

Rationale and Design of the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) Trial

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Abstract

Exenatide once-weekly is an extended release formulation of exenatide, a glucagon-like peptide (GLP)-1 receptor agonist, which can improve glycemic control, body weight, blood pressure, and lipid levels in patients with type 2 diabetes mellitus (T2DM). The EXenatide Study of Cardiovascular Event Lowering (EXSCEL) will compare the impact of adding exenatide once-weekly to usual care with usual care alone on major cardiovascular outcomes.

EXSCEL is an academically-led, phase III/IV, double-blind, pragmatic placebo-controlled, global trial conducted in 35 countries aiming to enrol 14,000 patients with T2DM and a broad range of cardiovascular risk over approximately 5 years. Participants will be randomized (1:1) to receive exenatide once-weekly 2 mg or matching placebo by subcutaneous injections. The trial will continue until 1360 confirmed primary composite cardiovascular endpoints, defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, have occurred.

The primary efficacy hypothesis is that exenatide once-weekly is superior to usual care with respect to the primary composite cardiovascular endpoint. EXSCEL is powered to detect a 15% relative risk reduction in the exenatide once weekly group, with 85% power and a 2-sided 5% alpha. The primary safety hypothesis is that exenatide once-weekly is noninferior to usual care with respect to the primary cardiovascular composite endpoint. Noninferiority will be concluded if the upper limit of the confidence interval is <1.30.

EXSCEL will assess whether exenatide once-weekly can reduce cardiovascular events in patients with T2DM with a broad range of cardiovascular risk. It will also provide long-term safety information on exenatide once-weekly in people with T2DM.

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Background

Type 2 diabetes mellitus (T2DM) is a growing global epidemic affecting approximately 350 million people,¹ the majority of whom will die from cardiovascular disease.^{2,3} Epidemiological analyses of United Kingdom Prospective Diabetes Study data from newly-diagnosed T2DM identified higher low-density lipoprotein cholesterol, lower high-density lipoprotein cholesterol, hyperglycemia, hypertension, and smoking as potentially modifiable cardiovascular risk factors.⁴ However, even after adjustment for these factors, people with T2DM remain at double the cardiovascular risk as those without T2DM.⁵ Although the prevalence of cardiovascular disease has declined progressively in the general population, the higher relative risk for cardiovascular disease in people with T2DM has not changed over the last 50 years.⁶ It would therefore be advantageous if new glucose-lowering medications could reduce cardiovascular risk, in addition to improving glycemic control.

Exenatide (Byetta, AstraZeneca, Wilmington, DE, USA) is the first in class glucagon-like peptide (GLP)-1 receptor agonist. It reduces glucose levels in people with T2DM by a number of mechanisms, including enhancing insulin secretion in a glucose-dependent manner, thus minimizing the risk of hypoglycemia in the absence of an insulin secretagogue or exogenous insulin. Exenatide has also been shown to have beneficial effects on blood pressure, blood lipids, and to facilitate weight loss.⁷⁻¹¹ Mechanistic data suggest that exenatide can improve cardiac function in patients with chronic heart failure,¹² improve endothelial dysfunction,¹³ and reduce infarct size after ST-segment elevation myocardial infarction.^{12,14} A patient-level integrated meta-analysis showed no evidence for increased cardiovascular disease risk with use of exenatide in

subjects with T2DM,¹⁵ while a retrospective analysis of a medical and pharmaceutical insurance claims database found a lower relative cardiovascular disease risk associated with exenatide treatment than with other glucose-lowering drugs.¹⁶ A small increase in heart rate has been observed with GLP-1 receptor agonists, which appears to be a class effect.¹⁷

The EXenatide Study of Cardiovascular Event Lowering (EXSCEL) will evaluate the effect of a once-weekly formulation of exenatide (Bydureon)¹⁸ on major cardiovascular events when given in addition to usual care.

Study Design

Overview

EXSCEL is a multinational, placebo-controlled, double-blind, parallel-group pragmatic trial randomizing patients with T2DM to receive once-weekly exenatide or matching placebo (unloaded microspheres), in addition to their usual care (Figure 1). It will assess the impact of once-weekly exenatide therapy in approximately 14,000 patients, with or without known cardiovascular disease, from heterogeneous practice environments in 35 countries from North and South America, Europe, Africa, Asia, and Australasia.

EXSCEL is planned to continue until 1360 patients with a confirmed primary composite cardiovascular endpoint (defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) have been accrued, or until the independent Data Safety Monitoring Board (DSMB) recommends otherwise. All patients who prematurely discontinue study treatment should continue subsequent study visits and post-treatment follow-up evaluations.

Trial Population

Adults with T2DM, with or without additional cardiovascular risk factors or prior cardiovascular events, are eligible if their usual care haemoglobin A1c (HbA1c) is 48 mmol/mol to 86 mmol/mol (6.5% to 10.0%) inclusive. Study participants can be treated with up to 3 oral glucose-lowering drugs of any type or insulin (alone or in combination with up to 2 oral glucose-lowering drugs). Detailed inclusion and exclusion criteria and the rationale for their selection are outlined in Supplementary Appendix A. During the trial, patients will still be managed by their usual care provider and treated according to local standards of care for diabetes and cardiovascular risk factor management. They will attend study clinics only for provision of study medication and follow-up. In some cases, the site investigator may also be the usual care provider.

Study Drug

Patients will be allocated centrally at random in a 1:1 ratio to receive once-weekly subcutaneous injections of exenatide (Bydureon) 2 mg, or matching placebo, stratified by whether or not they have a history of cardiovascular disease. Once-weekly exenatide was approved for the treatment of patients with T2DM by the European Medicines Agency in 2011 and the United States Food and Drug Administration (FDA) in 2012. It acts by augmenting insulin secretion and reducing glucagon secretion in a glucose-dependent manner.¹⁹ Once-weekly exenatide was developed by encapsulating exenatide in microspheres of a biodegradable polymer, resulting in sustained drug delivery over a period of weeks after subcutaneous injection.¹⁸

Concurrent Glycemic Therapy

It is expected that patients will see their usual care provider at least twice per year for routine care. Whilst there is no requirement to achieve glycemic equipoise between the 2 randomized groups, it is anticipated that there will be little or no between-group difference in achieved glucose levels during the double-blind treatment period, as diabetes therapy will be adjusted by the usual care providers according to local guidelines. This can involve the addition or substitution of any glucose-lowering therapies, including insulin, but excluding GLP-1 receptor agonists. Concomitant medication changes are permitted at any time but, unless there are safety concerns, usual care providers will be asked to avoid them immediately after randomization while HbA1c levels are reflecting the initial effect of study medication.

Treatment Protocol and Follow-up

EXSCEL is a pragmatic trial²⁰ designed to investigate the effectiveness of once-weekly exenatide with a view to providing generalizable results. The entry criteria are consistent with the range of patients who might receive once-weekly exenatide in routine clinical practice, including those at high and moderate cardiovascular risk.

To minimize interference with usual care, the number of monitoring visits will be limited. Patients will be trained at randomization to self-administer once-weekly exenatide, and seen at 1 week to have their self-injection observed. Subsequently, patients will be seen at 2 months, 6 months, and every 6 months thereafter until study close out (Figure 1).

At all visits post randomization there will be an assessment of clinical events and serious adverse events, as well as a review of concomitant medication and adherence to study medication. At annual visits, additional procedures will include ascertainment of blood pressure, body weight, and heart rate; and the most recent HbA1c, lipid profile, and serum creatinine data will be ascertained opportunistically from local laboratory usual care records. Patients will also be asked to complete a standardized self-reported health status questionnaire (EQ-5D).²¹ The first patient was randomized on 18th June 2010 and follow-up will continue until a total of 1360 patients with an adjudicated and confirmed primary composite cardiovascular outcome have been accrued.

Primary Outcomes

The EXSCEL primary efficacy hypothesis is that once-weekly exenatide is superior to usual care with respect to the adjudicated primary composite cardiovascular endpoint. The primary safety hypothesis is that once-weekly exenatide is noninferior to usual care with respect to the adjudicated primary cardiovascular composite endpoint.

Secondary Outcomes

Adjudicated secondary endpoints are all-cause mortality, the individual components of the primary composite cardiovascular outcome (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke), hospitalization for acute coronary syndrome, and hospitalization for heart failure (Supplementary Appendix B lists all secondary and exploratory efficacy endpoints).

Participant Safety

Adverse events will be monitored over the course of the trial, starting from the time of randomization and through the duration of the patient's participation, including the 70-day post-trial medication follow-up period. In this pragmatic trial, only adverse events that are serious or lead to discontinuation of study medication will be recorded. EXSCEL will employ both patient- and investigator-directed education to minimize the risk of hypoglycemia. Symptoms and appropriate management of hypoglycemia will be reviewed at all study visits. Usual care providers will be responsible for the adjustment of concomitant therapy. Two or more severe episodes (hypoglycemia requiring assistance) between visits, despite appropriate titration of glucose-lowering therapies, will trigger permanent discontinuation of study medication.

Patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² (calculated using Modification of Diet in Renal Disease [MDRD]-4)²² will be excluded as exenatide is renally excreted.²³ During the trial, patients with 2 successive values below this eGFR threshold will be discontinued from study medication. If a usual care annual creatinine value is not available, it will be measured by the site to support patient safety.

In view of concerns raised in animal studies about a possible increase in thyroid C-cell adenomas and carcinomas,^{24,25} the FDA has requested that calcitonin be assayed by a central laboratory at screening and annually thereafter. These will be scrutinised centrally. If the screening value is >40 ng/L, or a subsequent annual value is ≥ 50 ng/L, study medication will be permanently discontinued and the patient referred for clinical evaluation.

Statistical Considerations

Sample Size and Power Calculations

The sample size was estimated initially to be 9600, assuming an annual 3.8% primary composite cardiovascular endpoint event rate, 1% annual lost to follow-up rate, 5% annual study drug discontinuation rate, and with a 60:40 ratio of those with or without a history of cardiovascular disease. Given that the observed (blinded) overall primary endpoint event rate to date was lower than expected, the sample size was increased to 14,000 in 2013, and the proportion of patients with history of cardiovascular disease at entry increased to approximately 70%. The power to assess the primary safety objective of noninferiority of once-weekly exenatide compared with placebo will be greater than 90%.

Analysis Plan

Kaplan-Meier curves for time to the first occurrence of a primary composite endpoint event will be used to depict the accumulation of events over time for the once-weekly exenatide and placebo treatment groups. The hazard ratio comparing the time to first occurrence of the primary composite endpoint event for the once-weekly exenatide-treated group with that of the placebo-treated group and its 95% confidence interval will be estimated using a Cox proportional hazards model stratified by baseline and cardiovascular risk group (prior cardiovascular event or no prior cardiovascular event) and using treatment group as a covariate. Proportionality of the hazards over time by randomized treatment group will be tested.

The primary efficacy hypothesis of superiority will be assessed by a superiority analysis in the intent-to-treat (ITT) population. Superiority will be concluded if the upper limit of the 95% confidence interval is <1.00 . Appropriate alpha adjustment will be made for the 2 formal interim efficacy analyses that will be performed by the independent DSMB statistician. These are planned to occur after approximately one-third and two-thirds of the 1360 primary composite cardiovascular events required have been adjudicated.

The primary safety hypothesis will be assessed by a noninferiority analysis in the intent-to-treat (ITT) population. Noninferiority will be concluded if the upper limit of the 95% confidence interval is <1.30 , as per the 2008 FDA Guidance.²⁶ Secondary and exploratory efficacy endpoints (Supplementary Appendix B) will be analysed individually in the ITT population. Pre-specified subgroup analyses for the primary composite cardiovascular outcome are listed in Supplementary Appendix C.

Biomarker and Genetic Assessments

Two optional substudies are included in EXSCEL for the first 9600 patients to be recruited. A genetic substudy aims to collect whole blood samples at baseline for future genetic research, and a biomarker substudy will collect urine and blood samples prior to study drug exposure and annually thereafter for proteomic and metabolomic research. Separate consent will be obtained for each of these substudies.

Health Economic Analysis

EXSCEL will collect physician-reported data on resource use and patient-reported quality of life to undertake cost-effectiveness analyses relevant to the countries taking part in the study. Resource use data on hospitalizations, visits, and medications will be combined with appropriate national unit costs to calculate a cost per patient per year. Quality of life data will be combined with survival data to calculate quality-adjusted time in the trial per patient.

Study Organisation

EXSCEL is run jointly by 2 academic research organisations, the Duke Clinical Research Institute (DCRI; Durham, NC, USA), and the University of Oxford Diabetes Trials Unit (DTU; Oxford, UK), in an academic collaboration with pharmaceutical companies. Amylin Pharmaceuticals Inc. (San Diego, CA, USA) was the original sponsor, later joined in an alliance with Eli Lilly and Company (Indianapolis, IN, USA). Subsequently, sponsorship transitioned to Bristol-Myers Squibb (Princeton, NJ, USA) and AstraZeneca (Gaithersburg, MD, USA) with the acquisition of Amylin by Bristol-Myers Squibb, and has now transitioned to AstraZeneca alone, **with Amylin being a wholly-owned subsidiary of AstraZeneca.**

Overall responsibility for the oversight and management of the trial lies with the EXSCEL Executive Committee, which is composed of 11 individuals, comprising 9 senior independent academic representatives who are experts in their field and 2 sponsor representatives. A clinical events committee (CEC), blinded to treatment allocation and consisting of physicians including endocrinologists, cardiologists, and oncologists, will adjudicate all components of the primary composite cardiovascular

outcome, secondary endpoints, and all cases of neoplasm and pancreatitis. The EXSCEL DSMB, comprising independent statisticians and specialists in diabetology, cardiovascular medicine, gastroenterology, and endocrine neoplasia, is responsible for active surveillance of safety data including all cases of neoplasm and pancreatitis. Members of the executive committee, CEC, and DSMB are listed in Supplementary Appendix D.

Ethical Considerations

The EXSCEL trial complies with the Declaration of Helsinki, its subsequent revisions, and Good Clinical Practice Guidelines. Institutional review board approval has been obtained for all sites and subjects sign informed consent before any study procedures commence. EXSCEL is registered on www.clinicaltrials.gov (NCT01144338).

Discussion

The EXSCEL trial will determine whether once-weekly exenatide, on top of usual diabetes care, reduces cardiovascular events in patients with T2DM compared with usual diabetes care without a GLP-1 receptor agonist.

EXSCEL is the largest GLP-1 receptor agonist cardiovascular outcome trial to date, recruiting 14,000 participants, and differs from other ongoing studies in a number of respects. Designed from the outset to test for superiority for the primary composite cardiovascular outcome, it will follow participants for up to 7 years with an expected median >3 years. EXSCEL will have around 30% of patients with no history of prior cardiovascular disease to permit evaluation of possible primary, as well as secondary,

cardiovascular risk reduction. By contrast, the ELIXA trial using lixisenatide (NCT01147250) involves only patients with a recent history of acute coronary syndrome, while the REWIND trial using dulaglutide (NCT01394952) requires prior cardiovascular disease or the presence of at least 2 cardiovascular risk factors. Similarly, the SUSTAIN trial using semaglutide (NCT01720446) requires the presence of subclinical or overt cardiovascular disease. The LEADER trial using liraglutide (NCT01179048) employs a standardized recommendation for the treatment of risk factors.

A patient-level integrated meta-analysis has showed no evidence for an increased cardiovascular disease risk associated with the use of exenatide twice daily in subjects with T2DM,¹⁵ while a retrospective analysis of a medical and pharmaceutical insurance claims database found a lower relative cardiovascular disease risk associated with exenatide twice daily treatment than with other glucose-lowering drugs.¹⁶ However, these database studies have several limitations including their retrospective nature, short duration, low baseline cardiovascular risk in the populations observed, and low cardiovascular disease event rates. These prior studies, while promising, are insufficient in establishing the cardiovascular safety and efficacy of exenatide once weekly in a population at increased risk of cardiovascular disease. Since EXSCEL was designed, 2 cardiovascular safety studies of dipeptidyl peptidase-4 (DPP-4) inhibitors, saxagliptin²⁷ and alogliptin,²⁸ have reported noninferiority to placebo with respect to their primary cardiovascular safety outcomes.

There are several mechanisms whereby once-weekly exenatide could potentially have a beneficial effect on cardiovascular outcomes. It improves hyperglycemia and

other cardiovascular risk factors such as blood pressure, lipids, and body weight without increasing the risk of hypoglycemia.⁷⁻¹¹ In addition, further pleiotropic effects on the cardiovascular system, both through GLP-1 receptor-mediated and other mechanisms, have been suggested.²⁹ Studies in animal models suggest beneficial effects of GLP-1 on atherogenesis, by inhibiting the inflammatory response in macrophages and endothelial adhesion³⁰ and modulating endothelial function.^{31,32} Further cardioprotective effects, by means of increased coronary flow,²⁹ reduced myocardial infarct size,³³ and improved left ventricular function, have also been suggested by animal data.^{30,34} Human mechanistic studies are consistent with these findings demonstrating an improvement in flow-mediated vasodilation in the postprandial state,¹³ reduced infarct size in patients with ST-segment elevation myocardial infarction,^{12,14} and an improvement in left ventricular ejection fraction in patients with heart failure.³⁵ These data together justify the conduct of a large-scale, adequately powered outcome trial testing for the superiority of a diabetes treatment regimen containing once-weekly exenatide on cardiovascular outcomes.

Safety Considerations

Studies with supratherapeutic GLP-1 receptor agonist doses in rodents have shown an increase in thyroid C-cell adenomas and carcinomas.^{24,33} In contrast to rodents, GLP-1 receptor expression on primate thyroid C-cells is very low, and no changes have been observed with *in vitro* stimulation of human C-cells by GLP-1 receptor agonists.^{10,24} Patients with a personal or family history of medullary thyroid cancer or Multiple Endocrine Neoplasia type 2 (MEN2) will be excluded from ESXCEL. Patients

randomized into EXSCEL will have their study medication discontinued if their screening calcitonin value is >40 ng/L, or subsequent annual values are \geq 50 ng/L.

Concerns have been raised about the potential association of incretin-based therapies with pancreatitis and pancreatic cancer.^{36,37} Any putative cases of pancreatitis or neoplasm of any type reported in EXSCEL participants will be captured as clinical events of interest and adjudicated. These data, along with observations from other long-term studies, will contribute to clarifying the risk-benefit analysis of these therapies.

As once-weekly exenatide is cleared by renal filtration and subsequent tubule degradation,²³ patients with an eGFR <30 mL/min/1.73 m² will be excluded and study medication discontinued in those whose eGFR falls below this value on 2 successive measurements.

The recently reported results of the SAVOR TIMI 53 trial showed an unexpected but statistically significant 27% increased relative risk for hospitalisation for congestive heart failure with saxagliptin, a DPP-4 inhibitor.²⁶ Although the mechanism of action of DPP-4 inhibitors differs from that of GLP-1 receptor agonists, hospitalisation for congestive heart failure is a prespecified EXSCEL secondary outcome, with all putative events adjudicated by the CEC and reviewed regularly in an unblinded manner by the DSMB.

Challenges

Over a dozen concurrent cardiovascular outcome trials are currently ongoing, aiming to collectively enrol in excess of 100,000 patients with T2DM,³⁸ creating a competitive environment for recruitment. In addition, the increasing availability of open-label once-

weekly exenatide and other GLP-1 receptor agonists further constrains the number of eligible participants.

Retaining participants in EXSCEL and achieving high concordance with an injectable therapy creates a challenge, especially as 50% of participants will receive placebo injections for a number of years. However, all patients who prematurely discontinue study treatment will be encouraged to continue subsequent study visits and post-treatment follow-up evaluations.

Conclusion

In summary, EXSCEL is an ongoing multinational, double-blind, placebo-controlled, randomized trial of once-weekly exenatide that will provide important data on its long-term cardiovascular safety and potential cardiovascular benefit. Given its pragmatic design, inclusion of patients with a broad range of cardiovascular risk and no restrictions on concomitant glucose-lowering therapies (other than GLP-1 receptor agonists), the trial is expected to provide results that are generalizable and directly transferable to daily patient care.

Conflicts of Interest

RRH has received research support from Bayer, BMS and Merck; attended advisory boards with Amgen, Bayer, Elcelyx, Merck, Novartis and Novo Nordisk; and given lectures supported by Bayer.

MAB has received research funding from Novartis and Bayer.

JG has received consulting fees, speaker fees, travel expenses and/or research support from Amylin, AstraZeneca, Boeringher Ingelhiem, Bristol-Myers Squibb, Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi, and Takeda.

AFH has received research grants from AstraZeneca, Bristol-Myers Squibb, Janssen, and Novartis; and honoraria from Bristol-Myers Squibb, and Janssen.

HS (none).

ZD (none).

JK (none).

NSK is an employee and stockholder of AstraZeneca.

RJM received research support from AstraZeneca, Bristol-Myers Squibb, and Novartis.

AO (none).

JBB is an investigator and/or consultant without any direct financial benefit under contracts between his employer and the following companies: Amylin Pharmaceuticals, Inc., Andromeda, Astellas, Astra Zeneca, Bayhill Therapeutics, Inc., Boehringer Ingelheim GmbH & Co. KG, Bristol-Myers Squibb Company, Catabasis, Cebix, Inc., CureDM, Diartis Pharmaceuticals, Elcelyx Therapeutics, Inc., Eli Lilly and Company, Exsulin, Genentech, GI Dynamics, GlaxoSmithKline, Halozyme Therapeutics, F. Hoffmann-La Roche, Ltd., Intarcia Therapeutics, Johnson & Johnson, Lexicon, LipoScience, Macrogenics, Medtronic, Merck, Metabolic Solutions Development Co., Metabolon, Inc., Metavention, Novan, Novo Nordisk A/S, Orexigen Therapeutics, Inc., Osiris Therapeutics, Inc., Pfizer, Inc., Quest Diagnostics, Rhythm Pharmaceuticals, Sanofi, Spherix, Inc., Takeda, ToleRx, Transpharma Medical Ltd., TransTech Pharma,

Veritas and Verva. He is a paid consultant to PhaseBio Pharmaceuticals Inc and has received stock options for that effort.

JCC received research grant and/or honoraria for consultancy and/or giving lectures from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novo Nordisk, Pfizer and/or Sanofi. All proceeds have been donated to the Chinese University of Hong Kong to support research and education. The Chinese University of Hong Kong has received research grants and sponsorships from these companies.

NI is an employee and stockholder of Bristol-Myers Squibb,

SK is an employee and stockholder of Bristol-Myers Squibb.

APM reports personal honoraria for research activities from Novartis, Bayer, Pfizer, Cardioentis, outside the submitted work.

SPM reports grants from the following conflicts of interest from The Medicines Company, Novo Nordisk, Abbott Vascular, Amylin Pharmaceuticals, Boston Scientific, Volcano Corporation, and Terumo Medical. He has received consulting fees from Novo Nordisk and St. Jude Medical.

PÖ is an employee and stockholder of AstraZeneca.

MJP reports institutional research grants from AstraZeneca and Merck; and consulting/honoraria from Theracos (DSMB member).

NP has received research grants from Servier and speaking honoraria from Servier, Novo Nordisk and Amgen.

LEP was an employee and stockholder of Amylin Pharmaceuticals at the time of trial initiation.

AR received remuneration for Advisory board meetings from Merck, Sharp & Dohme, and AstraZeneca; and honoraria for lectures from Bayer, Novo Nordisk, Eli Lilly, Merck, Sharp & Dohme, and Novartis; research grant from Merck, Sharp & Dohme.

BZ reports grants support from Merck, Boehringer Ingelheim and Novartis. He serves on medical advisory boards for Eli Lilly, Merck, Novo Nordisk, Janssen, Takeda and Astra Zeneca.

RMC has received grants from Amylin, Novartis, Schering-Plough Research Institute, Scios, Eli Lilly, Johnsons & Johnson/Scios, Aterovax, Bayer, the NIH, and the Patient-Centered Outcomes Research Institute; grants and personal fees from Bristol-Myers Squibb, Janssen Research & Development, Merck, and Roche; personal fees from Genentech, GlaxoSmithKline, Heart.org/Daiichi Sankyo, Kowa, Servier, Medscape, Regeneron, TMC, Pfizer, Gambro, Gilead, DSI-Lilly, CV Sight, Heart.org/Bayer, Bayer Pharma AG, Bayer Healthcare, Parkview, Pozen, Orexigen, Nile, and WebMD; and other financial support from N30 Pharmaceuticals, Portola, and Nitrox LLC, all outside the submitted work.

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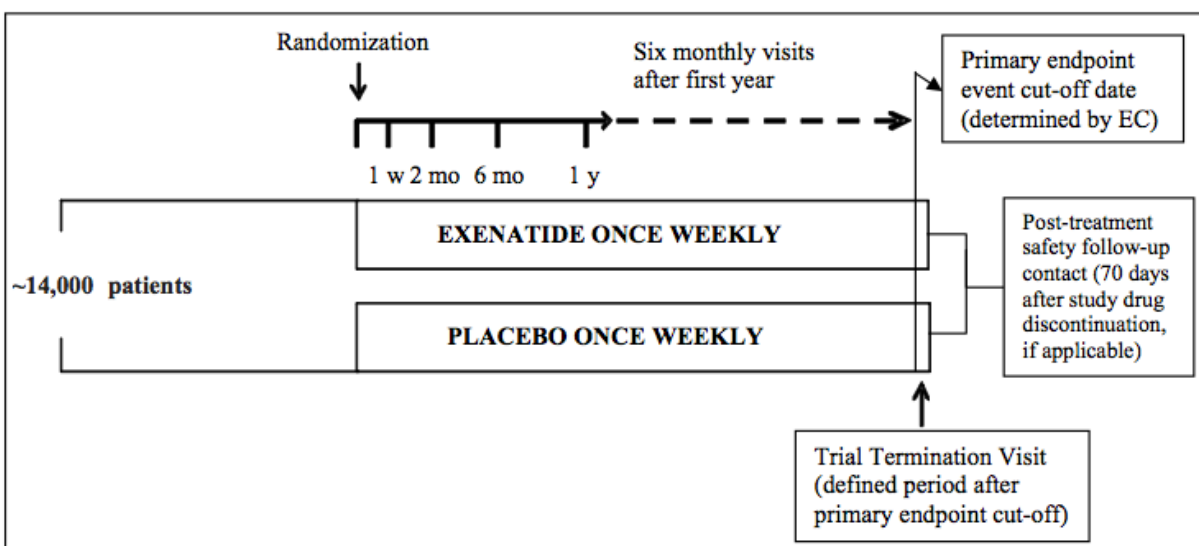
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Figure legends

Figure 1: Design of the EXenatide Study of Cardiovascular Event Lowering (EXSCEL)

trial

Figure 1: Design of the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) trial: It is planned to continue until 1360 patients with a confirmed primary composite cardiovascular endpoint have been accrued.



Appendix A: EXSCEL inclusion and exclusion criteria

Inclusion Criteria		
	Criterion	Rationale
a	Patient has T2DM	As EXSCEL is designed to evaluate the efficacy of EQW on CV risk reduction in patients with T2DM, this criterion ensures selection of the correct target study population.
b	Patient will be able to see a usual care provider at least twice a year	As a pragmatic clinical trial, the study is designed to integrate with routine clinical care in order to generalize to clinical practice. Glucose (or other CV factors) are managed per local guidelines rather than study specific pre-defined targets. This criterion enhances safety by ensuring that patients receive regular medical follow-up.
c	Patient has an HbA1c of >6.5 % and <10.0%	A lower limit of HbA1c (6.5%) is set <ul style="list-style-type: none"> (i) to minimize the risk of hypoglycaemia, (ii) most international guidelines do not recommend intensification of glucose-lowering therapy at HbA1c levels less than 6.5. An upper limit of HbA1c (10%) is set to ensure patients enrolled have had initial treatment and there are no delays in intensification of therapy.
d	Recruitment will be constrained such that approximately 30% will not have had a prior CV event and 70% will have had a prior CV event	The EXSCEL study seeks to characterize the effects of EQW on CV-related outcomes in patients with T2DM. It is therefore important ensure that the study population represents the full spectrum of CV risk in such patients.
e	Female patients must not be breastfeeding and agree to use an effective method of contraception or must not	This criterion aims to limit exposure of the study drug to infants and developing fetuses.

	otherwise be at risk of becoming pregnant	
f	Patient understands the trial procedures, alternative treatments available, the risks involved with the trial, and voluntarily agrees to participate by providing written informed consent	Consistent with the principles of the Declaration of Helsinki and Good Clinical Practice.
g	Patient agrees to provide permission to obtain all medical records necessary for complete data ascertainment during the follow-up period, and agrees to communication between the trial site and the usual care provider in order to facilitate routine care	Bidirectional communication between the site and usual care provider enhances patient safety. Additionally, this criterion is required to ensure study endpoints collection is as accurate and comprehensive as possible.
h	Patient is ≥ 18 years of age at enrolment	As the safety and efficacy of EQW has not yet been established in the pediatric population (i.e., < 18 years), the age cutoff was selected to ensure patient safety. In young adults, the baseline risk of CV disease is very low and hence any change in the risk score is unlikely to be demonstrable within the duration of the study.

CV indicates cardiovascular; EQW, exenatide once weekly; T2DM, type 2 diabetes mellitus.

Exclusion Criteria		
	Criterion	Rationale
a	Patient has a diagnosis of T1DM or a history of ketoacidosis	EXSCEL is a study of CV risk lowering in patients with T2DM. It is important to exclude patients with other types of DM.
b	Patient has a history (≥ 2 episodes) of severe hypoglycaemia within 12 months of enrolment	Patients with recurrent episodes of severe hypoglycaemia (defined as being sufficiently disoriented or incapacitated as to require assistance) are at increased risk of serious adverse events, including mental confusion, unconsciousness, seizures, and death. This criterion enhances patient safety by minimizing the risk of hypoglycaemia in the trial population.
c	Patient has ever been treated with an approved or investigational GLP-1 receptor agonist.	This criterion is designed to minimize the risk of inadvertent unblinding – patients previously treated with GLP-1 receptor agonists may be aware of the typical symptoms associated with GLP-1 treatment (feeling of fullness, nausea, etc.) and to avoid any potential legacy effect of earlier treatment.
d	Patient is enrolled in another experimental protocol which involves the use of an investigational drug or device, or an intervention that would interfere with the conduct of the trial	This criterion enhances patient safety by minimizing the risk of drug-drug interactions. Furthermore adverse events cannot be attributed clearly to the study drug if participants are enrolled in multiple trials concurrently.
e	Patient has a planned or anticipated revascularization procedure	Revascularisation procedures substantially alter the subsequent risk of cardiovascular events and have the potential to affect the primary outcome, thus compromising data integrity.
f	Pregnancy or planned pregnancy during the trial period	This criterion aims to limit exposure of the study drug to infants and developing fetuses.

g	Patient has medical history that indicates a life expectancy of <2 years or might limit the individual's ability to take trial treatments for the duration of the trial	The EXSCEL study assesses all-cause mortality as an outcome. Since the anticipated duration of follow-up is 2 years or more, patients with end-of-life illness or those who are unable to take trial treatment (which involves a once weekly injection) may compromise data integrity.
h	Patient has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance which, in the opinion of the investigator or coordinator, might pose an unacceptable risk to the patient, confound the results of the trial (e.g., if patient cannot comply with requirements of the trial), or likely to interfere with the patient's participation for the full duration of the trial	This criterion enhances patient safety and ensures the study results are valid.
i	Patient has end-stage renal disease or an eGFR <30 mL/min/1.73m ²	Since exenatide is not recommended for use in individuals with severe renal impairment or end-stage renal disease, this criterion enhances patient safety.
j	Patient has a known allergy or intolerance to exenatide	Enhances patient safety by avoiding re-exposure to allergens and decreasing the potential for hypersensitivity reactions, which may result in swelling, difficulty breathing, skin reactions, etc.
k	Patient has a history of gastroparesis	Exenatide slows down gastric emptying – which could worsen the symptoms of gastroparesis.
l	Personal or family history of MTC or MEN2 or calcitonin level of >40 ng/L at baseline.	There have been putative concerns about the potential for exenatide to cause thyroid C-cell hyperplasia in rodent studies. To date, human studies have not shown an association between exenatide use and

		increased risk of thyroid neoplasm. As a safety measure, patients with an increased risk of MTC, conditions associated with an increased risk of MTC (such as MEN2), or elevated calcitonin levels (which is secreted by thyroid C-cells and is used as a marker for MTC) will be excluded.
m	Patient previously randomized to EXSCEL	Avoids duplicate enrolment.
n	Patient has a history of pancreatitis	There are concerns raised about the potential for GLP-1 receptor agonists to worsen the increased background risk for patients with T2DM to develop pancreatitis. As individuals with a prior episode of pancreatitis may be at increased risk for recurrence, this criterion enhances patient safety.
o	Is an employee of Amylin Pharmaceuticals, Bristol-Myers Squibb, or AstraZeneca	This criterion avoids the potential conflicts of interest from employees of the sponsor (and its affiliates) being randomized.

CV indicates cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; MEN2, Multiple endocrine neoplasia Type 2; MTC, medullary thyroid cancer; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Appendix B: List of primary and secondary efficacy endpoints

1. Primary Efficacy Endpoint

- Time to first confirmed CV event in the primary composite CV endpoint
Defined as the time from randomization to first confirmed CV-related death, nonfatal MI or nonfatal stroke.

2. Secondary Efficacy Endpoints

Measured as time from randomisation to

- All-cause mortality
Defined as time from randomization to death due to any cause.
- Time to first confirmed CV event for each component of the primary composite endpoint
Defined as time from randomization to a confirmed:
 - CV-related death
 - Nonfatal MI or
 - Nonfatal stroke.
- Time to hospitalization for acute coronary syndrome
Defined as time from randomization to a confirmed hospital admission for unstable angina, ST-elevation myocardial infarction or non-ST-elevation myocardial infarction
- Time to hospitalization for heart failure
Defined as time from randomization to hospital admission for congestive heart

failure requiring treatment with intravenous diuretics, inotropes, or vasodilator therapy

3. Additional Efficacy Endpoints

- Time to revascularization procedure

Defined as time from randomization to time of first cardiovascular or peripheral revascularization procedure. This will include:

- Percutaneous coronary intervention with or without stenting
 - Coronary artery bypass grafting
 - Revascularization and/or stenting for peripheral arterial disease
 - Carotid endarterectomy
 - Carotid stenting.
- Time to initiation of first co-interventional agent
 - Additional oral antihyperglycaemic agent
 - Chronic insulin therapy
 - Number of episodes of severe hypoglycemia requiring medical assistance
 - Absolute values and change from baseline in:
 - HbA1c
 - Body weight
 - Blood pressure
 - Lipid profile
 - Heart rate
 - Patient-reported quality of life assessed by the EQ-5D (EuroQol 5 Dimension) questionnaire.

Physician-reported medical resource use and total direct medical costs.

- Incremental cost-effectiveness analysis of once-weekly exenatide as part of usual care compared with usual care without once-weekly exenatide

Appendix C: Subgroup analyses

- Class of antihyperglycaemic agent at entry (monotherapy/combination)
- Ethnicity/race
- Region
- Sex
- Age (<65 or ≥65 years)
- Baseline HbA1c (<8.0% or ≥8.0%)
- Baseline BMI (<30 or ≥30 kg/m²)
- Duration of diabetes (<5 or ≥5 years)
- Baseline eGFR (<60 mL/min or ≥60 mL/min)
- History of previous cardiovascular events

Appendix D: EXSCEL Committee Members

Executive Committee

Rury R. Holman (Co-chair; Diabetes Trials Unit, University of Oxford, Oxford, UK), Adrian F. Hernandez (Co-chair; Duke Clinical Research Institute, Durham, NC, USA), John B. Buse (University of North Carolina at Chapel Hill, Chapel Hill, NC, USA), Juliana C. Chan (The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China), Nayyar Iqbal (AstraZeneca, Gaithersburg, MD, USA), Aldo Maggioni (ANMCO Research Centre, Florence, Italy), Steven P. Marso (University of Missouri, Kansas City, MO, USA), Peter Öhman (AstraZeneca, Gaithersburg, MD, USA), Neil Poulter (Imperial College London, London, UK), Ambady Ramachandran (India Diabetes Research Foundation and Dr. A. Ramachandran's Diabetes Hospitals, Chennai, India), and Bernie Zinman (Mount Sinai Hospital and University of Toronto, Toronto, Ontario, Canada). Previously: Robert M. Califf (Co-chair; Duke Translational Medicine Institute, Durham, NC, USA), Lisa E. Porter (Dance Biopharm, Inc, Brisbane, CA, USA).

Data Safety and Monitoring Board

Jean Rouleau (Chair; Institute of Circulatory & Respiratory Health of the Canadian Institutes of Health and Research Canada, Montreal, Quebec, Canada), Rob Gagel (The University of Texas MD Anderson Cancer Center, Houston, TX, USA), Fred Gorelick (Yale School of Medicine, New Haven, CT, USA), John McMurray (University of Glasgow, Glasgow, UK), Stuart Pocock (London School of Hygiene and Tropical Medicine, London, UK), Matt Riddle (Oregon Health and Science University, Portland,

OR, USA), and Tim Collier (Independent statistician; London School of Hygiene and Tropical Medicine, UK).

Clinical Leads

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Robert J. Mentz (Duke Clinical Research Institute, Durham, NC, USA).

Previously: M. Angelyn Bethel (Diabetes Trials Unit, University of Oxford, Oxford, UK),

H. Sourij (Diabetes Trials Unit, University of Oxford, Oxford, UK).

Clinical Events Committee

Duke Clinical Research Institute: Jennifer Green, Renato Lopes, Rajendra Mehta, Chet Patel, Wanda Lakey, Bimal Shah, Keyur Patel, Jodi Hawes, Michael Morse, Zubin Eapen, Daniel George.

Fondazione IRCCS Policlinico San Matteo: Sergio Leonardi.

Strategic Advisory Committee

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Duke Clinical Research Institute: Dianne Leloudis, Adrian Hernandez

Diabetes Trials Unit: Jyothis George, Paul Heal

Bristol-Myers Squibb: George Klinger, Leigh Townes

AstraZeneca: Nardev Khurmi, Lynne Durborow

PAREXEL: Carmen Anders

Operations Committee

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Belgium: Chantal Mathieu; Brazil: Renato Lopes; Bulgaria: Tsvetalina Tankova;
Canada: Shaun Goodman, Jean Francois Yale; Chile: Fernando Lanas; China: Dayi Hu,
Li Nong Ji, Chang Yu Pan; Colombia: Miguel Urina; Czech Republic: Petr Widimský;
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Julio Wainstein; Italy: Stefano Del Prato; South Korea: Kun Ho Yoon; Latvia: Valdis
Pīrāgs; Lithuania: Neli Jakuboniene; Malaysia: Sim Kui-Hian; Mexico: Jose Luis Leiva-
Pons; Netherlands: Adriaan Kooy; New Zealand: Russell Scott; Philippines: Araceli
Panelo; Poland: Poitr Dziemidok; Romania: Ioan Andrei Veresiu; Russia: Alexander
Dreval; Slovakia: Ján Murín; South Africa: Mahomed Omar; Spain: Albert Lecube;
Taiwan: Wayne Sheu; Thailand: Piyamitr Sritara; Ukraine: Alexander Parkhomenko;
United Kingdom: Naveed Sattar; United States: David Aguilar, Richard Bergenstal.