES

As per protocol

4. ENDPOINTS

As per protocol

5. STUDY POPULATION

5.1. Total Vaccinated cohort

The Total Vaccinated cohort (TVc) will include all vaccinated subjects (at least one dose) with respect to the vaccine actually administered.

5.2. Modified Total Vaccinated cohort

The mTVc will be the primary population for efficacy analysis, which excludes subjects in the TVc from efficacy analysis who did not receive two doses of the planned vaccine or who develop a confirmed case of herpes zoster (HZ) prior to 1 month (30 days) after the second vaccination.

5.3. According To Protocol cohort for analysis of efficacy

The According To Protocol cohort (ATPc) for analysis of efficacy will include all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom efficacy data concerning endpoint measures are available, but excluding all subjects who developed a confirmed case of HZ prior to 1 month (30 days) after the second vaccination. The list of criteria used to exclude subjects from ATPc will be defined prospectively prior to database freeze.

The ATPc will be the analysis set for supportive efficacy analysis, only including subjects who developed a confirmed case of HZ during the follow-up period starting from 1 month after the second vaccination (Month 3).

Cohort	Elimination codes	Eli Type
ATP cohort for analysis of efficacy	*900, 1030-1070, 1500-2010, 2500,3500*	MA/*ES*
mTVC	*900,1030,1050,1070, 1500, 2500, 3500*	FU/MA/*ES*
TVC cohort	*900,* 1030 (subjects not vaccinated)	MA/*ES*

6. STATISTICAL METHODS

6.1. Interim analysis for futility

One futility analysis is planned. The following conditions are planned prior to futility analyses of vaccine efficacy against HZ in study ZOSTER-006. The number of HZ cases mentioned refers to the cases in the primary cohort for efficacy (mTVC).

1. At least 49 HZ cases across all age group in ZOSTER-006;
2. At least :
    a. 11 HZ cases in subjects in the 50-59 years of age (YOA) stratum in ZOSTER-006;
    b. 12 HZ cases in subjects in the 60-69 YOA stratum in ZOSTER-006;
    c. 15 HZ cases in subjects in the 70+ YOA strata in both ZOSTER-006 and ZOSTER-022.

6.1.1. Futility rules agreed by GSK Management

The following futility rule has been agreed by GSK management (ref Futility rules document):

A predictive power of 10% was selected as the threshold below which the ZOSTER-006 study would be declared futile.

6.1.2. Statistical methodology for analysis of futility

Two different approaches are proposed to evaluate futility, based on all observed HZ cases from ZOSTER-006 and ZOSTER-022 at futility analysis. The first approach will use a Frequentist approach. The second one will use a Bayesian approach. The primary method will be the Frequentist approach.

6.1.2.1. Frequentist approach

This approach has three steps:

1. Vaccine efficacy (VE) and relative risk (RR) for HZ will be tabulated for each age stratum (50-59, 60-69 and 70+ YOA);
2. An N-weighted VE, using expected numbers of cases in each age stratum at final analysis in ZOSTER-006 as weight, will be calculated;
3. Calculate the predictive power based on the calculated N-weighted VE and other parameters used when setting up the futility criteria (O'Brian-Fleming boundaries, assumed VE and criteria of success at final analysis).

6.1.2.2. Bayesian approach

Using all HZ cases accrued from ZOSTER-006 and ZOSTER-022, we will predict the accrual of further HZ cases using interim VE and incidence estimates (or distribution) and analyse both interim and predicted data with the planned method for Final analysis (stratified Poisson). A non-informative Bayesian Poisson ratio model will be built for each of the 3 age-strata, and interim data will be used to estimate the posterior distribution of VE and incidence. The accrual of further HZ cases up to the final analysis will be simulated, using posterior predictive distribution, and the analysis of interim and simulated cases analysed.

The proportion of simulated trials leading to success would be used as a proxy of the predictive power (probability of success) at final analysis.

6.1.2.3. Testing the futility rule

The predictive powers calculated by both the Frequentist and the Bayesian approaches will be compared to the futility rule.

- If the calculated Predictive power is less than the futility boundary, the study will be declared futile, and the IDMC will provide this statement to the team.
- If the calculated Predictive power is greater than the futility boundary, the study will be declared not futile, and the IDMC will provide this statement to the team.

In case of disagreement between the Frequentist the Bayesian approaches, the Frequentist approach will be considered as primary.

6.2. Final analysis for Efficacy

The primary analysis will be based on the mTVC cohort for analysis of efficacy. A secondary analysis based on the Total Vaccinated Cohort (TVC) and the ATPc for efficacy will be performed to complement the mTVC analysis.

When overall VE is presented, the age stratification factor will include the 3 main age strata. When VE by age is presented, the same model will be run using only the data pertaining to the strata under consideration.

Additional tables will present the overall VE by region and overall VE by time (e.g., using 1-year intervals).

All p-values reported are related to the null hypothesis test VE = 0, or absence of effect of the vaccine, and will account for p-value adjustment for multiple testing scheme when applicable.

6.2.1. Reduction of HZ

The following conditions are planned prior to final HZ analyses of study ZOSTER-006. The number of HZ and PHN cases mentioned refers to the cases in the primary cohort for efficacy.

1. At least 196 HZ cases across all age groups for the overall HZ efficacy analysis;
2. ~75% of the initial sample size (not accounting for any sample-size reassessment) in each strata with at least 36 months follow-up and the remaining subjects having completed at least 30 months follow-up after Dose 2 in order to ensure enough safety data;
3. Approximately 60 HZ cases in subjects 50-59 YOA and approximately 60 HZ cases in subjects 60-69 YOA for the HZ analysis by age in the 50-59 and 60-69 YOA age strata, respectively;
4. A total of at least 88 PHN cases when pooled with ZOSTER-022 PHN cases accrued.

Primary Inferential Analyses

The primary analysis method of the vaccine VE will consider the exact inference on the relative risk stratified for age strata and regions conditionally to the total number of HZ cases observed and time at risk. The method is implemented in the Poisson procedure of the StatXact package provided by Cytel. Relative risks will be calculated overall and by age-strata. Stratification will include age and regions for the overall analysis and region alone when analysis by age strata.

Incidence rates and VE with 95% CI will be tabulated for primary efficacy endpoint. P-value (to test H0 = [VE≤25%]) will be tabulated for the primary endpoint.

The efficacy of ZOSTER vaccine against HZ will be demonstrated if the LL of the two-sided 95% CI of VE is above 25%.

Secondary Inferential Analyses

The elapsed time following the HZ-case exclusion period after the second vaccination to the first HZ episode may be analyzed using Cox's proportional hazard regression stratified for age strata and region with vaccine groups as covariates. Wald test and CIs will be produced.

Ties will be handled using the Efron method. Cox adjusted survival curves will be produced for each combination of vaccine group and age category.

Descriptive statistics

For each treatment group, the number of subjects at risk, person-time, number of confirmed events (HZ) and incidence rate, and incidence of confirmed HZ cases will be tabulated overall and by age strata. The results will be presented over the whole study and by visit interval. Similar tables will describe the median time-to-event and hazard rate.

Survival curves for each vaccine group will be calculated non-parametrically, tabulated and presented graphically overall and by age strata using the Kaplan-Meier (i.e., Product-Limit) method.

Sensitivity analysis of the overall VE after each multiple of 12 months following last vaccination will be provided in order to assess consistency of VE over time.

6.2.2. Secondary objectives

6.2.2.1. Reduction in overall PHN risk

The overall reduction in PHN risk will be evaluated similarly to the HZ risk using the exact inference on the relative risk stratified for age strata and regions conditionally to the total number of HZ cases observed and time at risk. Similarly to the HZ VE, a Poisson distribution for the number of PHN cases under placebo and vaccine groups is assumed.

The efficacy of ZOSTER vaccine against PHN will be demonstrated if the LL of the two-sided 95% CI of VE is above 0%.

6.2.2.2. Reduction of duration of severe 'worst' pain in subjects with an HZ episode

The time-to-cessation of severe 'worst' pain will be analyzed using a survival methodology. The primary analysis will consist in a Cox-proportional model to assess the hazard rate reduction in ZBPI worst pain duration due to the vaccine in those subjects that presented HZ.

The efficacy of ZOSTER vaccine against duration of several worst pain will be demonstrated if the LL of the two-sided 95% CI of VE derived from the Hasard ratio is above 0%.

A change-point piecewise exponential model [Arani, 2001; Desmond, 2002] may be used as sensitivity analysis to compare hazard rates related to acute (0-30 days), sub-acute (30-120 days) and chronic (120+ days) pain between vaccine group and placebo. The cut-off points 30 days and 120 days were suggested according to Desmond [Desmond, 2002]. Those cut-off points may additionally be estimated using the data. The comparisons across both sub-acute pain and chronic pain will be combined using a likelihood-ratio test.

For each treatment group, the number of subjects at risk (with confirmed HZ), number of subjects with severe "worst" pain and incidence rate will be tabulated overall and by age strata. Similar tables will describe the median, median, minimum and maximum duration of severe "worst" pain.

Survival curves for each vaccine group will be calculated non-parametrically and presented graphically overall and by age strata using the Kaplan-Meier (i.e., Product-Limit) method.

6.2.2.3. Reduction of HZ-related mortality and hospitalizations

The reduction of HZ-related mortality and hospitalizations will be evaluated through;

- The vaccine VE will consider the exact inference on the relative risk stratified for age strata and regions conditionally to the total number of HZ cases observed and time at risk. The method is implemented in the Poisson procedure of the StatXact package provided by Cytel. Relative risks will be calculated overall and by age-strata. Stratification will include age and regions for the overall analysis and region alone when analysis by age strata.

The efficacy of ZOSTER vaccine against HZ-related mortality and hospitalizations will be demonstrated if the LL of the two-sided 95% CI of VE is above 0%.

6.2.2.4. Reduction in incidence of HZ associated complications

The overall incidence of HZ associated complications, in subjects with an HZ episode, overall and by age group will be presented and compared with placebo using asymptotic standardized unconditional binomial test [Miettinen, 1985]. The analysis will be stratified by age group and weights associated to each stratum will be pre-specified.

The efficacy of ZOSTER vaccine against HZ associated complications will be demonstrated if the LL of the VE is above 0%.

6.2.2.5. Reduction in use of pain medications

The reduction in use of pain medication will be evaluated through;

- The vaccine VE will consider the exact inference on the relative risk stratified for age strata and regions conditionally to the total number of HZ cases observed and time at risk. The method is implemented in the Poisson procedure of the StatXact package provided by Cytel. Relative risks will be calculated overall and by age-strata. Stratification will include age and regions for the overall analysis and region alone when analysis by age strata.

The efficacy of ZOSTER vaccine in reduction in use of pain medications will be demonstrated if the LL of the two-sided 95% CI of VE is above 0%.

All analyses will be presented overall and by age strata. The main age strata for reporting purposes are 50-59, 60-69 and ≥70 YOA. In addition, the results for the ≥ 70 YOA stratum will also be presented separately for 70-79 and ≥ 80 YOA subjects. The study is not powered prospectively to demonstrate efficacy in these 2 sub-strata taken separately. Another set of analyses in subjects ≥ 60 YOA will also be presented.

Any exploratory or sensitivity analysis may be performed in addition to the analyses described below on an ad-hoc basis. The significance level of those analyses may not however be fully controlled.

6.2.3. Exploratory objectives

6.2.3.1. Reduction in Burden-of-Illness

The overall reduction in Burden-of-Illness will be evaluated through:

- The “Chop-lump” test [Follmann, 2009] for the overall reduction in Burden-of-Illness scores in all subjects between vaccine and placebo will be implemented and compared to the original analysis of the Burden-of-Illness proposed by Chang, 1994;
- VE with respect to the BOI due to HZ (VE BOI) is defined as the relative reduction in the BOI score in the vaccine group as compared with that in the placebo group and calculated as 1 - relative risk (i.e., 1- the HZ BOI score in the vaccine group divided by the HZ BOI score in the placebo group).

6.2.3.2. Reduction in HZ severity score

The reduction in HZ severity score will be evaluated through:

- The “Chop-lump” test [Chang, 1994] for the reduction in HZ severity scores in subjects with HZ between vaccine and placebo will be implemented.

The HZ severity analysis applies to subjects with HZ and includes the first 4 weeks following the HZ episode.

Additional analyses may be performed using partial AUC, calculated from 0 to specific elapsed time after HZ onset. That approach accounts partially for any difference in pain score profiles or pattern (e.g., long duration with low scores versus short score with high scores) even though subjects may have the same overall AUC.

6.2.3.3. Reduction in PHN incidence in subjects with an HZ episode

The reduction in PHN incidence in subjects with an HZ episode will be evaluated through:

- The incidence of PHN in subjects with an HZ episode, overall and by age group will be presented and compared with placebo using asymptotic standardized unconditional binomial test [Miettinen, 1985]. The analysis will be stratified by age group and weights associated to each stratum will be pre-specified.

6.2.3.4. Improvement of subject’s quality of life by ZBPI

Descriptive statistics and inferential analysis of QoL subscale of ZBPI (item 9: questions A to G) total scores and scores per item over time will be provided overall and by age group.

7. STATISTICAL CALCULATIONS

7.1. Derived and transformed data

7.1.1. Handling of missing data

For a given subject and a given efficacy measurement, missing or non-evaluable measurements will not be imputed for the primary analysis. The missing endpoint and censoring are supposed to occur independently, and the pattern of the missingness being either Completely At Random (MCAR) or Missing At Random (MAR) only.

Sensitivity analyses will be pre-specified prior to unblinding for each main efficacy endpoint in order to assess the sensitivity of the conclusions to missing-data pattern. When repeated measurements are planned, primary methodology will include mixed effect model for repeated measurement analysis [Mallinckrodt, 2008].

7.1.2. Efficacy data

The HZ incidence rate is determined with reference to the first confirmed HZ case observed in the patient, should several HZ cases occur in the same subject.

The HZ-free period for a subject is calculated from HZ onset to time zero relative to the cohort considered: first vaccination for TVc and beyond the HZ-case exclusion period following the second injection for mTVc and ATP.

The number of Person-Years at risk over an interval of time is the sum of the confirmed HZ-free episodes over all subjects at risk during that interval, either up to the cut-off date for the analysis, the censoring date or the occurrence of the first HZ case for a subject.

RR is defined as the ratio of the incidence rates of the vaccine group over the placebo group.

VE is defined as the 1 – RR.

The following outputs will be derived from the efficacy data recorded using the ZBPI:

Duration of severe worst pain

For each confirmed HZ cases the follow up time is considered as starting from the date of HZ episode and ending the last day of ZBPI questionnaire period. The confirmed HZ cases without severe “worst” pain are considered as non-event cases. The cases with severe “worst” pain are considered as an event cases, their time to event is calculated as being the ***inverse of*** duration of pain ***(1/t)***. Those transformations allow computing vaccine efficacy in term of severe “worst” pain-free period.

HZ burden-of-illness score

For each confirmed case of HZ, responses to the “worst pain” question in the ZBPI are used to calculate a “HZ severity-of-illness” score, defined as the area under the curve (AUC) of HZ-associated pain plotted against time during the 182-day period after the onset of the case. Subjects developing HZ will present “severity-of-illness” scores ranging from 0 up to, theoretically, 1820. A score of 0 is recorded for subjects in whom HZ did not develop during the study period.

HZ severity score

The methodology described for the HZ burden-of-illness score will be applied to the 4 weeks during which a daily measure is taken and provide the HZ severity score. The HZ severity score will apply only to subjects with HZ. Subjects not infected with HZ will not take part in this analysis.

7.2. Number of decimals

The following decimal description will be used for the efficacy analyses.

Display Table	Parameters	Number of decimal digits
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2
All summaries	p-value	3
Efficacy	VE, including LL & UL of CI	2
	IR	2
	T, T/N	1
	p-value	3

7.3. Primary method for Vaccine Efficacy:

VE will consider the exact inference on the relative risk stratified for age strata and regions conditionally to the total number of HZ cases observed and time at risk. Stratification will include age and regions for the overall analysis and region alone when analysis by age strata.

This method computes an exact confidence interval (CI) around the rate ratio (ratio of the event rates in the vaccinated versus control group) and takes into account the follow-up time of the subjects within each group. VE is then defined as 1 minus the rate ratio.

The follow-up time for each subject will start

- at the day after first vaccination (Month 0) if analyses are done on the Total vaccinated cohort for efficacy, or
- at 30 days after second vaccination (Month 3) if analyses are done on the mTVC or ATP cohort for efficacy.

The follow-up time for each subject will end

- at the time of the event; or,
- at date of last visit for subjects who completed the study and did not have an event; or,
- at the latest visit for which data is available for subjects who did not yet complete the study at the time of the interim analysis or final analysis (if criteria to reach final analyses are met before all subjects complete their last visit) and did not have an event:
    - For HZ endpoints, we take the minimum date of the start of the rash or start of the pain to assess the HZ, whichever comes first.

The follow-up time will be calculated in days as Date of end of follow-up period – Date of vaccination, and expressed in person-years at risk (number of days/365.25).

7.4. Vaccine Efficacy using Cox regression model

In addition to the primary analysis, VE and its CI will also be calculated using a Cox regression model. This methodology can take into account specific risk factors which might have been imbalanced, by chance, at the beginning of the trial between the vaccinated and control group. Risk factors that will be investigated are age strata and country. VE is then calculated as 1 minus the hazard ratio.

Cox regression assumes proportional hazards throughout the follow-up period. This assumption will be checked by a test based on the Schoenfeld residuals.

If there is strong evidence that the hazard rate is not constant over the surveillance period, then a non-parametric analysis will be performed.

7.5. Time-to-first event methodology: follow-up time and status

The study participants will be actively followed for the occurrence of HZ, PHN and use of pain medications during entire study follow up. The events linked to primary and secondary efficacy outcomes (with onset time) will be identified and in case multiple events are observed for the same subject, only the first event will be considered.

For **primary and secondary endpoints**, the follow-up time and the status will be recorded as follows:

- If the subject gets his/her first event of corresponding primary or secondary endpoints during the study follow up period, the status will be 1 and the associated time will be the number of days between start date of the considered period (30 days after last study vaccination) and the date of the appearance of the event. If he/she gets the same event afterwards, it will not be considered in the analysis.
- If a subject does not get the event of corresponding endpoint during the study follow up, the status will be 0 and the associated time will be the number of days the subject is followed (if a subject is dropped-out from the study, his/her date of last contact will be taken into account).
- Subjects meeting censoring criteria will be included in the analysis.

7.6. Methods for Confidence Intervals (CIs)

7.6.1. CIs for Vaccine Efficacy

7.6.1.1. Poisson distribution

The CI for vaccine efficacy can then be derived from the exact CI from RR (Miettinen, 1985). This method is implemented in the Poisson procedure of the StatXact package provided by Cytel.

7.6.1.2. Binomial distribution

The Vaccine Efficacy (VE) can be estimated by:

$$VE = 1 - \frac{n1/N1}{n2/N2} = 1 - \frac{n1}{r * n2}$$

where n1 = number of cases in the vaccinated group

N1 = follow-up time the vaccinated group

n2 = number of cases in the control group

N2 = follow-up time in the control group

$$\mathbf{r} = \frac{N1}{N2}$$

Conditionally to the total number of cases n = n1+ n2 and r, let p denote the proportion of cases in the vaccine group,

$$VE = 1 - \frac{n1}{n} * \frac{n}{r * (n - n1)} = 1 - p * \frac{1}{r * (1 - p)} = 1 - \frac{p}{r * (1 - p)}$$

where p = n1/n is binomially distributed.

Therefore, there is a monotonic link between VE, the true vaccine efficacy, and p, the true proportion of subjects in the vaccine group among the total cases in the two groups.

The CI for vaccine efficacy can then be derived from the exact CI from p (Dragalin, Fedorov and Cheuvart, 2002). This method is implemented in the Binomial procedure of the StatXact package provided by Cytel.

7.6.1.3. Cox regression

The CI for vaccine efficacy can then be derived from the Wald CI from Hazard Ratio. This method is implemented in the PHREG procedure of the SAS/STAT package (SAS V9.2).

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Description	**Analysis ID (SDD sub-folder)**	**TFL short title**	*Blinded team status*
Futility analysis at 25% of HZ accrual	2	Interim	*Blinded*
Final ***HZ*** Analysis	1	Final	*Blinded*
End of study analysis	EOS	EOS	*Unblinded*

8.2. Prior to *End of Study* Analysis

Blinded review of efficacy data will be performed in order to anticipate rate of accrual of HZ events within each age strata.

Unblinded evaluation of futility efficacy will be performed by the IDMC.

Access to results of Final HZ efficacy but all team remain blinded at level of subjects treatment

8.3. Statistical considerations for interim analysis

When 49 confirmed HZ cases have accrued in ZOSTER-006 and at least 20% of HZ cases are observed in each age strata [50-59 years], [60-69 years] and [70+ years] (see section 6.1), an interim analysis for futility will be performed.

8.3.1. Interim analysis for Benefit

GSK has no plan to proceed with early registration for efficacy (i.e., following the interim analysis) due to the following reasons:

- The expected low accrual rate of PHN cases and the need to collect a sufficient number of events to achieve a robust estimate of PHN VE;
- The duration of protection conferred by the vaccine is an important characteristic and because this futility analysis occurs at an early stage of the trial it will not be able to provide the required data if the study is stopped prematurely;
- Accumulation of longer term safety data than will be available at the interim analysis.

If the futility analysis occurs and leads to a recommendation by the IDMC to file prior to study end for ethical reasons, it is mandated that, prior to final analysis, the significance level for all primary objectives, and also key secondary objectives, is set to 0.0001 for both HZ and overall PHN, considering the alternative hypotheses of true vaccine efficacies above 40%. As a consequence, the significance level of the final analysis will be adjusted to 4.9998% 2-sided.

8.3.2. Interim analysis for Futility

Two different approaches are proposed, based on all observed cases in both ZOSTER-006 and ZOSTER-022 at interim. The first approach will calculate the predictive power using a Frequentist approach. The second one will evaluate the predictive power using a Bayesian approach.

8.3.2.1. Frequentist approach

This approach has three steps:

1. VE and RR for HZ will be tabulated in each age stratum (50-59, 60-69 and 70+ YOA);
2. An N-weighted VE, using as weight the expected number of HZ cases in each age stratum at final analysis in ZOSTER-006, will be calculated;
3. Calculate the predictive power based on the calculated N-weighted VE and other parameters used when setting up the futility criteria (O'Brian-Fleming boundaries, assumed VE and Criteria of success at final analysis).

Evaluate Vaccine efficacy in each strata

Using all cases retrieved in both ZOSTER-006 and ZOSTER-022, we will evaluate VE in each of the three following age strata (50-59, 60-69 and 70+ YOA).

The method used will be similar to the method described in section 7.1.2. VE and 95% CI will be tabulated.

Evaluate N-Weighted Vaccine efficacy

Using details given in Appendix 1:

1. Calculate RR (as 1-VE) and Loge (RR) of each of the three age strata;
2. Calculate the Weight of each age stratum as expected number of cases at final analysis (using incidence rates of the interim analysis) (noted wi; i = 1 to 3);
3. Calculate the sum of weighted Loge(RR) of the three age strata and divide by the sum of weights;
4. Use the back transformation (1-exp(.)) to retrieve the correspondent weighted VE.

The 95% CI is approximated from the Asymptotic normality of the Loge(RR) and the associated variance of the Loge(RR) from Agresti (1990):

1. Calculate the Standard Error (SE) of RR in each of the three age strata by
   SE = sqrt((1/(nv+0.5))-(1/(Nv+0.5))+(1/(np+0.5))-(1/(Np+0.5)));
2. Calculate the global SE using the Variance properties by
   SE = sqrt((Sum wi^2 SE^2) / (sum wi)^2);
3. Calculate 95% CI as Loge(RR)± 1.96 SE and deduce by back transformation the 95% CI of weighted VE.

The weighted VE calculated is noted as N-weighted VE, more details are provided in Appendix 1.

Calculate predictive power

The two following SAS procedures will be used to calculate the predictive power. The SEQDESIGN procedure used to evaluate designs interim analyses and the SEQTEST procedure performs the interim analyses based on the sample sizes and boundary values produced by the SEQDESIGN procedure.

1. Based on the O'Brian-Fleming Method, evaluation of the boundary values using the PROC SEQDESIGN:

   The SEQDESIGN procedure designs interim analyses for clinical trials. PROC SEQDESIGN computes the boundary values for the trial. The boundary values are derived in such a way that the overall Type I and Type II error probability levels are maintained at the levels specified in the design. Method chosen is the O'Brian-Fleming method. The SEQDESIGN procedure computes the boundary values. The following parameters have been fixed (during the determination of the futility rules) : Assumed VE = 69% , Criteria of success LL > 25%, Gamma = -5 (Gamma family spending function linked to O'Brian-Fleming boundaries), Beta = 0.0031 (Type II error), Alpha = 0.025 (Type one error)

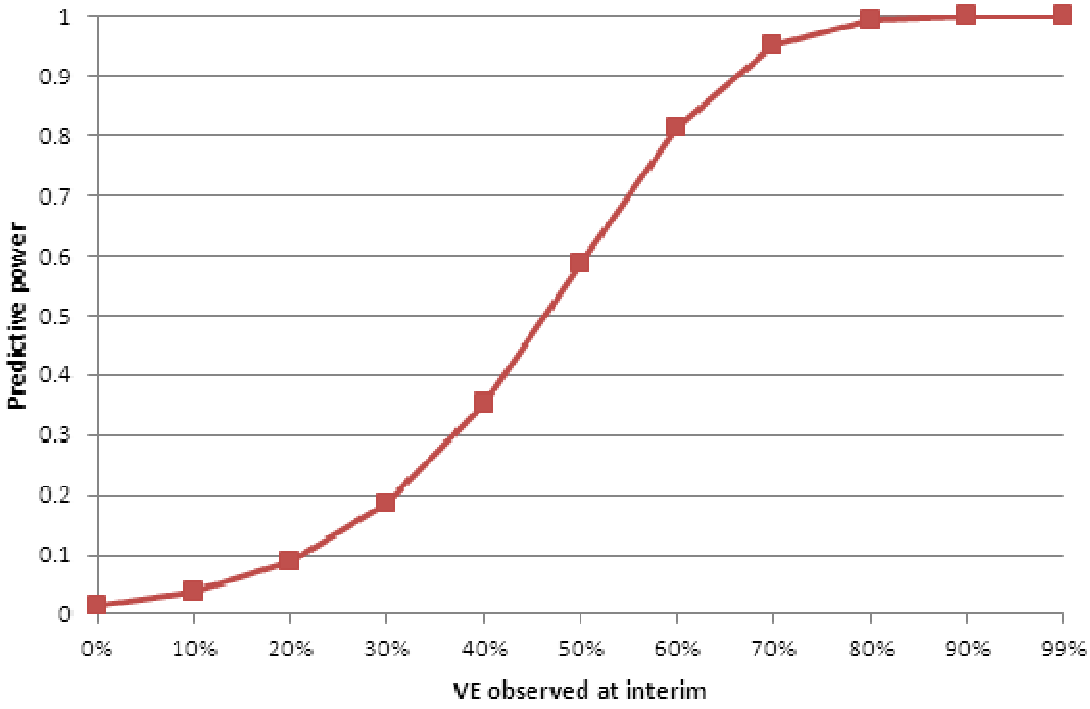
2. Calculate the Predictive power using the PROC SEQTEST:

   Based on the weighted VE calculated at interim, the SEQTEST procedure compare the test statistic on interim data with the corresponding boundary values computed by the SEQDESIGN procedure and provide the predictive power.

   The predictive power calculated is the posterior probability that the test statistic at the final stage would exceed the rejection critical value given the observed statistic and a prior distribution of the hypothetical reference. A non-informative prior is used in the procedure.

Illustration of the predictive power for different VE observed at interim is given in the Figure 1.

Figure 1 **Predictive power to demonstrate the primary objective with lower limit of 95% CI ≥ 25% for different observed VEs with 49 cases**



8.3.2.2. Bayesian approach

All HZ cases accrued from ZOSTER-006 and ZOSTER-022 will be used.

A Bayesian framework is used to simulate accrual of HZ cases in each age stratum under vaccine and placebo over the period of time between interim and final analysis.

The duration of accrual is determined in order for the median number of HZ cases to reach between 196 and 200 over the 3 age strata. The joint posterior distribution of placebo incidence and vaccine efficacy is calculated separately for each age stratum using unblinded interim data and non-informative priors.

The joint distribution of the number of HZ cases under placebo and vaccine is simulated based on the joint posterior distribution of placebo incidence and vaccine efficacy and assuming (conditionally) independent Poisson distribution for the number of HZ cases.

Provided that the sum of simulated HZ cases across the 3 age strata is between 196 and 200, the simulations are analysed using the frequentist methodology planned for the final analysis.

A success is considered when the LL of the 95% confidence interval for VE is above 25%.

The probability of success of the final analysis given the interim data is estimated as the ratio of successes over the total number of simulations presented a total of 196 to 200 HZ cases.

Details on the Bayesian framework is described in Laurent & Legrand (2011).

8.3.2.3. Testing the futility rule

Both predictive powers calculated by the frequentist approach will be compared to the futility rule.

- If the Predictive power calculated is less than the futility boundary, the study will be declared futile, and the IDMC will provide this statement to the team.
- If the Predictive power calculated is greater than the futility boundary, the study will be declared not futile, and the IDMC will provide this statement to the team.

The IDMC will have access to the full analysis results and will provide GSK the applicable statement.

8.4. Final analysis

Two analyses are planned: Final HZ efficacy analysis and End of study analysis.

8.4.1. Conditions for triggering analyses

The conditions described below are minimum requirements prior to the specified analyses.

The following conditions are planned prior to final HZ efficacy and end of study analyses of study ZOSTER-006. The number of HZ and PHN cases mentioned refers to the cases in the primary cohort for efficacy.

1. ***At least 196 HZ cases across all age group for the overall HZ analysis;***
2. ***~75% of the initial sample size (not accounting for any sample-size reassessment) in each strata with at least 36 months follow-up and the remaining subjects have completed at least 30 months follow-up after Dose 2 in order to ensure enough safety data;***
3. ***Approximately 60 HZ cases in subjects 50-59 YOA and approximately 60 HZ cases in subjects 60-69 YOA for the HZ analysis by-age in 50-59 and 60-69 YOA age strata respectively;***

The ZOSTER-006 study will continue until an adequate number of PHN cases will be accrued in both ZOSTER-006 and ZOSTER-022.

The end of study analysis of ZOSTER-006 will occur when the following conditions are met:

1. *All previous conditions are met for final HZ efficacy analysis in study ZOSTER-022;*
2. *A total of at least 35 PHN cases in subjects ≥ 70 YOA when pooled with ZOSTER-022 PHN cases.*

The end of study analysis cannot be performed before the final HZ efficacy analysis.

8.4.2. Control of type I error for the two steps analyses

Although, the analyses of ZOSTER-006 will be performed in two steps. Each objective will be assessed only once. Therefore no adjustment of type I error is needed.

8.4.3. Maintaining the blind

It is planned to maintain the whole team (Central, Local, Investigators) and subjects blinded up to end of study.

A firewall team will be set up in order to allow the planned analyses to be performed and results reported to the relevant authorities. All details of this approach can be found in the firewall charter.

Dependent on the outcome of the studies ZOSTER-006 and ZOSTER-022, an single-blind long-term follow-up study is planned. Therefore, after study end of ZOSTER-006 and ZOSTER-022 the study blind will continue to be kept for those subjects who participated in the primary studies and are willing to participate in the single-blind long-term follow-up study; the central study team will be unblinded.

8.4.4. List of objectives assessed at each analysis step

The following table will provide an overview of the analyses which will be performed at final HZ efficacy analysis (step 1) and end of study analysis (step 2), respectively.

For ZOSTER-006, step 1 will include analyses of the following objectives:

- *all HZ VE objectives;*
- *all reactogenicity/safety and immunogenicity objectives.*

At step 2, all objectives of study ZOSTER-006 will be analyzed. Objectives already analyzed at step 1 will be re-analyzed (as confirmatory descriptive in case of inferential analysis at step 1 or descriptive analysis otherwise).

At step 2, overall PHN VE in subjects ≥ 70 YOA, and other pre-specified endpoints will be analyzed in the pooled analyses of studies ZOSTER-006 and ZOSTER-022.

8.4.5. Database freeze

For the first step analysis, the time for database freeze for immunogenicity may not coincide with efficacy/safety database freeze.

Table 1 Overview of analyses performed at each analysis step (ZOSTER-006, pooled analysis of ZOSTER-006 and ZOSTER-022)

			First step Final HZ efficacy analysis*		*Second step** End of study analysis*	
			Analysis of objective Yes (Y) No (N) Not applicable (NA)	*Type of analysis I: inferential D: descriptive CD; confirmatory descriptive*	*Analysis of objective Yes (Y) No (N)*	*Type of analysis I: inferential D: descriptive CD; confirmatory descriptive*
ZOSTER-006						
Primary						
	Efficacy					
		To evaluate VE in the prevention of HZ compared to placebo in adults ≥ 50 YOA, as measured by the reduction in HZ risk.	*Y*	*I*	*Y*	*CD*
Secondary						
	Efficacy					
		To evaluate VE in the prevention of HZ compared to placebo in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, as measured by the reduction in HZ risk;	*Y*	*I*	*Y*	*CD*
		To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;	*N*	*-*	*Y*	*D*
		To evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;	*N*	*-*	*Y*	*I*
		To evaluate VE in the reduction of overall and HZ-related mortality and hospitalizations compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;	*N*	*-*	*Y*	*I*

			First step Final HZ efficacy analysis*		*Second step** End of study analysis*	
			Analysis of objective Yes (Y) No (N) Not applicable (NA)	*Type of analysis I: inferential D: descriptive CD; confirmatory descriptive*	*Analysis of objective Yes (Y) No (N)*	*Type of analysis I: inferential D: descriptive CD; confirmatory descriptive*
		To evaluate VE in the reduction in incidence of HZ-associated complications compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;	*N*	*-*	*Y*	*I*
		To evaluate VE in the reduction in use of pain medications compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;	*N*	*-*	*Y*	*I*
	Safety					
		To evaluate vaccine safety and reactogenicity.	*Y*	*D*	*Y*	*D*
Exploratory						
	Efficacy					
		To evaluate VE in reducing the severity of acute HZ-associated pain compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;	*N*	*-*	*Y*	*I*
		To evaluate VE in improving Quality of Life (QoL) compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;	*N*	*-*	*Y*	*I*
		To evaluate VE in the mitigation of Burden-Of-Illness (BOI) caused by HZ compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA.	*N*	*-*	*Y*	*I*

			*First step** *Final HZ efficacy analysis*		*Second step*** *End of study analysis*	
			Analysis of objective Yes (Y) No (N) Not applicable (NA)	*Type of analysis I: inferential D: descriptive CD; confirmatory descriptive*	*Analysis of objective Yes (Y) No (N)*	*Type of analysis I: inferential D: descriptive CD; confirmatory descriptive*
	Immunogenicity					
		To evaluate vaccine induced cell mediated and humoral immune responses and the persistence of each type of response after two injections of study vaccine in subjects ≥ 50 YOA, and by age strata;	*Y*	*I, D*	*Y*	*CD, D*
		To evaluate anti-varicella-zoster virus (VZV) neutralizing antibody (Ab) titres in a subset of subjects at Month 0 (pre-vaccination), and at Months 3, 14, 26 and 38, in subjects ≥ 50 YOA, and by age strata.	*Y*	*I, D*	*Y*	*CD, D*
Pooled analysis of ZOSTER-006 and ZOSTER-022						
Co-primary						
	Efficacy					
		To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 70 YOA;	*NA*		*Y*	*I*
		To consolidate VE estimation in the prevention of HZ compared to placebo in subjects ≥ 70 YOA across both phase III studies;	*NA*		*Y*	*CD*
Secondary						
	Efficacy					
		To evaluate VE in the prevention of PHN compared to placebo in subjects ≥ 50 YOA across both phase III studies;			*Y*	*I*
		To evaluate VE in the prevention of PHN compared to placebo in subjects ≥ 50 YOA with confirmed HZ;			*Y*	*I*

			First step Final HZ efficacy analysis*		*Second step** End of study analysis*	
			Analysis of objective Yes (Y) No (N) Not applicable (NA)	*Type of analysis I: inferential D: descriptive CD; confirmatory descriptive*	*Analysis of objective Yes (Y) No (N)*	*Type of analysis I: inferential D: descriptive CD; confirmatory descriptive*
		To evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;			*Y*	*CD*
	Safety					
		To evaluate vaccine safety and reactogenicity in subjects ≥ 70 YOA.	*NA*		*Y*	*D*
Exploratory						
	Efficacy					
		To evaluate VE in reducing the severity of acute HZ-associated pain compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;	*NA*		*Y*	*CD*
		To evaluate VE in improving QoL compared to placebo in subjects ≥ 70 YOA, with confirmed HZ;	*NA*		*Y*	*CD*
	Immunogenicity					
		To evaluate vaccine induced humoral immune responses and the persistence of each type of response after two injections of study vaccine in subjects ≥ 50 YOA and by age cohort;	*NA*		*Y*	*CD*
		To evaluate anti-varicella-zoster virus (VZV) neutralizing antibody (Ab) titres in a subset of subjects at Month 0 (pre-vaccination), and at Months 3, 14, 26 and 38, in subjects ≥ 50 YOA and by age strata;	*NA*		*Y*	*CD*
		To assess correlation of the humoral immune responses at Month 3 with protection against HZ.	*NA*		*Y*	*D*

** The first step for Zoster-006 will occur more than approximately 6 months before the first step for Zoster-022.*
*** The second analysis step for both studies will occur at the same time.*

8.4.6. Study reports

Depending on the further evolution of the case accrual rate, the generated data may be presented in one or more study reports per study (ZOSTER-006).

- ***The first study report for each study will contain assessment of the HZ VE objectives (ZOSTER-006) and of safety, reactogenicity and immunogenicity objectives.***

- ***A final study report for each study will contain the assessment of remaining objectives not assessed at the first step, including, but not limited to, the confirmatory descriptive re-analysis of the previously assessed objectives. The final study report for each study will also contain the results presented in the first report (to provide a comprehensive all in one report). Assessment of the objectives of the pooled analyses of both studies will be included in the final ZOSTER-022 study report. Analysis of correlate of protection may require extensive exploratory analyses and therefore may be available as an annex report after completion of this final ZOSTER-022 study report.***

9. CHANGES FROM PLANNED ANALYSES

No changes from protocol planned analyses.

10. REFERENCES

[Alan] Alan Agresti. Introduction to categorical analysis. 1990.

Arani RB., Soong S-J, Weiss HL, et al. Phase specific analysis of herpes zoster associated pain data: a new statistical approach. *Statist., Med.* 2001;20:2429–2439.

Chan ISF, Wang WWB, Heyse J. Encyclopedia of Biopharmaceutical Statistics. *Vaccine Clinical Trials*. 2003;1005–1022.

Chang MN, Guess HA, Heyse JF. Reduction in burden of illness: a new efficacy measure for prevention trials. *Stat Med.*1994;13:1807–1814.

Cohen JI, Straus SE, Arvin AM. Varicella zoster virus and its replication. 2007; p. 2774-2818. In D. M. Knipe and P. M. Howley (ed.), *Fields virology*, 5th ed. Lippincott/The Williams & Wilkins Co., Philadelphia, PA.

Coplan PM, Schmader K, Nikas A, et al. Development of a measure of the burden of pain due to herpes zoster and postherpetic neuralgia for prevention trials: adaptation of the brief pain inventory. *J Pain*. 2004;5(6):344–356.

Desmond Renee A, Weiss Heidi L, Arani Ramin B, Soong Seng-jaw, Wood Martin J, Fiddian Paul A, Gnann John W, Whitley Richard J. Clinical Applications for Change-Point Analysis of Herpes Zoster Pain. *Journal of Pain and Symptom Management.* 2002, 23:510–516.

Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis.* 2007;44 Suppl 1:S1–26.

Dworkin et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. *The Journal of Pain*. 2008;9(2):105–121.

Farrar JT, Young JP Jr, LaMoreau L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on a 11-point numerical pain rating scale. *Pain*. 2001;94:149–158.

Follmann DA, Fay MP, Proschan, MA. Chop-lump tests for Vaccine trials. *Biometrics.* 2009;65: 885–893.

Hanley and Lippman-Hand. If nothing goes wrong, is everything all right? Interpreting zero numerators. *JAMA.* 1983;249:1743–1745.

Laurent S, Legrand C., 2011, A Bayesian framework for the ratio of two Poisson rates in the context of vaccine efficacy trials. ESAIM: Probability and Statistics, doi:10.1051/ps/2010018

Mallinckrodt C, Lane P, Schnell D, Peng Y, Mancuso J. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials, *DIJ*. 2008;42:303–319.

Miettinen OS, Nurminen M. Comparative analysis of two rates. *Statistics in Medicine*. 1985; 4:213–226.

Oxman MN, Levin MJ, Johnson GR, et al. Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352:2271–2284.

Rowbotham MC. What is a “Clinically meaningful” reduction in pain? *Pain*. 2001;94:131–132.

11. ABBREVIATIONS

ATP	According-To-Protocol
AUC	Area Under Curve
BOI	Burden-Of-Illness
CI	Confidence Interval
Eli_type	Internal GSK database code for type of elimination code
eCRF	Electronic Case Report Form
HZ	Herpes ZOSTER
GSK	GlaxoSmithKline
IDMC	Independent Data Monitoring Committee
IR	Incidence Rates
LL	Lower limit
MAR	Missing At Random
MCAR	Missing Completely At Random
mTVc	Modified Total Vaccinated Cohort
N.A.	Not Applicable
OTH	Other
PHN	Postherpetic Neuralgia
QoL	Quality of Life
R	R free software from free fondation software
RDE	Remote Data Entry
RR	Relative Risk
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBIR	GSK Biological's Internet Randomization System
SE	Standard Error
sqrt	Square root
SR	Study Report
SYN	Synopsis
TFL	Tables Figures and Listing template annexed to SAP
TVc	Total Vaccinated Cohort
UL	Upper Limit

VE	Vaccine Efficacy
YOA	Years Of Age
ZBPI	Zoster Brief Pain Inventory

Appendix 1 N-Weighted Vaccine efficacy

The N-weighted estimate of vaccine efficacy is used to yield a single estimate of efficacy across the different age strata. At time of futility analysis, all cases accrued in ZOSTER-022 will be also used in the evaluation of the futility rule in order to account for all information available at this time.

The Stratified Poisson analysis planned for the final analysis use implicitely the number of cases accrued in each strata as weight. In order to correct the bias made by including the cases from ZOSTER-022 (only in the [70+ years] strata, we propose to use the weighted VE (using number of cases by strata expected at final analysis as weight) as estimation of the vaccine efficacy at futility analysis.

Expected value of VE : The mean (or expected value of) VE across the three strata can be computed and be used as a measure of central tendency, to characterize the average VE that can be expected in the ZOSTER-006.

Definition of Expected value: For a random variable X with two possible values (x1, x2) with corresponding probabilities (p, q), the mean (or expected value) of the random variable X is defined as:

Expected value = mean =E(X) =x1.p = x2.p (13.1)

The expected value of VE across the three strata that can be computed and used to characterize the average VE that can be expected from the FAS may be obtained analogously using the computations shown in Equation 13.1 as follows.

Calculation of Expected values of VE: Let the expected value of VE be denoted by E(VE). Then E(VE) cane be computed as

E(VE) = 100% x (1-exp(Expected value of loge [relative risk])) (13.2)

The rationale for such a computation is that the estimate of loge[relative risk] that is asymptotically normally distributed.. The asymptotic normal distribution property of the estimate of loge[relative risk] can be used to obtain a 95% confidence interval corresponding to the estimate of E (VE). The N-weighted average estimate of vaccine efficacy in the FAS were computed based on the calculations given in Equation 13.2. The use of the term "N-weighted" arises from the calculation of the expected value of loge[relative risk].