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Vilanterol and fluticasone furoate for asthma (Review)

Dwan K, Milan SJ, Bax L, Walters N, Powell C

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Vilanterol and fluticasone furoate for asthma.

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Vilanterol and fluticasone furoate for asthma (Review)

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[Intervention Review]

Vilanterol and fluticasone furoate for asthma

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ABSTRACT

Background

Vilanterol (VI) is a long-acting beta₂-agonist (LABA) that binds to the beta₂-adrenoceptor on the airway smooth muscle, producing bronchodilation. LABA therapy, which is well established in adults as part of the British Thoracic Society (BTS) Guidelines for the Management of Asthma, leads to improvement in symptoms and lung function and reduction in exacerbations. At present, the commonly used LABAs licensed for use in asthma management (formoterol and salmeterol) require twice-daily administration, whereas VI is a once-daily therapy.

Fluticasone furoate (FF) is an inhaled corticosteroid (ICS), and ICS therapy is recommended by the BTS asthma guidelines. ICSs, the mainstay of asthma treatment, lead to a reduction in both airway inflammation and airway hyper-responsiveness. Regular use leads to improvement in symptoms and lung function. ICSs are currently recommended as 'preventer' therapy for patients who use a 'reliever' medication (e.g. short-acting beta₂ agonist (SABA), salbutamol) three or more times per week. Most of the commonly used ICS treatments are twice-daily medications, although two once-daily products are currently licensed (ciclesonide and mometasone).

At the present time, only one once-daily ICS/LABA combination (FF/VI) is available, and several other combination inhalers are recommended for twice-daily administration.

Objectives

To compare effects of VI and FF in combination versus placebo, or versus other ICSs and/or LABAs, on acute exacerbations and on health-related quality of life (HRQoL) in adults and children with chronic asthma.

Search methods

We searched the Cochrane Airways Group Register of trials, clinical trial registries, manufacturers' websites and reference lists of included studies up to June 2016.

Selection criteria

We included randomised controlled trials (RCTs) of adults and children with a diagnosis of asthma. Included studies compared VI and FF combined versus placebo, or versus other ICSs and/or LABAs. Our primary outcomes were health-related quality of life, severe asthma exacerbation, as defined by hospital admissions or treatment with a course of oral corticosteroids, and serious adverse events.

Vilanterol and fluticasone furoate for asthma (Review)

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Data collection and analysis

Two review authors independently extracted data and analysed outcomes using a fixed-effect model. We used standard Cochrane methods.

Main results

We identified 14 studies that met our inclusion criteria, with a total of 6641 randomised participants, of whom 5638 completed the study. All studies lasted between two and 78 weeks and showed good methodological quality overall.

We included 10 comparisons in this review, seven for which the dose of VI and FF was 100/25 mcg (VI/FF 100/25 mcg vs placebo; VI/FF 100/25 mcg vs same dose of FF; VI/FF 100/25 mcg vs same dose of VI; VI/FF 100/25 mcg vs fluticasone propionate (FP) 500 mcg twice-daily; VI/FF 100/25 mcg vs fluticasone propionate/salmeterol (FP/SAL) 250/50 mcg twice-daily; VI/FF 100/25 mcg vs FP/SAL 250/25 mcg twice-daily; FF/VI 100/25 vs FP/SAL500/50) and three for which the dose of VI and FF was 200/25 mcg (VI/FF 200/25 mcg vs placebo; VI/FF 200/25 mcg vs FP 500 mcg; VI/FF 200/25 mcg vs same dose of FF).

We found very few opportunities to combine results from the 14 included studies in meta-analyses. We tabulated the data for our pre-specified primary outcomes. In particular, we found insufficient information to assess whether once-daily VI/FF was better or worse than twice-daily FP/SAL in terms of efficacy or safety.

Only one of the 14 studies looked at health-related quality of life when comparing VI and FF 100/25 mcg versus placebo and identified a significant advantage of VI/FF 100/25 mcg (mean difference (MD) 0.30, 95% confidence interval (CI) 0.14 to 0.46; 329 participants); we recognised this as moderate-quality evidence. Only two studies compared VI/FF 100/25 mcg versus placebo with respect to exacerbations; both studies reported no exacerbations in either treatment arm. Five studies (VI/FF 100/25 mcg vs placebo) sought information on serious adverse events; all five studies reported no serious adverse events in the VI/FF 100/25 mcg or placebo arms. We found no comparison relevant to our primary outcomes for VI/FF at a higher dose (200/25 mcg) versus placebo.

The small number of studies contributing to each comparison precludes the opportunity to draw robust conclusions for clinical practice. These studies were not of sufficient duration to allow conclusions about long-term side effects.

Authors' conclusions

Some evidence suggests clear advantages for VI/FF, in combination, compared with placebo, particularly for forced expiratory volume in one second (FEV₁) and peak expiratory flow; however, the variety of questions addressed in the included studies did not allow review authors to draw firm conclusions. Information was insufficient for assessment of whether once-daily VI/FF was better or worse than twice-daily FP/SAL in terms of efficacy or safety. It is clear that more research is required to reduce the uncertainties that surround interpretation of these studies. It will be necessary for these findings to be replicated in other work before more robust conclusions are revealed. Only five of the 13 included studies provided data on health-related quality of life, and only six recorded asthma exacerbations. Only one study focused on paediatric patients, so no conclusions can be drawn for the paediatric population. More research is needed, particularly in the primary outcome areas selected for this review, so that we can draw firmer conclusions in the next update of this review.

PLAIN LANGUAGE SUMMARY

Vilanterol and fluticasone furoate for chronic asthma in adults and children

Review question

We considered in this review whether the combination of vilanterol (VI) and fluticasone furoate (FF) is better than placebo for people with asthma. We also compared VI and FF with other inhaled steroids and long-acting beta₂-agonist medications.

Background

Asthma is an inflammatory lung condition whereby the pathway through the airways may become very restricted. By the year 2025, it is estimated that 400 million people will have this condition. Asthma can very seriously affect people's quality of life, and the combination of VI and FF may help to reduce difficulties related to the impact on everyday life of breathlessness and other associated symptoms.

Study characteristics

We included 14 studies in this review, involving a total of 6641 participants. All studies lasted between two and 78 weeks. All people included in these studies had received a diagnosis of asthma. Trials included both men and women, and one study included children and young people.

All studies looked at VI and FF versus another medication or placebo. In all studies, the VI/FF combination was taken through a dry powder inhaler.

Key results

We found that participants who received a combination of FF and VI therapy had improved lung function compared with those given placebo, but evidence was insufficient to permit any other conclusions because researchers attempted to answer too many different questions. Evidence was lacking on whether the combination of VI and FF therapy once-daily is better or worse than a twice-daily alternative. More studies are needed, so that we can gain a better understanding of the evidence overall.

Quality of the evidence

Overall, the evidence presented in this review is taken from well-designed studies at low risk of bias in terms of decisions on who received which treatment, blinding and how to report outcomes for participants who did not finish the study. However, because we were not able to combine results for many of our outcomes of interest, or because the outcome was rare, we judged the quality of the evidence overall to be low to moderate.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

| VI and FF compared with placebo for asthma | | | | | |
|--|--|--------------------------|------------------------------|--|---------------------------------|
| Patient or population: people with asthma Settings: community Intervention: VI and FF Comparison: placebo | | | | | |
| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Quality of the evidence (GRADE) |
| | Assumed risk | Corresponding risk | | | |
| | Placebo | VI and FF | | | |
| Health-related quality of life | 0.61 (SE 0.061), n = 149 | 0.91 (SE 0.055), n = 180 | MD 0.30, 95% CI 0.14 to 0.46 | Bleecker 2012 (N = 609 participants, 515 completed study) compared VI/FF 100/25 mcg vs placebo in respect of health-related quality of life and indicated a significant advantage for VI/FF 100/25 mcg | Moderate ^a |
| Asthma exacerbation | | | Not estimable | Only 2 studies (Allen 2013 and Kempford 2012a) compared VI/FF 100/25 mcg vs placebo in respect of exacerbations; both studies reported no exacerbations in either treatment arm | Very low ^b |
| Serious adverse events | | | Not estimable | Five trials (Allen 2013; Bleecker 2012; Kempford 2012a; Oliver 2012; Oliver 2013) made this same com- | Very low ^b |

| | | | | | |
|----------------------|------------------------------------|-------------------------------------|--|---|-----------------------|
| | | | | parison in relation to serious adverse events; all 5 reported no serious adverse events in VI/FF100/25 mcg or placebo arms | |
| FEV ₁ | 0.196 L (SE 0.0310), n = 193 | 0.368 L (SE 0.0304), n = 200 | MD 0.17 L, 95% CI 0.09 to 0.26 | Significant difference in favour of VI/FF 100/25 mcg vs placebo with respect to mean change in trough FEV ₁ (pre-bronchodilator and pre-dose) from baseline to week 12 in 1 trial (Bleecker 2012) (N = 609 participants, 515 completed study) (MD 0.17 L, 95% CI 0.09 to 0.26), and a similar effect was found in a small cross-over trial (Kempford 2012a) over a 2-week period in the morning (MD 0.377 L, 90% CI 0.293 to 0.462) and in the evening (MD 0.422 L, 90% CI 0.337 to 0.507) | Moderate ^c |
| Peak expiratory flow | -0.4 L/min (SE 2.42), n = 203 | 32.9 L/min (SE 2.42), n = 201 | MD 33.30 L/min, 95% CI 26.59 to 40.01 | Bleecker 2012 (N = 609 participants, 515 completed study) compared VI/FF 100/25 mcg vs placebo as mean change from baseline in daily morning (AM) PEF averaged over 12-week treatment period; researchers noted a significant difference in favour of VI/FF 100/25 mcg (MD 33.30 L/min, | Moderate ^c |

| | | | | |
|-----------------|-------------------------|-------------------------|---------------------------------|---|
| | | | | 95% CI 26.59 to 40.01). The same trial showed a similar advantage in favour of VI/FF 100/25 mcg vs placebo in the evening over this period (28.20 L/min, 95% CI 21.67 to 34.73). A small cross-over trial (Kempsford 2012a) produced a similar effect in favour of VI/FF 100/25 mcg vs placebo over a 2-week period in the morning (MD 44.0 L/min, 90% CI 31.2 to 56.9) and in the evening (MD 69.0 L/min, 90% CI 55.9 to 82.1) |
| Asthma symptoms | 14.6 (SE 2.15), n = 202 | 32.5 (SE 2.14), n = 201 | MD 17.90, 95% CI 11.95 to 23.85 | Only 1 trial (Bleecker 2012) (N = 609 participants, 515 completed study) made VI/FF vs placebo comparison with respect to asthma symptoms, indicating a clear advantage for VI/FF 100/25 mcg Moderate ^a |
| Adverse events | | | Not estimable | Several trials reported a Moderate ^d range of adverse events for which overall aggregation was not possible. These are tabulated in Table 8 |

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)

AM: morning; CI: confidence interval; FEV₁: forced expirator volume in one second; FF: fluticasone furoate; GRADE: Grades of Recommendation, Assessment, Development and Evaluation Working Group; MD: mean difference; OR: odds ratio; PEF: peak expiratory flow; PM: afternoon; RR: risk ratio; SE: standard error; VI: vilanterol

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: We are very uncertain about the estimate

^aPoint deducted to reflect that these data were derived from only one trial

^bInvestigators reported no events in either arm of these trials

^cPoint deducted to reflect that data contributing to the main result (MD 0.17 L, 95% CI 0.09 to 0.26) were obtained from only one trial

^dPoint deducted, as we were unable to combine data on this outcome; results are presented in a separate table

BACKGROUND

Description of the condition

Asthma, a chronic respiratory disease, may be well controlled at times, but periods of marked deterioration in symptoms and lung function (referred to as an exacerbation) may abruptly occur. Currently, the number of people with asthma is estimated at 300 million, and forecasts suggest that by 2025, the total will be closer to 400 million (WHO 2007). Between 2001 and 2009, the number of people with asthma increased from 20 million to 25 million in the United States, where prevalence rates are slightly lower among adults (8%) than children (10%) (CDC 2012; CDCP 2011). Considerable differences in asthma prevalence have been noted among different ethnic groups. Between 2008 and 2010, US rates were as follows: multiple-race 14.1%, Alaskan Native 9.4%, American Indian 9.4%, black 11.2%, white 7.7% and Asian 5.2% (CDCP 2011). The prevalence of wheezing symptoms in children varies geographically, with the UK having the highest recorded prevalence of current wheezing at 32.3%, and Ethiopia the lowest at 1.7% (Parel 2008).

Asthma is associated with impaired quality of life (Clayton 2005), and the condition presents financial implications (Wu 2007). Each year, asthma exacerbations impact approximately 10 million people in the USA (Krishnan 2006). Other countries report similarly high incidence rates; in the UK, more than 65,000 hospital admissions for asthma occurred in the period from 2005 to 2006 (NHS 2011). Well-recognised factors can be addressed to prevent hospital admissions in children with acute asthma (Ordonez 1998). In recent years, evidence-based clinical guidelines have emerged, at both national (e.g. BTS/SIGN 2014; NIH 2007) and international (e.g. GINA 2015) levels, to provide guidance for the management of asthma. Asthma is a consequence of airways inflammation, but with appropriate clinical management, health-related quality of life can be maintained for considerable periods (WHO 2011). Mortality specifically associated with both asthma and asthma morbidity is a major health concern (Braman 2006).

Description of the intervention

Asthma is a chronic inflammatory disorder of the airways that is characterised by reversible airways obstruction. A combination of inhaled corticosteroid (ICS) and long-acting beta₂-agonist (LABA) is recommended for patients at step three of the British Thoracic Society guidelines, that is, patients not controlled by ICS alone. Evidence suggests that addition of a LABA to ICS alone can lead to improved lung function, improved symptoms, reduced use of rescue medications and reduced asthma exacerbations among patients with uncontrolled symptoms (BTS/SIGN 2014). Although generally less effective, the combination of ICS

and a leukotriene antagonist (LTRA) is a valid alternative to ICS combined with LABA (Montuschi 2008; Montuschi 2010).

Inhaled corticosteroids are fundamental in the treatment of asthma, and fluticasone furoate (FF) belongs to this class of drugs. Inhaled corticosteroids work by reducing inflammation and airway hyper-responsiveness (Barnes 1998), thus improving symptoms of asthma and lung function (Montuschi 2011). Most available ICS' are administered twice-daily, and studies have shown that once-daily use is less effective and leads to an increase in the requirement for rescue medication (BTS/SIGN 2014; Weiner 1995).

Vilanterol (VI) is a new drug that belongs to the LABA class. It has a rapid onset of action in experimental models and a 24-hour duration of bronchodilating effects in patients with asthma (Fuso 2013). Long-acting beta₂-agonist therapy added to ICS treatment in asthma has been shown to improve lung function, reduce asthma symptoms and decrease exacerbation rates (Remington 2005). Available LABAs licensed for the treatment of patients with asthma require twice-daily administration. Indacaterol and olodaterol are approved for chronic obstructive pulmonary disease (COPD) and require once-daily administration.

At the present time, several combination inhalers containing both ICS and LABA are available for the treatment of adults with asthma. However, all of these involve twice-daily dosing, which is less convenient for patients and leads to reduced adherence with long-term therapy. Clinicians anticipate that providing a once-daily combination inhaler would lead to increased adherence with treatment long-term among people with asthma.

Investigators have provided few data on once-daily combination treatments other than VI and FF for asthma. A 12-week randomised controlled double-blind study of 531 children aged six to 15 years showed that taking a single inhaler containing budesonide and formoterol once-daily maintained pulmonary function, but taking the same inhaler twice-daily resulted in improved pulmonary function, fewer discontinuations for worsening asthma and less need for daytime rescue medication (Eid 2010). Once-daily budesonide/formoterol has shown improved asthma control when compared with once-daily budesonide alone (at a four times higher dose) in children four to 11 years of age (Bisgaard 2006).

How the intervention might work

Inhaled corticosteroids serve as the cornerstone of asthma treatment and are initiated when patients require use of short-acting 'reliever' medications on a regular basis. As well as the benefits mentioned previously, patients who are compliant with ICS therapy demonstrate a reduction in asthma exacerbations and in mortality related to asthma (Powell 2003). It is well recognised that poor adherence is a major issue among patients with poorly controlled symptoms (BTS/SIGN 2014). One of the issues that may contribute to this is the twice-daily dosing regimen of most ICS'. Fluticasone furoate is a relatively new long-acting ICS. It remains active for at least 24 hours after administration. Early studies have

shown improvement in lung function tests and a favourable safety and tolerability profile (Bleecker 2011; Woodcock 2011).

In recent years, investigators have provided increasing evidence for the addition of LABAs to ICS therapy for the treatment of patients with asthma, and the benefit appears to consist of more than bronchodilatation alone. The action of corticosteroids is mediated by cytoplasmic glucocorticoid receptors (GRs); after binding with corticosteroids, GRs translocate to the nucleus, where they are able to regulate gene expression (Montuschi 2011). Long-acting beta₂-agonists have also been shown to induce GR nuclear translocation, although not as effectively as glucocorticoids. Study of sputum epithelial cells and macrophages of people with asthma has shown that the LABA, salmeterol, given in combination with fluticasone propionate (FP), was more effective than low-dose FP alone in enhancing GR nuclear translocation (Usmani 2005).

Interleukin-8 (IL-8) is a chemokine that has been implicated in the abnormal airway inflammation seen in patients with asthma; studies have shown that study participants with clinically stable asthma have higher levels of IL-8 in bronchoalveolar lavage samples than normal healthy control participants (Nocker 1996). A study looking at IL-8 production from neutrophils stimulated by cigarette smoke reported that salmeterol and FP additively suppressed IL-8 release from neutrophils when compared with either agent alone. This effect is not seen in all human cell types and appears to be cell-specific. The mechanism of action is not yet clear, but researchers have suggested that increased translocation of GRs to the nucleus may be involved (Mortaz 2008).

For patients whose condition is uncontrolled by regular ICS therapy, current British Thoracic Society (BTS) guidelines recommend the addition of a LABA, such as salmeterol or formoterol (BTS/SIGN 2014). Both of these medications have a twice-daily dosing regimen that affects adherence and, therefore, asthma control. Long-acting beta₂-agonists are of benefit because of their bronchodilation effect, and VI is a new selective beta₂-agonist within this class (Cazzola 2011). It has been shown that VI is well tolerated with no significant adverse effects (Kempford 2013), and that it leads to an increase in symptom-free periods and a reduction in the use of rescue medication (Lotvall 2012).

In summary, limited studies suggest that effective once-daily ICS and LABA therapy would allow a once-daily dosing regimen (e.g. Kuna 2006), leading to the possibility of increased adherence and improved asthma control in adults and in children.

Why it is important to do this review

Published randomised trials have examined use of VI and FF in combination. This review aims to establish whether VI combined with FF may play a positive role in the management of chronic asthma among children and adults. This is important to determine, as a VI/FF combination would consist of a once-daily medication. This dosing regimen may lead to increased medication

adherence, improved health-related quality of life (HRQoL) and reduced asthma exacerbations and symptoms.

OBJECTIVES

To compare effects of VI and FF in combination versus placebo, or versus other ICSs and/or LABAs, on acute exacerbations and on HRQoL in adults and children with chronic asthma.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) reported as full text, those published as abstract only and unpublished data.

Types of participants

We included studies involving adults and children with a diagnosis of asthma. We excluded participants with the following comorbidities: co-existing chronic disease such as smoking-related COPD, congenital heart disease and diseases such as cystic fibrosis and chronic renal failure. We also excluded people who are current smokers and pregnant women.

Types of interventions

We planned to include studies comparing the following interventions.

- VI and FF versus placebo.
- VI and FF versus ICS and required short-acting beta₂-agonist (SABA).
- VI and FF versus other combination inhalers.
- VI and FF versus ICS and LABA in separate inhalers.

We also planned to include the following co-interventions, provided they were not part of the randomised treatment: bronchodilators, systemic steroids, leukotriene antagonists, oral aminophylline and macrolide antibiotics.

Types of outcome measures

Primary outcomes

- Health-related quality of life.
- Severe asthma exacerbation as defined by hospital admission or treatment with a course of oral corticosteroids (OCS)
- Serious adverse event*.

Secondary outcomes

- Measures of lung function: forced expiratory flow in one second (FEV₁), peak expiratory flow (PEF).
- Asthma symptoms.
- Adverse events/side effects.

A study report describing one or more of the outcomes listed here was not an inclusion criterion for the review.

*Defined as any adverse event or adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation or results in persistent or significant disability or incapacity.

Search methods for identification of studies

Electronic searches

We identified studies by searching the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Information Specialist for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, and by handsearching of respiratory journals and meeting abstracts (please see [Appendix 1](#) for further details). We searched all records in the CAGR using the search strategy presented in [Appendix 2](#). We also conducted a search of ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/). We

searched all databases from their inception to 24 June 2016, and we imposed no restriction on language of publication.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We searched relevant manufacturers' websites for trial information.

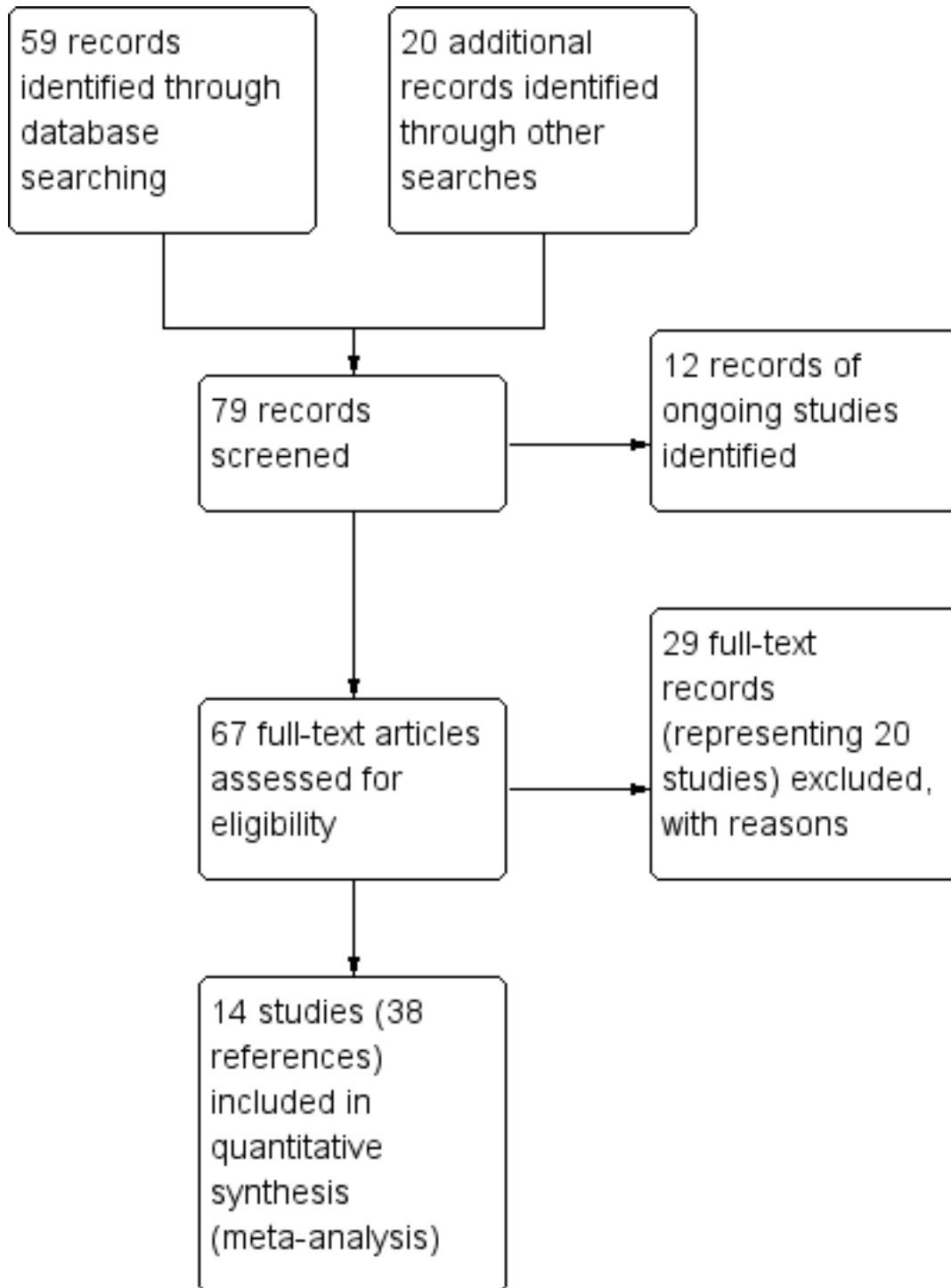
We searched on 24 June 2015 for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed).

Data collection and analysis

Selection of studies

Two review authors (LB, NW) independently screened the titles and abstracts of all studies identified for possible inclusion as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved full-text study reports/publications, and two review authors (LB, NW) independently screened the full text, identified studies for inclusion and identified and recorded reasons for exclusion of ineligible studies. We planned to resolve disagreements through discussion or, if required, by consultation with a third review author (CP); however, this was not necessary. We identified and excluded duplicates and collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram ([Figure 1](#)) and entered data regarding all studies into the [Characteristics of included studies](#) table.

Figure 1. Study flow diagram.



Data extraction and management

We used a data collection form that had been piloted on at least one study in the review to record study characteristics and outcome data. Two review authors (CP, SJM) extracted study characteristics from reports of included studies. We extracted the following study characteristics.

- Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and locations, study settings, withdrawals and date of study.
- Participants: number (N), mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications and excluded medications.
- Outcomes: primary and secondary outcomes specified and collected and time points reported.
- Notes: funding for trial and notable conflicts of interest of trial authors.

Two review authors (CP, SJM) independently extracted outcome data from the included studies. We noted in the [Characteristics of included studies](#) table if outcome data were not reported in a useable way. We planned to resolve disagreements by consensus or by consultation with a third review author (NW); however, this was not necessary. One review author (KD) transferred data into the Review Manager ([Review Manager 2014](#)) file. We double-checked that data were entered correctly by comparing data presented in the systematic review with those provided in study reports. A second review author (SJM) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (CP, SJM) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We planned to resolve disagreements by discussion or by consultation with another review author (KD); however, this was not necessary. We assessed risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We graded each potential source of bias as high, low or unclear, and provided a quote from the study report together with a justification

for our judgement in the 'Risk of bias' table. We summarised risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). When information on risk of bias was related to unpublished data or to correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering each treatment effect, we took into account the risk of bias for studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to this published protocol and reported any deviations from it in the [Differences between protocol and review](#) section of the systematic review.

Measures of treatment effect

We planned to analyse dichotomous data as odds ratios (ORs) and continuous data as mean differences (MDs) or standardised mean differences (SMDs), and to present them with 95% confidence intervals (CIs). We entered data presented as a scale with a consistent direction of effect.

We undertook meta-analyses only when data were available, and when it was meaningful to do so (i.e. when treatments, participants and the underlying clinical question were similar enough for pooling to make sense).

We will narratively describe skewed data reported as medians and interquartile ranges if reported for future updates of this review.

When a single trial reported multiple trial arms, we included only the relevant arms.

Unit of analysis issues

We identified cross-over trials and sought data for a paired analysis from the trial report or study authors to appropriately include data in the review using the inverse variance method. However, this was unsuccessful, and we provided the data in additional tables. We identified no cluster-randomised trials, but future versions of this review will analyse data at the level of the individual while allowing for clustering in the data by using the intracluster correlation coefficient. If this is not reported in the trial, we will impute it from similar studies.

Dealing with missing data

We planned to contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome

data when possible (e.g. when a study is identified as abstract only) when uncertainties arise during completion of the study. In practice for this review, we had to do this with only one of the study authors.

Assessment of heterogeneity

We visually assessed statistical heterogeneity between studies by inspecting forest plots and using the Chi² test (P value < 0.1 was considered significant owing to the low power of the test). We calculated the I² statistic, which describes the percentage of variability in effect estimates that is due to heterogeneity rather than to sampling error (chance). Values of I² range from 0 to 100, with 0 representing no heterogeneity and 100 representing considerable heterogeneity.

For this review:

- 0% to 40%: Heterogeneity might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: shows considerable heterogeneity.

Assessment of reporting biases

If we cannot pool more than 10 studies for a future update of this review, we will create and examine a funnel plot to explore possible small-study biases and publication bias.

Data synthesis

We used a fixed-effect model and performed a sensitivity analysis with a random-effects model when heterogeneity was substantial. We will combine data on outcomes at six months and at 12 months in future versions of this review if sufficient data become available. We will describe other time points when data become available.

'Summary of findings' table

We created a 'Summary of findings' table by using the following outcomes.

- Health-related quality of life.
- Asthma exacerbation as defined by hospital admission or treatment with a course of OCS.
- Serious adverse events.
- Adverse events/side effects.

We used the five GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to studies that contribute data to the meta-analyses for pre-specified outcomes. We followed the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins

2011) and used GRADEpro software. We justified all decisions to downgrade or upgrade the quality of studies by using footnotes; we included comments to aid the reader's understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

- Age (nought to five years, six to 16 years, 16 plus years).

We planned to use the following outcomes in subgroup analyses.

- Health-related quality of life.
- Asthma symptoms.

We planned to use the formal test for subgroup interactions in Review Manager (Review Manager 2014), but sufficient data were not available.

Sensitivity analysis

We planned to carry out the following sensitivity analyses, but sufficient data were not available.

- Excluding studies with an overall high risk of bias.
- Excluding cross-over trials and cluster-randomised trials.
- Using a random-effects model.

RESULTS

Description of studies

Results of the search

We identified 29 records through electronic searches conducted in October 2013, and we identified 15 similar records in October 2014, together with eight additional records in October 2015 and an additional nine in June 2016, yielding a total of 59 records obtained from electronic searches. Additional searches from trial registries provided 20 additional records (Figure 1).

Thirty-eight records (representing 14 studies) met our criteria for inclusion; we have described these in the [Characteristics of included studies](#) table.

We excluded 29 records (representing 20 studies) and listed our reasons for exclusion in the [Characteristics of excluded studies](#) table.

We identified 12 ongoing studies and provided details of these studies in the [Characteristics of ongoing studies](#) table.

Included studies

In all, 14 studies met our criteria for inclusion, with a total of 6641 randomised participants, of whom 5638 completed the study ([Characteristics of included studies](#)). Eight of these studies included both adolescents and adults (12 years of age and older): [Allen 2013](#); [Bateman 2014](#); [Bernstein 2014](#); [Bleecker 2012](#); [Busse 2013](#); [Lin 2013](#); [NCT01134042](#); [Woodcock 2013](#). Five studies recruited only adult participants (18 years of age and older): [Hojo 2015](#); [Kempford 2012](#); [Lee 2014](#); [Oliver 2012](#); [Oliver 2013](#), and one study recruited only paediatric participants (between five and 11 years of age): [NCT01453023](#).

We noted considerable variation in the range of comparisons presented in the eight studies that included both adolescents and adults (12 years of age and older).

- One compared FF/VI 100/25 mcg versus FF/VI 200/25 mcg versus placebo versus prednisolone ([Allen 2013](#)).
- One compared FF/VI 100/25 mcg versus FF 100 mcg ([Bateman 2014](#)).
- One compared FF/VI 100/25 mcg versus FF/VI 200/25 mcg and versus FF 100 mcg ([Bernstein 2014](#)).
- One compared FF/VI 100/25 mcg versus FF 100 mcg and versus placebo ([Bleecker 2012](#)).
- One compared FF/VI 100/25 mcg versus FF/VI 200/25 mcg and versus FP 500 mcg ([Busse 2013](#)).

- One compared FF/VI 200/25 mcg versus FP 500 mcg ([Lin 2013](#)).
- One compared FF 200 mcg versus FF/VI 200/25 mcg and versus FP 500 mcg ([NCT01134042](#)).
- One compared FF/VI 100/25 mcg versus FP/salmeterol (SAL) 250/50 mcg ([Woodcock 2013](#)).

We observed similar variation in the range of comparisons presented in the five studies that included only adults.

- One compared FF/VI 100/25 versus FP/SAL500/50 ([Hojo 2015](#)).
- One compared FF/VI 100/25 mcg AM versus FF/VI 100/25 mcg PM and versus placebo ([Kempford 2012](#)).

- One compared FF 100 mcg versus FF/VI 100/25 mcg and versus placebo ([Oliver 2012](#)).
- One compared FF 100 mcg versus FF/VI 100/25 mcg and versus umeclidinium ([Lee 2014](#)).
- One compared FF/VI 100/25 mcg versus FF 100 mcg and versus placebo versus VI 25 mcg ([Oliver 2013](#)).

The study that included only children presented the following comparison.

- FF/VI 100/25 mcg versus FF 100 mcg ([NCT01453023](#)).

We have provided additional detailed information on the included studies in the [Characteristics of included studies](#) table and in [Table 1](#).

Excluded studies

We excluded 20 studies for the following reasons: Participants in the study did not have a diagnosis of asthma (N = 9, 45%); the ICS used in the study was not FF (N = 3, 15%); pooled analysis included data from the clinical trials (N = 2, 10%); study was withdrawn before participants were enrolled (N = 1, 5%); VI and FF were not used together in the intervention arm (N = 1, 5%); focus of trial was on VI and FP, not on VI and FF (N = 1, 5%) and evaluation of dry powder inhaler (DPI) (N = 1, 5%); trial compared budesonide/formoterol maintenance and reliever therapy versus FF/VI (N = 1, 5%); and study evaluated exhaled nitric oxide time profile as a biomarker of airway Inflammation (N = 1, 5%) ([Characteristics of excluded studies](#)).

Risk of bias in included studies

Allocation

We judged 12 of the included studies to be at low risk with respect to selection bias. We considered risk of selection bias in the two remaining studies ([Bleecker 2012](#); [Hojo 2015](#)) to be unclear ([Figure 2](#); [Figure 3](#)).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

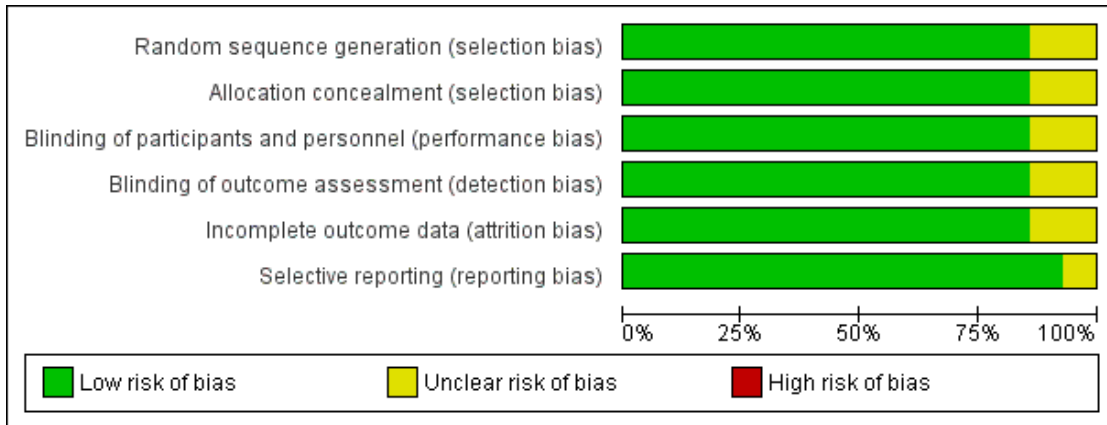


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

| | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) |
|----------------|---|---|---|---|--|--------------------------------------|
| Allen 2013 | + | + | + | + | + | + |
| Bateman 2014 | + | + | + | + | + | + |
| Bernstein 2014 | + | + | + | + | + | + |
| Bleecker 2012 | ? | ? | + | + | + | + |
| Busse 2013 | + | + | + | + | + | + |
| Hojo 2015 | ? | ? | ? | ? | ? | ? |
| Kempsford 2012 | + | + | ? | ? | ? | + |
| Lee 2014 | + | + | + | + | + | + |
| Lin 2013 | + | + | + | + | + | + |
| NCT01134042 | + | + | + | + | + | + |
| NCT01453023 | + | + | + | + | + | + |
| Oliver 2012 | + | + | + | + | + | + |
| Oliver 2013 | + | + | + | + | + | + |
| Woodcock 2013 | + | + | + | + | + | + |

Blinding

For blinding, we judged 12 of the included studies to be at low risk. For [Kempford 2012](#) and [Hojo 2015](#), we judged the risk to be unclear ([Figure 2](#); [Figure 3](#)).

Incomplete outcome data

For attrition bias, we judged 12 of the included studies to have low risk. We considered risk of selection bias in the two remaining studies ([Hojo 2015](#); [Kempford 2012](#)) to be unclear ([Figure 2](#); [Figure 3](#)).

Selective reporting

For reporting bias, we judged 13 studies to be at low risk of bias; for [Hojo 2015](#), we judged this risk to be unclear ([Figure 2](#); [Figure 3](#)).

Effects of interventions

See: [Summary of findings for the main comparison](#) Vilanterol and fluticasone furoate compared with placebo for asthma

VI and FF 100/25 mcg versus placebo

Primary outcomes

Health-related quality of life

See [Table 2](#).
[Bleecker 2012](#) provided data on the change in quality of life (as measured by the Asthma Quality of Life Questionnaire (AQLQ) at 12 weeks), indicating a significant difference in favour of VI and FF 100/25 mcg (mean difference (MD) 0.30, 95% confidence interval (CI) 0.14 to 0.46; [Analysis 1.1](#)). The minimal important difference on this scale is 0.5 unit.

Severe asthma exacerbation as defined by hospital admission or treatment with a course of oral corticosteroid

See [Table 3](#).
No exacerbations were reported in the VI and FF 100/25 mcg or placebo arms in the two short-term trials ([Allen 2013](#); [Kempford 2012](#)) pooled in [Analysis 1.2](#).

Serious adverse events

See [Table 4](#).
No serious adverse events were observed in the VI and FF 100/25 mcg or placebo arms in the five studies ([Allen 2013](#); [Bleecker 2012](#); [Kempford 2012](#); [Oliver 2012](#); [Oliver 2013](#)) aggregated in [Analysis 1.3](#). These studies were of short duration; the longest ([Bleecker 2012](#)) had a treatment period of 12 weeks.

Secondary outcomes

Measures of lung function: forced expiratory flow in one second (FEV₁), peak expiratory flow (PEF)

See [Table 5](#); [Table 6](#).
Data contributed by [Bleecker 2012](#) on FEV₁ (litres) indicated a significant difference in favour of VI and FF 100/25 mcg (MD 0.17, 95% CI 0.09 to 0.26; [Analysis 1.4](#)). A similar effect was reported for peak expiratory flow rate (PEFR) AM L/min (MD 28.20, 95% CI 21.67 to 34.73; [Analysis 1.5](#)) and PEFR AM L/min (MD 28.20, 95% CI 21.67 to 34.73; [Analysis 1.6](#)).

Asthma symptoms

See [Table 7](#).
[Bleecker 2012](#) reported a significant difference in favour of VI and FF 100/25 mcg with respect to change in asthma symptoms as measured by the Asthma Control Test (ACT) (MD 1.90, 95% CI 1.22 to 2.58; [Analysis 1.7](#)).

VI and FF 100/25 mcg versus same dose of FF

Primary outcomes

Health-related quality of life

[Bleecker 2012](#) provided data on the change in quality of life (as measured by the AQLQ at 12 weeks) that indicated no statistically reliable difference between the two arms of this trial (MD 0.15, 95% CI -0.00 to 0.30; [Analysis 2.1](#)).

Severe asthma exacerbation as defined by hospital admission or treatment with a course of oral corticosteroid

Two studies provided data on exacerbations ([Bateman 2014](#); [Bleecker 2012](#)). The difference between the two arms was not significant (odds ratio (OR) 1.38, 95% CI 0.86 to 2.22; [Analysis 2.2](#)).

Serious adverse events

No serious adverse events were observed in either of the two arms in three of the five included studies (NCT01453023; Oliver 2012; Oliver 2013) combined in Analysis 2.3. The difference between the two arms was not significant (OR 1.61, 95% CI 0.42 to 6.17).

Secondary outcomes

Measures of lung function: FEV₁, PEF

The trough FEV₁ at 12 weeks was significant in favour of VI and FF 100/25 mcg in a single study (Bernstein 2014) (MD 0.08L, 95% CI 0.02 to 0.14; Analysis 2.4).

Researchers reported a significant difference in favour of VI and FF 100/25 mcg for PEF AM (change from baseline at 12 weeks) (MD 20.29, 95% CI 15.72 to 24.85; Analysis 2.5) and for PEF PM (change from baseline at 12 weeks) (MD 18.52, 95% CI 14.03 to 23.01; Analysis 2.6).

Data from a three-period crossover study (Lee 2014), which are reported in a format that cannot be aggregated in lung function analyses, also show a significant difference in favour of VI and FF 100/25 mcg of a similar magnitude for trough FEV₁ and PEF AM and PM.

Asthma symptoms

One study (Bleecker 2012) contributed data to this outcome, reporting no significant differences between the two arms with respect to change in asthma symptoms as measured by ACT (MD 0.60, 95% CI -0.04 to 1.24; Analysis 2.7). The minimal important difference on this scale is 0.5 unit.

VI and FF 100/25 mcg versus same dose of VI

For this comparison, data on only one outcome were available for analysis: serious adverse events. Investigators observed no serious adverse events in either of the two arms of a single short-term trial (Oliver 2013; Analysis 3.1).

VI and FF 100/25 mcg versus FP 500 mcg twice-daily

Primary outcomes

For this comparison, data were available for analysis on only two outcomes: exacerbations and serious adverse events.

Severe asthma exacerbation as defined by hospital admission or treatment with a course of oral corticosteroid

Only one study of 52 weeks' duration contributed data to this analysis (Busse 2013). Researchers reported no significant differences between VI and FF 100/25 mcg versus FP 500 mcg twice-daily for this outcome (OR 0.49, 95% CI 0.10 to 2.47; Analysis 4.1).

Serious adverse events

Only Busse 2013 contributed data to this analysis. Investigators observed significantly fewer serious adverse events in the VI and FF 100/25 mcg arm (OR 0.20, 95% CI 0.05 to 0.80; Analysis 4.2).

VI and FF 100/25 mcg versus FP/SAL 250/50 mcg twice-daily

Primary outcomes

Health-related quality of life

One study (Woodcock 2013) of 24 weeks' duration considered change in quality of life (as measured by the AQLQ at 12 weeks). Investigators reported no significant differences between VI and FF 100/25 mcg versus FP/SAL 250/50 mcg twice-daily (MD 0.09, 95% CI -0.03 to 0.21; Analysis 5.1).

Severe asthma exacerbation as defined by hospital admission or treatment with a course of oral corticosteroid

Researchers reported no significant differences between the two arms in terms of exacerbations (OR 0.50, 95% CI 0.05 to 5.52; Analysis 5.2).

Serious adverse events

Study authors described no significant difference between the two arms for serious adverse events (OR 0.80, 95% CI 0.21 to 2.99; Analysis 5.3).

Secondary outcomes

Measures of lung function: FEV₁, PEF

Woodcock 2013 reported no significant differences between the two arms for FEV₁ (MD -0.02, 95% CI -0.07 to 0.03; Analysis 5.4).

Asthma symptoms

Study authors also described no significant differences between the two arms in terms of asthma symptoms (MD 0.24, 95% CI -0.20 to 0.68; [Analysis 5.5](#)).

VI and FF 100/25 mcg versus FP/SAL 250/25 mcg twice-daily

Primary outcomes

For this comparison, data on only two outcomes were available for analysis: exacerbations and serious adverse events.

Severe asthma exacerbation as defined by hospital admission or treatment with a course of oral corticosteroid

Only two studies provided data for this outcome: one short-term trial ([Allen 2013](#)) and one of 52 weeks' duration ([Busse 2013](#)). Investigators reported no significant differences between the two arms (OR 2.02, 95% CI 0.50 to 8.19; [Analysis 6.1](#)).

Serious adverse events

[Allen 2013](#) and [Busse 2013](#) also contributed data for serious adverse events, noting no significant differences between the two arms (OR 0.33, 95% CI 0.03 to 3.18; [Analysis 6.2](#)).

VI and FF 200/25 mcg versus placebo

For this comparison, data on four outcomes were available for analysis: exacerbations, serious adverse events, FEV₁ and symptoms.

Primary outcomes

Severe asthma exacerbation as defined by hospital admission or treatment with a course of oral corticosteroid

Only one short-term trial contributed data to this outcome ([Allen 2013](#)), indicating no exacerbations in either arm.

Serious adverse events

Study authors also described no adverse events in either arm ([Allen 2013](#)).

Secondary outcomes

Measures of lung function: FEV₁, PEF

Only one study (24 weeks' duration; [NCT01134042](#)) provided data for this outcome (FEV₁ in litres), noting a significant advantage for VI and FF 200/25 mcg (MD 0.21, 95% CI 0.13 to 0.29; [Analysis 7.3](#)).

Asthma symptoms

[NCT01134042](#) described a similar significant advantage related to change in asthma symptoms for VI and FF 200/25 mcg (MD 0.90, 95% CI 0.12 to 1.68; [Analysis 7.4](#)).

VI and FF 200/25 mcg versus FP/SAL 500/50 mcg

Primary outcomes

The four week cross-over trial addressing this comparison did not include the review's primary outcomes ([Hojo 2015](#)).

Secondary outcomes

Measures of lung function: FEV₁, PEF

[Hojo 2015](#) reported an improvement in AM PEF in the VI/FF 200/25 mcg condition. However, investigators provided no information on this outcome in relation to the FP/SAL 500/50 mcg condition.

Asthma symptoms

Only [Hojo 2015](#) looked at this comparison, noting no significant improvement on the ACT with either treatment.

VI and FF 200/25 mcg versus FP 500 mcg

Primary outcomes

Health-related quality of life

Two studies ([Lin 2013](#); [NCT01134042](#)) of 12 and 24 weeks' duration, respectively, looked at change in quality of life at 12 weeks (MD 0.05, 95% CI -0.08 to 0.17; [Analysis 8.1](#)) and at 24 weeks (MD 0.03, 95% CI -0.15 to 0.21; [Analysis 8.2](#)). Neither analysis indicated a significant difference between the two arms.

Severe asthma exacerbation as defined by hospital admission or treatment with a course of oral corticosteroid

Busse 2013 (52 weeks' duration) and Lin 2013 provided data for this outcome, noting no significant differences between the two arms (OR 0.70, 95% CI 0.22 to 2.20; Analysis 8.4).

Serious adverse events

Busse 2013, Lin 2013 and NCT01134042 contributed data, indicating no significant differences between the two arms for this outcome (OR 0.61, 95% CI 0.25 to 1.49; Analysis 8.5).

Secondary outcomes

Measures of lung function: FEV₁, PEF

Only one study (Lin 2013) provided data on PEF, reporting a significant advantage in favour of VI and FF 200/25 mcg (MD 28.60, 95% CI 20.23 to 36.97; Analysis 8.6). NCT01134042 provided additional data specifically for AM and PM PEF. With respect to both the former (MD 33.00, 95% CI 24.84 to 41.16; Analysis 8.7) and the latter (MD 26.20, 95% CI 18.04 to 34.36; Analysis 8.8), a significant advantage favoured VI and FF 200/25 mcg.

Asthma symptoms

Lin 2013 reported the proportion of symptom-free days as a percentage for this comparison (MD 4.80, 95% CI -2.84 to 12.44; Analysis 8.9), revealing no significant differences for VI and FF 200/25 mcg versus FP 500 mcg in this analysis. However, for change in asthma symptoms, NCT01134042 provided an indication of significance in favour of VI and FF 200/25 mcg (MD 0.80, 95% CI 0.01 to 1.59; Analysis 8.10), based on the ACT, which has a minimal important difference of 0.5 unit.

VI and FF 200/25 mcg versus same dose of FF

Primary outcomes

Health-related quality of life

One study (NCT01134042) considered change in health-related quality of life at 12 weeks (MD 0.08, 95% CI -0.08 to 0.24; Analysis 9.1) and at 24 weeks (MD 0.05, 95% CI -0.14 to 0.24; Analysis 9.2). Both cases reported no significant differences between VI and FF 200/25 mcg versus the same dose of FF for this outcome.

Severe asthma exacerbation as defined by hospital admission or treatment with a course of oral corticosteroid

No data were available for inclusion in our analyses for this outcome.

Serious adverse events

NCT01134042 provided data showing no significant differences between VI and FF 200/25 mcg versus the same dose of FF for this outcome (OR 6.06, 95% CI 0.72 to 50.84; Analysis 9.3).

Secondary outcomes

Measures of lung function: FEV₁, PEF

NCT01134042 contributed data showing a significant advantage in favour of VI and FF 200/25 mcg for FEV₁ (litres) (MD 0.19, 95% CI 0.10 to 0.28; Analysis 9.4), PEF AM (MD 33.60, 95% CI 25.41 to 41.79; Analysis 9.5) and PEF PM (MD 30.70, 95% CI 22.51 to 38.89; Analysis 9.6).

Asthma symptoms

Data from NCT01134042 revealed no significant differences between VI and FF 200/25 mcg versus the same dose of FF for this outcome (MD 0.30, 95% CI -0.50 to 1.10; Analysis 9.7).

DISCUSSION

Summary of main results

We found very few opportunities to combine results from the 14 included studies into meta-analyses. We tabulated the data for our pre-specified primary outcomes: health-related quality of life (Table 2), exacerbations (Table 3) and serious adverse events (Table 4). We included nine comparisons in this review, six for which the dose of vilanterol (VI) and fluticasone furoate (FF) was 100/25 mcg (VI and FF 100/25 mcg vs placebo; VI and FF 100/25 mcg vs same dose of FF; VI and FF 100/25 mcg vs same dose of VI; VI and FF 100/25 mcg vs fluticasone propionate (FP) 500 mcg twice-daily; VI and FF 100/25 mcg vs FP/salmeterol (SAL) 250/50 mcg twice-daily; VI and FF 100/25 mcg vs FP/SAL 250/25 mcg twice-daily) and three for which the dose of VI and FF was 200/25 mcg (VI and FF 200/25 mcg vs placebo; VI and FF 200/25 mcg vs FP 500 mcg; VI and FF 200/25 mcg vs same dose of FF). In this review, we focused on our pre-specified primary outcomes: health-related quality of life, severe asthma exacerbation as defined by hospital admission, treatment with a course of oral corticosteroid and serious adverse events.

In the comparison between VI and FF 100/25 mcg versus placebo, only one study (Bleecker 2012) provided data on health-related quality of life, showing a significant difference in favour of VI and FF 100/25 mcg (mean difference (MD) 0.30, 95% confidence interval (CI) 0.14 to 0.46; Analysis 1.1) when using the Asthma Quality of Life Questionnaire (AQLQ) with a minimally important difference of 0.5 unit. The two studies contributing data (Allen 2013; Kempford 2012) reported no exacerbations in the VI and FF 100/25 mcg or placebo arms, and the five aggregated studies (Allen 2013; Bleecker 2012; Kempford 2012; Oliver 2012; Oliver 2013) described no serious adverse events in the VI and FF 100/25 mcg or placebo arms. When viewed together, these data provide some evidence of benefit; however, in light of the small number of studies contributing to this impression and their mostly very short duration, it should be noted that this does not constitute strong evidence for efficacy nor for safety.

The second comparison (VI and FF 100/25 mcg vs same dose of FF) indicated no statistically reliable difference for health-related quality of life between the two arms of the single contributing study (Bleecker 2012; MD 0.15, 95% CI -0.00 to 0.30). Only two studies provided data on exacerbations (Bateman 2014; Bleecker 2012), noting that the difference between the two arms was not significant (odds ratio (OR) 1.38, 95% CI 0.86 to 2.22). Researchers noted no serious adverse events in either of the two arms in three of the five included studies (NCT01453023; Oliver 2012; Oliver 2013), and no significant differences between the two conditions for this outcome (OR 1.61, 95% CI 0.42 to 6.17). The small number of studies contributing data to this comparison precludes opportunities for drawing robust conclusions for this comparison as well.

In terms of our comparison between VI and FF 100/25 mcg versus same dose of VI, data were available for analysis on only one of our pre-specified primary outcomes: serious adverse events; no serious adverse events were observed in either of the two arms of the aggregated study (Oliver 2013).

For the comparison between VI and FF 100/25 mcg versus FP 500 mcg twice-daily, data were available for analysis for only two outcomes: exacerbations and serious adverse events. Only one study contributed data with respect to the former (Busse 2013), reporting no significant differences between the two interventions (OR 0.49, 95% CI 0.10 to 2.4). With regard to serious adverse events only, Busse 2013 contributed data, revealing significantly fewer serious adverse events in the VI and FF 100/25 mcg arm (OR 0.20, 95% CI 0.05 to 0.80). Again, the small number of contributing studies precludes the opportunity for reaching any robust conclusions.

Researchers also compared VI and FF 100/25 mcg versus FP/SAL 250/50 mcg twice-daily. In terms of health-related quality of life, which was considered by only one study (Woodcock 2013), data show no significant differences between the two arms (MD 0.09, 95% CI -0.03 to 0.21) and no significant differences between the two arms in terms of exacerbations (OR 0.50, 95% CI 0.05 to

5.52), or between the two arms for serious adverse events (OR 0.80, 95% CI 0.21 to 2.99).

Finally, in terms of comparisons including VI and FF at 100/25 mcg, we considered VI and FF 100/25 mcg versus FP/SAL 250/25 mcg twice-daily. Data on only two outcomes were available for analysis: exacerbations and serious adverse events.

For exacerbations, only two studies (Allen 2013; Busse 2013) provided data, revealing no significant differences between the two arms (OR 2.02, 95% CI 0.50 to 8.19). These studies also contributed data on serious adverse events, showing no significant differences between the two arms (OR 0.33, 95% CI 0.03 to 3.18). In summary, with respect to VI and FF at 100/25 mcg, it is not possible to draw strong conclusions in relation to our pre-specified primary outcomes.

Investigators also considered VI and FF at the higher dose of 200/25 mcg. For the comparison VI and FF 200/25 mcg versus placebo, data on only two of our primary outcomes were available for analysis: exacerbations and serious adverse events. Only one study contributed data on these two outcomes (Allen 2013), noting no exacerbations in either arm and no adverse events in either arm.

Study authors also compared VI and FF 200/25 mcg versus FP 500 mcg. Two studies (Lin 2013; NCT01134042) looked at change in quality of life at 12 weeks (MD 0.05, 95% CI -0.08 to 0.17) and at 24 weeks (MD 0.03, 95% CI -0.15 to 0.21; Analysis 8.2); neither analysis indicated a significant difference between the two arms. Busse 2013 and Lin 2013 provided data on exacerbations, showing no significant differences between the two arms (OR 0.70, 95% CI 0.22 to 2.20). Three studies (Busse 2013; Lin 2013; NCT01134042) contributed data on serious adverse events, showing no significant differences between the two arms for this outcome (OR 0.61, 95% CI 0.25 to 1.49).

In addition, study authors described the comparison between VI and FF 200/25 mcg versus same dose of FF. NCT01134042 considered change in health-related quality of life at 12 weeks (MD 0.08, 95% CI -0.08 to 0.24) and at 24 weeks (MD 0.05, 95% CI -0.14 to 0.24), with neither analysis indicating a significant difference between the two interventions. No data were available for inclusion in our analyses on exacerbations. With regard to serious adverse events, NCT01134042 provided data, revealing no significant differences between the two interventions for this outcome (OR 6.06, 95% CI 0.72 to 50.84).

In summary, the evidence gathered in relation to our primary outcomes for VI and FF at 100/25 mcg and at 200/25 mcg is too inconclusive to provide the basis of robust conclusions.

Overall completeness and applicability of evidence

At the present time, inhaled corticosteroid (ICS) and long-acting beta₂-agonist (LABA) combination inhalers are recommended at step 3 of the British Thoracic Society (BTS) guidelines for asthma

management in children and adults. This means that patients taking a low dose of ICS should have their treatment 'stepped up' to include a LABA in addition to continued ICS only if their asthma is not well controlled. This treatment pathway has a clear evidence base. The question is whether the combination of VI and FF could be also be used at this stage. Owing to the wide range of comparisons and the short duration of most trials, applicability of the evidence is very limited.

From the limited number of available studies, some evidence has supported the use of VI/FF, particularly with regard to forced expiratory volume in one second (FEV₁) and peak expiratory flow (PEF) (Bleecker 2012; Kempsford 2012; NCT01134042); however, additional studies are required to support its role. Research has suggested that the combination may improve health-related quality of life compared with placebo (Bleecker 2012), but longer-term placebo-controlled studies are required to support this finding. The evidence reviewed reveals no significant short-term increase in asthma exacerbations (Allen 2013; Kempsford 2012) nor in serious adverse events (Allen 2013; Bleecker 2012; Kempsford 2012; Oliver 2012; Oliver 2013) in the VI/FF group. Evidence is presently insufficient for comparison of VI/FF versus alternative twice-daily combination therapy inhalers.

Studies have excluded participants with an episode of life-threatening asthma, so potentially, these trials may have excluded a group of participants with more severe disease.

Most studies included adult and adolescent participants, and only one study enrolled only paediatric participants (NCT01453023). Confirmation of benefit for paediatric patients is important - particularly as a once-daily dosing regimen may improve adherence in the paediatric population. Large variability in study duration and in the severity of asthma heterogeneity makes it difficult to examine safety and side effects.

Quality of the evidence

In our judgement, 12 of the 14 studies had low risk of selection bias; in Bleecker 2012 and Hojo 2015, the risk was considered to be unclear. We also judged performance bias and detection bias based on blinding processes to be low in 12 of the 14 studies; in Kempsford 2012 and Hojo 2015, we judged this risk to be unclear. We evaluated attrition bias to be similarly low in 12 of the 14 studies; we judged the risk to be unclear in Kempsford 2012 and Hojo 2015. In our judgement, risk of reporting bias was low in 13 studies, and we judged Hojo 2015 as having unclear risk in this respect. In summary, we believe the quality of the evidence with respect to risk of bias was generally uniform across the various categories assessed (Figure 3).

The small number of included studies precluded formal assessment of publication bias using funnel plots. However, we designed our search strategy, which extended to conference abstracts and ongoing studies, with the goal of identifying unpublished studies.

Potential biases in the review process

Potential for publication bias can be seen in this review in that unpublished trials may not have been included. These studies may have had positive or negative outcomes that would have affected described treatment benefits. We undertook a thorough and systematic search of databases, and to the best of our knowledge, we assessed all relevant studies for inclusion in this review. Two review authors independently evaluated all studies that met the inclusion criteria to reduce potential selection bias. Assessment of each study was consistent in relation to the inclusion criteria.

Agreements and disagreements with other studies or reviews

We found the main body of evidence for use of VI and FF in the randomised controlled trials (RCTs) represented in this review. We are not aware of any other systematic review on this topic.

AUTHORS' CONCLUSIONS

Implications for practice

Current evidence from 14 studies involving 6641 participants included in this review suggests that the combination of FF and VI may provide safe and effective therapy in the short term compared with placebo. Evidence suggests some improvement in health-related quality of life, FEV₁ and peak expiratory flow rate (PEFR). However, the limited number of studies combined with the variety of endpoints and the short duration of most trials indicates that firm conclusions cannot be drawn. In particular, information was insufficient for assessment of whether once-daily VI/FF was better or worse than twice-daily FP/SAL in terms of efficacy or safety. Additional studies, which would allow meta-analyses to be undertaken, are required before robust conclusions can be drawn.

Very limited evidence is available for its use in paediatric patients, so additional studies in this area are required before conclusions can be drawn for this population.

Implications for research

The 14 studies included in this review are of high quality. However, the diverse nature of the questions addressed in these studies presents a considerable challenge in summarising an overview of the data. It is clear that more research is required to reduce uncertainties arising in the interpretation of currently available evidence. These findings may need to be replicated before robust conclusions can be drawn. Given the short duration of many studies, investigators have not addressed the adrenal axis and cortisol suppression, and we could not comment on concerns around increased asthma deaths associated with other LABAs. These may

be important areas for further study. Only five studies provided data on health-related quality of life, and only six recorded asthma exacerbations. Only one study enrolled paediatric participants, so presently we can draw no conclusions for the paediatric population. Additional data, particularly related to the primary outcomes of this review, derived from longer-term trials comparing current standard combination therapy would be especially helpful. Data on comparison of VI/FF versus twice-daily LABA/ICS are sparse, and this topic should be the focus of future research.

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NCT01711463 *{published data only}*

NCT01711463. A randomized, double-blind, placebo-controlled, four-way crossover study to evaluate and compare the pharmacodynamics and pharmacokinetics of fluticasone furoate/vilanterol in different dose combination (50/25mcg, 100/25mcg and 200/25mcg) after single and repeat dose administration from a novel dry powder device in healthy Chinese subjects. <http://clinicaltrials.gov/show/NCT01711463> (accessed 18/6/15).

NCT02712047 2016 *{published data only}*

NCT02712047. A randomised, placebo-controlled, double-blind, two period crossover study to characterise the exhaled nitric oxide time profile as a biomarker of airway inflammation in adult asthma patients following repeat administration of inhaled fluticasone furoate (FF)/vilanterol (VI) 100/25 mcg, 2016. <https://clinicaltrials.gov/show/NCT02712047> (accessed 9/8/16). [CRS: 4900132000023253;]

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NCT01573624 *{published data only}*

NCT01573624. A multi-center, randomized, double-blind, dose-ranging study to evaluate GSK573719 in combination with fluticasone furoate, fluticasone furoate alone, and an active control of fluticasone furoate/vilanterol combination in subjects with asthma. <http://clinicaltrials.gov/show/NCT01573624> (accessed 18/6/15).

NCT01706198 *{published data only}*

EUCTR2011-005553-31-GB. Study to evaluate the effectiveness of fluticasone furoate/vilanterol delivered once daily via a novel dry powder inhaler (NDPI) compared with existing asthma maintenance therapy alone in subjects with asthma. <http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-005553-31-GB> (accessed 18/6/15).

NCT01706198. A 12-month, open label, randomised, effectiveness study to evaluate fluticasone furoate (FF, GW685698)/Vilanterol (VI, GW642444) inhalation powder delivered once daily via a novel dry powder inhaler compared with usual maintenance therapy in subjects with asthma. <http://clinicaltrials.gov/show/NCT01706198> (accessed 18/6/15).

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NCT02301975. An efficacy and safety study of fluticasone furoate/vilanterol 100/25 microgram (mcg) inhalation powder, fluticasone propionate/salmeterol 250/50 mcg

inhalation powder, and fluticasone propionate 250 mcg inhalation powder in adults and adolescents with persistent asthma. <https://clinicaltrials.gov/ct2/show/NCT02301975> (accessed 19/6/15).

NCT02301975 2015 *{published data only}*

NCT02301975. A randomized, double-blind, double-dummy, parallel group, multicenter study of once daily fluticasone furoate/vilanterol 100/25 mcg inhalation powder, twice daily fluticasone propionate/salmeterol 250/50 mcg inhalation powder, and twice daily fluticasone propionate 250 mcg inhalation powder in the treatment of persistent asthma in adults and adolescents already adequately controlled on twice-daily inhaled corticosteroid and long-acting beta2 agonist, 2015. <https://clinicaltrials.gov/show/NCT02301975> (accessed 9/8/16). [CRS: 4900132000009126;]

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NCT02446418. A 6-month, open label, randomised, efficacy study to evaluate fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) inhalation powder delivered once daily via the dry powder inhaler ELLIPTA compared with usual ICS/LABA maintenance therapy delivered by dry powder inhaler in subjects with persistent asthma, 2015. <https://clinicaltrials.gov/show/NCT02446418> (accessed 9/8/2016). [CRS: 4900132000009127;]

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Allen 2013

| | |
|---------------|---|
| Methods | Randomised double-blind multi-centre trial |
| Participants | <p>Total sample N = 185 participants, 177 completed study FF/VI 100/25 mcg, n = 56 (54 completed study) FF/VI 200/25 mcg, n = 56 (55 completed study) Placebo, n = 58 (55 completed study) Prednisolone, n = 15 (13 completed study)</p> <p>Age FF/VI 100/25 mcg, mean 34.4 (SD 15.63) FF/VI 200/25 mcg, mean 34.0 (SD 13.74) Placebo, mean 36.1 (SD 15.42) Prednisolone, mean 37.5 (SD 14.19)</p> <p>Males FF/VI 100/25 mcg, 25 (45%) FF/VI 200/25 mcg, 33 (59%) Placebo, 31 (53%) Prednisolone, 9 (60%)</p> <p>Baseline FEV₁ (% predicted) FF/VI 100/25 mcg, mean 79.9 (SD 12.58) FF/VI 200/25 mcg, mean 77.5 (SD 13.22) Placebo, mean 77.0 (SD 11.88) Prednisolone, mean 78.6 (SD 13.17)</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Outpatient with ability to comply with study requirements and complete two 24-hour clinic visits • Clinical diagnosis of asthma for ≥ 12 weeks • Reversibility FEV₁ $\geq 12\%$ and ≥ 200 mL • FEV₁ $\geq 50\%$ of predicted <p>Exclusion criteria</p> <ul style="list-style-type: none"> • History of life-threatening asthma • Respiratory infection or oral candidiasis • Asthma exacerbation • Uncontrolled disease or clinical abnormality • Allergies to study drugs, study drugs' excipients, medications related to study drugs • Taking another investigational medication or prohibited medication |
| Interventions | <p>Arm 1: FF/VI dose 100/25 mcg inhalation powder once-daily for 6 weeks' treatment + 1 oral placebo capsule each day on the last 7 days of the study</p> <p>Arm 2: FF/VI 200/25 mcg inhalation powder once-daily for 6 weeks' treatment + 1 oral placebo capsule each day on the last 7 days of the study</p> <p>Arm 3: placebo inhalation powder once-daily for 6 weeks' treatment + 1 oral placebo capsule each day on the last 7 days of the study</p> |

| | | |
|----------------------------|---|------------------------------|
| | <p>Arm 4: placebo inhalation powder once-daily for 6 weeks' treatment + 1 oral prednisolone 10 mg capsule each day on the last 7 days of the study</p> | |
| <p>Outcomes</p> | <p>Primary outcome</p> <ul style="list-style-type: none"> ● Ratio from baseline of serum cortisol weighted mean (0-24 hours) at day -1/1 (baseline) and day 42 <p>Secondary outcomes</p> <ul style="list-style-type: none"> ● Ratio from baseline of serum cortisol area under concentration-time curve (AUC) (0-24 hours) at day -1/1 (baseline) and day 42 ● Ratio from baseline of serum cortisol trough (0-24 hours) at day -1/1 (baseline) and day 42 ● Ratio from baseline of 0 to 24 hours urinary free cortisol excretion at day -1/1 (baseline) and day 42 ● Plasma FF and VI PK concentration ● AUC(0-t) and AUC(0-24) for FF at day 42 ● Cmax for FF at day 42 ● Tmax and Tlast of FF at day 42 ● AUC(0-t) for VI at day 42 ● Cmax for VI at day 42 ● Tmax and Tlast of VI at day 42 ● Number of participants with any AE or SAE during treatment period ● Change from baseline in basophil, eosinophil, lymphocyte, monocyte and segmented neutrophil values at day 42/early withdrawal ● Change from baseline in eosinophil, total neutrophil, platelet and white blood cell (WBC) count values at day 42/early withdrawal ● Change from baseline in haemoglobin values at day 42/early withdrawal ● Change from baseline in haematocrit values at day 42/early withdrawal ● Change from baseline in ALT, ALP, AST, CK and GGT values at day 42/early withdrawal ● Change from baseline in albumin and total protein values at day 42/early withdrawal ● Change from baseline in direct bilirubin, indirect bilirubin, total bilirubin and creatinine values at day 42/early withdrawal ● Change from baseline in chloride, CO2 content/bicarbonate, glucose, potassium, sodium, and urea/BUN values at day 42/early withdrawal ● Change from baseline in SBP and DBP at days 14, 28 and 42, and maximum post baseline ● Change from baseline in pulse rate at days 14, 28 and 42, and maximum post baseline | |
| <p>Notes</p> | <p>Data collected from 17 locations in Germany (6), Poland (7) and USA (4) Funded by GlaxoSmithKline Study duration: 6 weeks</p> | |
| <p><i>Risk of bias</i></p> | | |
| <p>Bias</p> | <p>Authors' judgement</p> | <p>Support for judgement</p> |

Allen 2013 (Continued)

| | | |
|---|----------|--|
| Random sequence generation (selection bias) | Low risk | Central randomisation schedule was generated by the sponsor through a validated computerised system (RandAll, Glaxo-SmithKline, Stevenage, UK) |
| Allocation concealment (selection bias) | Low risk | Participants were randomised via the Registration and Medication Ordering System (GlaxoSmithKline) |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Double-blind. Placebo inhalers and capsules were identical in appearance to active treatments |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Double-blind. Placebo inhalers and capsules were identical in appearance to active treatments |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Details of the 8 withdrawals included in NCT01086410 report |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

Bateman 2014

| | |
|--------------|--|
| Methods | Randomised double-blind parallel-group trial |
| Participants | <p>Total sample N = 2020 participants, 1748 completed study FF/VI 100/25, n = 1009 (885 completed study) FF 100, n = 1011 (863 completed study)</p> <p>Age FF/VI 100/25, mean 41.1 (SD 17.10) FF 100, mean 42.3 (SD 16.82)</p> <p>Males FF/VI 100/25, 348 (34%) FF 100, 321 (32%)</p> <p>Baseline FEV₁ (% predicted) FF/VI 100/25, mean 24.4 (SD 12.71) FF 100, mean 24.3 (SD 12.10)</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Clinical diagnosis of asthma • Reversibility FEV₁ ≥ 12% and ≥ 200 mL and greater approximately 10 to 40 minutes following 2 to 4 inhalations of albuterol • FEV₁ 50% to 90% of predicted • Currently using ICS therapy • History of ≥ 1 asthma exacerbations requiring treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalisation in previous year |

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| | <p>Exclusion criteria</p> <ul style="list-style-type: none"> • History of life-threatening asthma in previous 5 years (requiring intubation and/or associated with hypercapnia, hypoxic seizure or respiratory arrest) • Respiratory infection or oral candidiasis • Uncontrolled disease or clinical abnormality • Allergies • Taking another investigational medication or prohibited medication |
| Interventions | <p>Arm 1: FF/VI dose 100/25 mcg inhalation powder inhaled orally once-daily in the evening</p> <p>Arm 2: FF dose 100 mcg inhalation powder inhaled orally once-daily in the evening</p> |
| Outcomes | <p>Primary outcome</p> <ul style="list-style-type: none"> • Number of participants with ≥ 1 SAE <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Number of SAEs • Change from baseline in evening pre-dose trough FEV₁ at week 36 |
| Notes | <p>Data collected from 182 locations in Argentina (9), Australia (6), Germany (28), Japan (14), Mexico (6), Philippines (5), Poland (15), Romania (6), Russian Federation (16), Ukraine (13) and USA (64)</p> <p>Funded by GlaxoSmithKline</p> <p>Study duration: variable (≥ 24 to 78 weeks)</p> |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|---|
| Random sequence generation (selection bias) | Low risk | Central randomisation schedule was generated by the sponsor through a validated computerised system (RandAll, GlaxoSmithKline, Stevenage, UK) |
| Allocation concealment (selection bias) | Low risk | Participants were randomised via the Registration and Medication Ordering System (GlaxoSmithKline) |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Described as double-blind |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Described as double-blind |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Information on 271 participants failing to complete study included in trial report |

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|--------------------------------------|----------|--|
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |
|--------------------------------------|----------|--|

Bernstein 2014

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|--------------|--|
| Methods | Randomised double-blind parallel-group multi-centre study |
| Participants | <p>Total sample N = 2019 screened, N = 1039 randomised, 956 completed study FF/VI 100/25, n = 346 (314 completed study) FF 100, n = 347 (296 completed study) FF/VI 200/25, n = 346 (321 completed study)</p> <p>Age FF/VI 100/25, mean 45.9 (SD 16.14) FF 100, mean 44.7 (SD 15.89) FF/VI 200/25, mean 46.6 (SD 14.72)</p> <p>Males FF/VI 100/25, 141 (40.75%) FF 100, 148 (42.65%) FF/VI 200/25, 122 (35.26%)</p> <p>Baseline FEV₁ (% predicted) Not reported</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • > 12 years of age • FEV₁ 40% to 80% of predicted • Reversibility FEV₁ ≥ 12% and ≥ 200 mL and greater approximately 10 to 40 minutes following 4 inhalations of salbutamol/albuterol • Received ICS for > 12 weeks before study <p>Exclusion criteria</p> <ul style="list-style-type: none"> • History of life-threatening asthma within past 5 years • Unresolved upper or lower respiratory tract, sinus or middle ear infection in past 4 weeks that led to a change in asthma management • Asthma exacerbation requiring oral corticosteroids in 12 weeks before visit 1, or exacerbation resulting in overnight hospitalisation and additional asthma treatment in 6 months before visit 1 • Evidence of atelectasis (segmental or larger), bronchopulmonary dysplasia, chronic obstructive pulmonary disease or concurrent respiratory disease • Any clinically significant, uncontrolled condition or disease state • Chronic stable hepatitis B or C if screening alanine transaminase (ALT) is > 2 > upper limit of normal (ULN) • Chronic co-infection with hepatitis B and hepatitis C • Clinical visual evidence of candidiasis • Use of any investigational drug within 30 days before visit 1, or within 5 half-lives (t_{1/2}), whichever is longer of the 2 • Allergies or adverse reactions to drug or milk protein: any adverse reaction to any beta₂-agonist, sympathomimetic drug or intranasal, inhaled or systemic corticosteroid therapy • Taking another investigational medication or prohibited medication |

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| | <ul style="list-style-type: none"> • Current smoker or smoking history of 10 pack-years or used inhaled tobacco products within the past 3 months • Shift workers |
| Interventions | <p>Randomised 1:1:1</p> <p>Arm 1: FF/VI dose 100/25 mcg inhalation powder inhaled orally once-daily in the evening</p> <p>Arm 2: FF 100 mcg inhalation powder inhaled orally once-daily in the evening</p> <p>Arm 3: FF/VI dose 200/25 mcg inhalation powder inhaled orally once-daily in the evening</p> |
| Outcomes | <p>Primary endpoint</p> <p>Weighted mean (WM) serial FEV₁ 0 to 24 hours post dose at week 12</p> <p>Secondary endpoints</p> <ul style="list-style-type: none"> • Change from baseline in trough FEV₁ • Change from baseline in % rescue-free 24-hour periods • Change from baseline in % symptom-free 24-hour periods • Change from baseline in morning and evening PEF <p>Adverse events were assessed throughout the study</p> |
| Notes | <p>Data collected from 137 locations in Argentina (13), Chile (7), Germany (12), Mexico (4), Netherlands (7), Poland (8), Romania (13), Russian Federation (19), Sweden (5), Ukraine (12) and USA (37)</p> <p>Funded by GlaxoSmithKline</p> <p>Study duration: 12 weeks</p> |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|---|
| Random sequence generation (selection bias) | Low risk | Participants were randomised through a validated computerised system (RandAll Version 2.5, GlaxoSmithKline) |
| Allocation concealment (selection bias) | Low risk | The Registration and Medication Ordering System was used to register and randomise participants |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Described as double-blind |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Described as double-blind |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Information on 108 participants failing to complete study included in NCT01686633 report |

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| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |
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Bleecker 2012

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| Methods | Randomised double-blind placebo-controlled parallel-group multi-centre trial |
| Participants | <p>Total sample N = 609 participants, 515 completed study FF/VI 100/25, n = 201 (179 completed study) FF 100, n = 205 (185 completed study) Placebo, n = 203 (151 completed study)</p> <p>Age FF/VI 100/25, mean 40.7 (SD 16.38) FF 100, mean 40.4 (SD 16.78) Placebo, mean 38.1 (SD 16.49)</p> <p>Males FF/VI 100/25, 85 (42%) FF 100, 79 (39%) Placebo, 92 (45%)</p> <p>Baseline FEV₁ (% predicted) Not reported</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Outpatients 12 years of age or older • Male and female; female participants of childbearing potential must be willing to use birth control • Pre-bronchodilator FEV₁ 40% to 90% of predicted normal • Reversibility FEV₁ ≥ 12% and ≥ 200 mL • Current asthma therapy includes ICS use for ≥ 12 weeks before first visit <p>Exclusion criteria</p> <ul style="list-style-type: none"> • History of life-threatening asthma during past 10 years • Respiratory infection or oral candidiasis • Asthma exacerbation requiring OCS or overnight hospitalisation with additional asthma treatment • Uncontrolled disease or clinical abnormality • Allergies to study drugs or to excipients • Taking another investigational or prohibited medication • Night shift workers • Current smokers or participants with a smoking history of 10 or more pack-years |
| Interventions | <p>Arm 1: FF/VI dose 100/25 mcg inhalation powder inhaled orally once-daily for 12 weeks</p> <p>Arm 2: FF dose 100 mcg inhalation powder inhaled orally once-daily for 12 weeks</p> <p>Arm 3: Placebo inhalation powder inhaled orally once-daily for 12 weeks</p> |
| Outcomes | <p>Primary outcomes</p> <ul style="list-style-type: none"> • Mean change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV₁ at week 12 • Change from baseline in weighted mean serial FEV₁ over 0 to 24 hours post dose |

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| | <p>at week 12</p> <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Mean change from baseline in % of rescue-free 24-hour periods during 12-week treatment period • Change from baseline in % of symptom-free 24-hour periods during 12-week treatment period • Change from baseline in total AQLQ (+12) score at week 12/early withdrawal • Number of participants who withdrew owing to lack of efficacy • Serial FEV₁ over 0 to 1 hour post dose at randomisation • Clinic visit 12-hour post-dose FEV₁ at week 12 • Weighted mean serial FEV₁ over 0 to 24 hours post dose at baseline • Weighted mean serial FEV₁ over 0 to 4 hours post dose at baseline and at week 12 • Number of participants with bronchodilator effect • Mean change from baseline in daily AM PEF averaged over 12-week treatment period • Mean change from baseline in daily PM PEF averaged over 12-week treatment period • Change from baseline in ACT score at week 12 • Number of participants with indicated global assessment of change responses at week 4, week 8 and week 12/early withdrawal • Number of indicated unscheduled asthma-related healthcare visits during treatment period • Number of participants who used the inhaler correctly or incorrectly at baseline, week 2 and week 4 • Number of participants with indicated reason for incorrect inhaler use who required additional instruction indicated number of times at baseline, week 2 and week 4 |
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| Notes | Data collected from 12 sites in Poland (1), Ukraine (10) and USA (1) Funded by GlaxoSmithKline Study duration: 12 weeks |
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Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|----------------------------|
| Random sequence generation (selection bias) | Unclear risk | Details not reported |
| Allocation concealment (selection bias) | Unclear risk | Details not reported |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Described as double -blind |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Described as double -blind |

Bleecker 2012 (Continued)

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| Incomplete outcome data (attrition bias) All outcomes | Low risk | Details of 94 participants withdrawn from the study are included in NCT01165138 report |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

Busse 2013

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| Methods | Randomised double-blind double-dummy parallel-group multi-centre trial |
| Participants | <p>Total sample N = 503 participants, 393 completed study FF/VI 100/25, n = 201 (161 completed study) FF/VI 200/25, n = 202 (161 completed study) FP 500 mcg twice-daily, n = 100 (71 completed study)</p> <p>Age FF/VI 100/25, mean 39.7 (SD 15.85) FF/VI 200/25, mean 38.5 (SD 15.64) FP 500 mcg twice-daily, 38.6 (SD 15.97)</p> <p>Males FF/VI 100/25, 71 (35%) FF/VI 200/25, 78 (39%) FP 500 mcg twice-daily, 38 (38%)</p> <p>Baseline FEV₁ (% predicted) FF/VI 100/25, mean 74.2 (SD 13.48) FF/VI 200/25, mean 74.1 (SD 14.13) FP 500 mcg twice-daily, mean 75.2 (SD 12.46)</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Clinical diagnosis of asthma • Reversibility FEV₁ ≥ 12% and ≥ 200 mL and greater approximately 10 to 40 minutes following 2 to 4 inhalations of albuterol • FEV₁ ≥ 50% of predicted • Currently using moderate- to high-dose ICS therapy <p>Exclusion criteria</p> <ul style="list-style-type: none"> • History of life-threatening asthma • Respiratory infection or oral candidiasis • Asthma exacerbation • Uncontrolled disease or clinical abnormality • Allergies • Taking another investigational or prohibited medication |
| Interventions | <p>Arm 1: FF/VI 100/25 mcg once-daily Arm 2: FF/VI 200/25 mcg once-daily Arm 3: FP 500 mcg twice-daily</p> |
| Outcomes | <p>Primary outcome measures</p> <ul style="list-style-type: none"> • Number of participants with any AE or SAE during treatment period • Number of participants with severe asthma exacerbations during treatment period |

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| | <ul style="list-style-type: none"> • Change from baseline in albumin and total protein at week 12, week 28 and week 52/early withdrawal • Change from baseline in ALP, ALT, AST, CK and GGT at week 12, week 28 and week 52/early withdrawal • Change from baseline in direct bilirubin, indirect bilirubin, total bilirubin and creatinine at week 12, week 28 and week 52/early withdrawal • Change from baseline in chloride, CO2 content/bicarbonate, glucose, potassium, sodium and urea/BUN at week 12, week 28 and week 52/early withdrawal • Change from baseline in % of basophils, eosinophils, haematocrit, lymphocytes, monocytes and segmented neutrophils in the blood at week 12, week 28 and week 52/early withdrawal • Change from baseline in eosinophil count, total ANC, platelet count and WBC count at week 12, week 28 and week 52/early withdrawal • Change from baseline in haematocrit at week 12, week 28 and week 52/early withdrawal • Change from baseline in haemoglobin at week 12, week 28 and week 52/early withdrawal • Number of participants with indicated shift from baseline to high, normal or no change, and with low post-baseline values for urinary cortisol excretion • Ratio of 24-hour urinary cortisol excretion at week 12 to baseline, week 28 to baseline and week 52 to baseline • Number of participants with evidence of oral candidiasis during treatment period • Maximum change from baseline in SBP and minimum change from baseline in DBP • Maximum change from baseline in pulse rate • Number of participants with indicated change from baseline in LOCS III posterior subcapsular opacity (P) at week 28 and week 52 • Number of participants with indicated change from baseline in IOP at week 28 and week 52 • Change from baseline in horizontal cup-to-disc ratio at week 28 and week 52 • Number of participants with indicated change from baseline in LOCS III cortical opacity (C) at week 28 and week 52 • Change from baseline in LOCS III nuclear color (NC) at week 28 and week 52 • Change from baseline in LOCS III nuclear opalescence (NO) at week 28 and week 52 • Change from baseline in LogMAR visual acuity at week 28 and week 52 • Maximum change from baseline in QTcB and QTcF • Mean 24-hour Holter heart rate for participants with 16 or more hours of recorded data • Maximum 24-hour Holter heart rate for participants with 16 or more hours of recorded data | |
| Notes | <p>Data collected from 46 sites in Germany (15), Thailand (4), Ukraine (9) and USA (18) Funded by GlaxoSmithKline Study duration: 52 weeks</p> | |
| <i>Risk of bias</i> | | |
| Bias | Authors' judgement | Support for judgement |

Busse 2013 (Continued)

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|---|----------|---|
| Random sequence generation (selection bias) | Low risk | Central randomisation schedule was generated by the sponsor through a validated computerised system (RandAll, Glaxo-SmithKline, UK) |
| Allocation concealment (selection bias) | Low risk | Participants were randomised via an automated telephone-based registration and medication ordering system (Registration and Medication Ordering System (RAMOS)) |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Reported as double-blind |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Reported as double-blind |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Details of 110 participants withdrawn from the study are provided in the ClinicalTrials.gov NCT01018186 report |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

Hojo 2015

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|---------------|---|
| Methods | Randomised cross-over trial |
| Participants | Total sample: 32 adults Age: participants over 20 years of age with severe asthma. Mean age, 62.2 years (SD 13.3) Baseline: % FEV ₁ mean, 70 (SD 11.9%); ACT mean, 20.3 (SD 2.79) ppb at time of entry to trial suggested relatively poor asthma control status |
| Interventions | Sequence 1: FF/VI 100/25 once-daily vs FP/salmeterol 500/50 twice-daily Sequence 2: FP/salmeterol 500/50 twice-daily vs FF/VI 100/25 once-daily Participants randomised to receive 4 weeks of treatment followed by 4-week washout period, then second 4 weeks of treatment with the remaining intervention |
| Outcomes | Fractional exhaled nitric oxide (FeNO) measured by NIOX-MINO Asthma control test Morning PEF Respiratory resistance/reactance measured by Forced Oscillation Technique Mostgraph-01 |

Hojo 2015 (Continued)

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| Notes | Reported as conference abstract. Minimal information available Study duration: Each treatment period ran for 4 weeks with a 4-week washout period between treatment periods | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear risk | Details not reported |
| Allocation concealment (selection bias) | Unclear risk | Details not reported |
| Blinding of participants and personnel (performance bias) All outcomes | Unclear risk | Details not reported |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Details not reported |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Details not reported |
| Selective reporting (reporting bias) | Unclear risk | Details not reported |

Kempsford 2012

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|--------------|---|
| Methods | Randomised double-blind cross-over trial |
| Participants | <p>Total sample N = 26 participants Age: mean, 38.1 (SD 11.30) Males: 18 (69%) Baseline FEV₁ (% predicted): not reported</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Participants with documented history of persistent asthma, with exclusion of other significant pulmonary disease • Male or female between 18 and 70 years of age inclusive • A female participant is eligible to participate if she is of non-childbearing potential. Females on HRT and whose menopausal status is in doubt will be required to use a contraception method if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrolment. Childbearing potential and agrees to use one of the protocol contraception methods • All participants must be using ICS, with or without SABA, for ≥ 12 weeks before screening • Participants with screening pre-bronchodilator FEV₁ ≥ 60% of predicted |

- During screening visit, participants must demonstrate the presence of reversible airway disease
- All participants must be able to replace all their current asthma treatments with albuterol/salbutamol aerosol inhaler at screening for use as needed for run-in period and throughout the duration of the study. Participants must be able to withhold albuterol/salbutamol for ≥ 6 hours before study visits
- Participants who are current non-smokers, who have not used any inhaled tobacco products in the 12-month period preceding the screening visit
- Body weight ≥ 50 kg and BMI within the range of 19.0 to 29.9 kg/m² (inclusive)
- No evidence of significant abnormality on the 12-lead ECG performed at screening
- AST and ALT $< 2 \times$ ULN; alkaline phosphatase and bilirubin $\leq 1.5 \times$ ULN (isolated bilirubin $> 1.5 \times$ ULN is acceptable if bilirubin is fractionated and direct bilirubin is $< 35\%$)
- Capable of giving written informed consent
- Able to satisfactorily use novel DPI

Exclusion criteria

- History of life-threatening asthma within past 5 years
- Culture-documented or suspected bacterial or viral infection that was not resolved within 4 weeks of screening and led to a change in asthma management or, in the opinion of the investigator, is expected to affect participant's asthma status or ability to participate in the study
- Any asthma exacerbation requiring OCS within 12 weeks of screening or resulting in overnight hospitalisation with additional treatment for asthma within 6 months before screening
- Participant with any clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the patient at risk through study participation
- Participant will not be eligible if he/she has clinical visual evidence of oral candidiasis at screening
- Pregnant females
- Lactating females
- Participant has participated in a clinical trial and has received an investigational product within 30 days before first dosing day in the current study
- Exposure to ≥ 4 new chemical entities within 12 months before first dosing day
- Any adverse reaction including immediate or delayed hypersensitivity to any beta₂-agonist, sympathomimetic drug or intranasal, inhaled or systemic corticosteroid therapy
- History of severe milk protein allergy
- History of drug or other allergy that, in the opinion of the investigator or the GSK medical monitor, contraindicates participation
- Use of prescription or non-prescription drugs within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before first dose of study medication, unless in the opinion of the Investigator and the GSK medical monitor, the medication will not interfere with study procedures or compromise participant safety
- Participants who have taken high doses of an ICS within 8 weeks of screening visit or OCS within 12 weeks of screening visit

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| | <ul style="list-style-type: none"> • Participants who have changed their ICS treatment within the past 4 weeks before screening or can be expected to do so during the study • History of regular alcohol consumption within 6 months of the study • Positive test for hepatitis B or hepatitis C within 3 months of screening • Positive breath carbon monoxide (CO) test • Positive pre-study drug/alcohol screen • Positive test for HIV antibody • When participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56-day period <ul style="list-style-type: none"> • No participant is permitted to perform night shift work for 1 week before screening until completion of study treatment periods • Unwillingness or inability to follow procedures outlined in the protocol | |
| Interventions | <p>Sequence 1: placebo, FF/VI 100/25 mcg AM, FF/VI 100/25 mcg PM</p> <p>Sequence 2: placebo, FF/VI 100/25 mcg PM, FF/VI 100/25 mcg AM</p> <p>Sequence 3: FF/VI 100/25 mcg AM, FF/VI 100/25 mcg PM, placebo</p> <p>Sequence 4: FF/VI 100/25 mcg AM, placebo, FF/VI 100/25 mcg PM</p> <p>Sequence 5: FF/VI 100/25 mcg PM, placebo, FF/VI 100/25 mcg AM</p> <p>Sequence 6: FF/VI 100/25 mcg PM, FF/VI 100/25 mcg AM, placebo</p> <p>Participants received all treatments once a day in the evening from a DPI for 14 days. Each 14-day treatment period was followed by a 14 to 21-day washout period</p> | |
| Outcomes | <p>Primary outcome</p> <ul style="list-style-type: none"> • Weighted mean FEV₁ over 0 to 24 hours post dose on day 14 <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Pre-treatment PEF (AM and PM) at days 1 to 12 • AM and PM pre-treatment trough FEV₁ at day 14 • Number of participants with any AE or SAE | |
| Notes | <p>Data collected from 1 site in New Zealand</p> <p>Funded by GlaxoSmithKline</p> <p>Study duration: Each treatment period ran for 14 days, with a 14 to 21-day washout period between treatment periods</p> | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Central randomisation schedule was generated by GSK Quantitative sciences using validated internal software |
| Allocation concealment (selection bias) | Low risk | Investigator or designee received medication assignment information and randomised participants using sequentially numbered containers |

Kempsford 2012 (Continued)

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| Blinding of participants and personnel (performance bias) All outcomes | Unclear risk | Reported as double-blind |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Reported as double-blind |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Details of the 2 withdrawals are included in the trial report |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

Lee 2014

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| Methods | Randomised double-blind 3-period cross-over incomplete block study |
| Participants | <p>Total sample 706 screened, N = 421 participants, 323 completed study</p> <p>Age Mean, 47.5 (SD 13.84)</p> <p>Males 132 (31%)</p> <p>Baseline FEV₁ (% predicted) 1.847 L (62.31%)</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> ● Outpatient ● > 18 years of age ● Diagnosis of asthma for > 6 months ● Pre-bronchodilator FEV₁ 40% to 80% of predicted ● Demonstrated reversibility by $\geq 12\%$ and ≥ 200 mL of FEV₁ within 40 minutes following albuterol ● Need for regular controller therapy for minimum of 8 weeks ● Stable dose of ICS for > 4 weeks <p>Exclusion criteria</p> <ul style="list-style-type: none"> ● History of life-threatening asthma ● Respiratory infection not resolved ● Asthma exacerbation ● Concurrent respiratory disease ● Current smoker ● Uncontrolled disease ● Positive hepatitis B surface antigen or positive hepatitis C antibody and/or HIV ● Visual clinical evidence of oropharyngeal candidiasis ● Drug or milk protein allergies ● Concomitant medications affecting course of asthma ● Use of any other investigational medication within 30 days or 5 drug half-lives (whichever is longer) ● Previous use of GSK573719 |

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| | <ul style="list-style-type: none"> Any disease preventing use of anticholinergics Any condition that impairs compliance with study protocol, including visit schedule and completion of daily diaries Any participant with a history of alcohol or substance abuse |
| Interventions | <p>Arm 1: FF 100 mcg once daily for 14 days</p> <p>Arm 2: FF/VI 100/25 mcg once daily for 14 days</p> <p>Arm 3: FF/UMEC 100/variable dose (15.6, 31.25, 62.5, 125, 250 mcg) once daily for 14 days</p> |
| Outcomes | <p>Primary outcome measure</p> <ul style="list-style-type: none"> Change from baseline in trough FEV₁ <p>Secondary outcome measures</p> <ul style="list-style-type: none"> Mean change from baseline in daily AM/PM PEF Mean change from baseline in rescue albuterol use |
| Notes | <p>32 centres - Argentina (6), Chile (7), Russia (11), Thailand (4) and USA (4)</p> <p>Funded by GlaxoSmithKline</p> <p>Study duration: Each treatment period ran for 14 days with a 12 to 14-day washout period between treatment periods</p> |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|---|
| Random sequence generation (selection bias) | Low risk | In a 3-period cross-over study, participants were randomised to a sequence of 3 of 7 treatments using SAS-generated codes in a validated computerised system (RandAll Version 2.5, GlaxoSmithKline) |
| Allocation concealment (selection bias) | Low risk | The Registration and Medication Ordering System was used to register and randomise participants |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Double-blinding in all 3 conditions |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Double-blinding in all 3 conditions |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Information on 98 participants who failed to complete the study included in the trial report |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

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| Methods | Randomised double-blind double-dummy parallel-group trial |
| Participants | <p>Total sample N = 309 participants, 255 completed study FF/VI 200/25, n = 155 (136 completed study) FP 500, n = 154 (119 completed study)</p> <p>Age FF/VI 200/25, mean 46.9 (SD 12.93) FP 500, n = 48.8 (SD 13.41)</p> <p>Males FF/VI 100/25. 59 (38%) FP 500. n = 64 (42%)</p> <p>Baseline FEV₁ (% predicted) FF/VI 100/25, mean 67.51 (SD 13.249) FP 500, n = 67.55 (SD 13.432)</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Informed consent: All participants must be able and willing to give written informed consent to take part in the study • Type of participant: outpatients, of Asian ancestry, 12 years of age or older at visit 1 (or 18 years of age or older if local regulations or regulatory status of the study medication permits enrolment of adults only) with a diagnosis of asthma as defined by the Global Initiative for Asthma (GINA, 2009) \geq 12 weeks before visit 1 • Gender: male or eligible female, defined as non-childbearing potential or childbearing potential and using an acceptable method of birth control consistently and correctly • Severity of disease: best FEV₁ 40% to 90% of predicted normal value at visit 1 screening visit. Predicted values will be based upon NHANES III using the Asian adjustment • Reversibility of disease: demonstrated \geq 12% and \geq 200 mL reversibility of FEV₁ within 10 to 40 minutes following 2 to 4 inhalations of albuterol/salbutamol inhalation aerosol (or 1 nebulised treatment with albuterol/salbutamol solution) at screening visit • Current antiasthma therapy: All participants must be using an ICS, with or without LABA, for \geq 12 weeks before visit 1 • SABA: All participants must be able to replace their current SABA with albuterol/salbutamol inhaler at visit 1 for use as needed for the duration of the study. Participants must be able to withhold albuterol/salbutamol for \geq 4 hours before study visits <p>Exclusion criteria</p> <ul style="list-style-type: none"> • History of life-threatening asthma: defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within the past 10 years • Respiratory infection: culture-documented or suspected bacterial or viral infection of upper or lower respiratory tract, sinus or middle ear that is not resolved within 4 weeks of visit 1 and led to a change in asthma management or, in the opinion of the investigator, is expected to affect participant's asthma status or ability to participate in the study • Asthma exacerbation: any asthma exacerbation requiring OCS within 12 weeks of visit 1 or resulting in overnight hospitalisation with additional treatment for asthma within 6 months before visit 1 • Concurrent respiratory disease: Participant must not have current evidence of |

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| | <p>pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, bronchopulmonary dysplasia, chronic bronchitis, emphysema, COPD or other respiratory abnormalities other than asthma</p> <ul style="list-style-type: none"> ● Other concurrent diseases/abnormalities: Participant must not have a clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the patient at risk through study participation, or would confound interpretation of efficacy results if the condition/disease was exacerbated during the study ● Oropharyngeal examination: Participant will not be eligible for the run-in if he/she has clinical visual evidence of candidiasis at visit 1 ● Allergies: drug allergy: any adverse reaction including immediate or delayed hypersensitivity to any beta₂-agonist, sympathomimetic drug or intranasal, inhaled or systemic corticosteroid therapy. Known or suspected sensitivity to constituents of the new powder inhaler; milk protein allergy: history of severe milk protein allergy ● Concomitant medications: use of protocol-defined prohibited medications within prohibited time intervals before screening (visit 1) or during the study ● Tobacco use: current smoker or smoking history of 10 pack-years (e.g. 20 cigarettes/d for 10 years). Participant may not have used inhaled tobacco products within the past 3 months (i.e. cigarettes, cigars, smokeless or pipe tobacco) ● Affiliation with investigator's site: Participant will not be eligible for this study if he/she is an immediate family member of the participating investigator, subinvestigator or study co-ordinator, or is an employee of the participating investigator ● Previous participation: Participant may not have been randomised previously to treatment in another phase III FF/VI combination product study ● Compliance: Participant will not be eligible if he/she or his/her parent or legal guardian has any infirmity, disability, disease or geographical location that seems likely (in the opinion of the Investigator) to impair compliance with any aspect of this study protocol, including visit schedule and completion of daily diaries |
| Interventions | <ul style="list-style-type: none"> ● Arm 1: FF/VI 200/25 mcg once-daily ● Arm 2: FP 500 mcg twice-daily |
| Outcomes | <p>Primary outcome</p> <ul style="list-style-type: none"> ● Mean change from baseline in daily PM PEF averaged over 12-week treatment period <p>Secondary outcomes</p> <ul style="list-style-type: none"> ● Mean change from baseline in daily AM PEF averaged over 12-week treatment period ● Mean change from baseline in % of rescue-free 24-hour periods during 12-week treatment period ● Mean change from baseline in % of symptom-free 24-hour periods during 12-week treatment period ● Change from baseline in total AQLQ score at week 12 |
| Notes | <p>Data collected from 24 sites in China (12), Republic of Korea (10) and Philippines (2) Funded by GlaxoSmithKline Study duration: 12 weeks</p> |
| <i>Risk of bias</i> | |

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|---|
| Random sequence generation (selection bias) | Low risk | Central randomisation schedule was generated by the sponsor through a validated computerised system (RandAll, Glaxo-SmithKline, UK) |
| Allocation concealment (selection bias) | Low risk | Participants were randomised via an automated telephone-based registration and medication ordering system (Registration and Medication Ordering System (RAMOS)) |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Reported as double-blind |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Reported as double-blind |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Details of attrition bias included in trial report. Three participants (1 FF/VI; 2 FP) reported a total of 5 serious adverse events and were withdrawn from the study |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

NCT01134042

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| Methods | Randomised double-blind parallel-group multi-centre trial |
| Participants | <p>Total sample N = 586 participants, 476 completed study FF 200 mcg once-daily, n = 198 (146 completed study) FF/VI 200/25 mcg once-daily, n = 197 (169 completed study) FP 500 mcg twice-daily, n = 195 (161 completed study)</p> <p>Age FF 200 mcg once-daily, mean 44.6 years (SD 14.33) FF/VI 200/25 mcg once-daily, mean 46.6 (SD 15.05) FP 500 mcg twice-daily, mean 47.3 (SD 14.06)</p> <p>Males FF 200 mcg once-daily, 81 (42%) FF/VI 200/25 mcg once-daily, 81 (42%) FP 500 mcg twice-daily, 79 (41%)</p> <p>Baseline FEV₁ (% predicted) FF 200 mcg once-daily, mean 66.66 (SD 12.388) FF/VI 200/25 mcg once-daily, mean 66.59 (SD 12.614)</p> |

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| | <p>FP 500 mcg twice-daily, mean 67.57 (SD 12.185)</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Outpatient \geq 12 years of age • Both genders; females of childbearing potential must be willing to use birth control method • Pre-bronchodilator FEV₁ 40% to 90% of predicted • Reversibility FEV₁ \geq 12% and \geq 200 mL • Current asthma therapy that includes an ICS for \geq 12 weeks before first visit <p>Exclusion criteria</p> <ul style="list-style-type: none"> • History of life-threatening asthma • Respiratory infection or oral candidiasis • Asthma exacerbation within 12 weeks • Concurrent respiratory disease or other disease that would confound study participation or affect participant safety • Allergies to study drugs, study drug excipients, medications related to study drugs • Taking another investigational medication or medication prohibited for use during this study |
| Interventions | <p>Arm 1: FF 200 mcg once-daily</p> <p>Arm 2: FF/VI 200/25 mcg once-daily</p> <p>Arm 3: FP 500 mcg twice-daily</p> |
| Outcomes | <p>Primary outcomes</p> <ul style="list-style-type: none"> • Change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV₁ at the end of the 24-week treatment period • Change from baseline in weighted mean serial FEV₁ over 0 to 24 hours post dose at week 24 <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Change from baseline in percentage of rescue-free and symptom-free 24-hour periods at the end of the 24-week treatment period • Change from baseline in total AQLQ (+12) score at week 12 and at week 24/early withdrawal • Clinic visit 12-hour post-dose FEV₁ at week 24 • Change from baseline in weighted mean serial FEV₁ over 0 to 4 hours post dose at week 24 • Mean change from baseline in daily trough AM and PM PEF averaged over first 12 weeks and 24 weeks of 24-week treatment period • Number of participants who withdrew owing to lack of efficacy during 24-week treatment period • Change from baseline in ACT scores at week 12 and at week 24 • Number of participants with indicated global assessment of change questionnaire responses at weeks 4, 12 and 24 • Number of indicated unscheduled asthma-related healthcare visits during treatment period |
| Notes | <p>Data collected from 71 sites in Germany (10), Japan (12), Poland (8), Romania (7), Russian Federation (11) and USA (23)</p> <p>Funded by GlaxoSmithKline</p> <p>Study duration: 24 weeks</p> |

| <i>Risk of bias</i> | | |
|---|--------------------|---|
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Central randomisation schedule was generated by the sponsor through a validated, computerised system (RandAll, Glaxo-SmithKline, Stevenage, UK) |
| Allocation concealment (selection bias) | Low risk | Participants were randomised via the Registration and Medication Ordering System (GlaxoSmithKline) |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Trial reported as double-blind |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Trial reported as double-blind |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Information on 110 participants not completing the study is reported at http://clinicaltrials.gov/show/NCT01134042 |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

NCT01453023

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| Methods | Randomised double-blind cross-over trial |
| Participants | <p>Total sample N = 26 participants, 23 completed study Age: mean 8.1 years (SD 1.97) Males: 15 (58%) Asthma severity, no. (%) Mild (well controlled with GINA step 2 low-dose ICS), 21 (84%) Moderate (well controlled with GINA step 3 medium-dose ICS), 4 (16%)</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Healthy as determined by a study physician on the basis of medical history, physical examination, laboratory testing and electrocardiogram (ECG), with no significant medical condition apart from asthma, eczema or rhinitis. Participant with a clinical abnormality or laboratory parameters outside the reference range for this study may be included if the investigator and the GSK medical monitor agree that the finding is not likely to introduce additional risk factors nor interfere with study procedures • Male and pre-menarcheal female participants 5 to less than 12 years of age on last planned treatment day are eligible for this study. A pre-menarcheal female is defined as any female who has not begun menses and is considered Tanner stage 2 or less |

- Diagnosis of asthma \geq 6 months before screening
 - Stable asthma therapy (FP, total daily dose \leq 400 mcg or equivalent) and SABA inhaler for \geq 4 weeks before screening
 - Participants must be controlled on existing asthma treatment at screening, which will be continued during run-in, washout and run-out periods (but not during active treatment periods). Control is defined as Childhood ACT score $>$ 19 and PEF $>$ 75% predicted
 - Participants must demonstrate an ability to accept and effectively use a demonstration inhaler from demonstration kits provided
 - Participants must weigh \geq 20 kg
 - Participant and parent/guardian are able to understand and comply with protocol requirements, instructions and protocol stated restrictions. Parent or guardian must have the ability to read, write and record diary information collected throughout the study. Parent or guardian must have the ability to manage study drug administration and PEF assessments
 - One or more parents/guardians have signed and dated the written informed consent before admission to the study. This will be accompanied by informed assent from the participant for children 7 to 11 years of age
- Exclusion criteria**
- Participants with a history of life-threatening asthma, an asthma exacerbation requiring systemic corticosteroids or emergency room attendance (within 3 months) or hospitalisation (within 6 months) before screening
 - Participants with any medical condition or circumstance making the volunteer unsuitable for participation in the study
 - Culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear, not resolved within 4 weeks of screening and leading to a change in asthma management, or, in the opinion of the investigator, is likely to affect participants' asthma status or ability to participate in the study
 - Clinical visual evidence of oral candidiasis at screening
 - Participants currently receiving (or received within 4 weeks of screening) asthma therapies including theophyllines, long-acting inhaled beta-agonists or oral beta-agonists, or who have changed their asthma medication within 4 weeks of screening
 - Significant abnormality of rate, interval, conduction or rhythm in the 12-lead ECG, as determined by the investigator, in conjunction with age and gender of the child and assessment provided by the remote analysis service
 - QTcF $>$ 450 milliseconds or ECG not suitable for QT measurement (e.g. poorly defined termination of the T wave)
 - Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and bilirubin $>$ 1.5 times ULN (isolated bilirubin $>$ 1.5 times ULN is acceptable if bilirubin is fractionated and direct bilirubin is less than 35%)
 - Known or suspected sensitivity to any constituents of the novel DPI (i.e. lactose or magnesium stearate) (e.g. history of severe milk protein allergy)
 - Any adverse reaction including immediate or delayed hypersensitivity to any beta₂-agonist, sympathomimetic drug or intranasal, inhaled or systemic corticosteroid therapy
 - Use of prescription or non-prescription drugs, including vitamins and herbal and dietary supplements (including St John's Wort) within 7 days or 5 half-lives (whichever is longer) before first dose of study medication, unless in the opinion of the investigator

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| | <p>and the GSK medical monitor the medication will not interfere with study procedures nor compromise participant safety</p> <ul style="list-style-type: none"> • Consumption of red wine, Seville oranges, grapefruit or grapefruit juice and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices from 7 days before first dose of study medication • Individual has participated in a clinical trial and has received an investigational product within 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer) • Exposure to more than 4 new chemical entities within 12 months before first dosing day • When participation in the study would result in donation of blood or blood products in excess of the lesser of 50 mL or 3 mL per kilogram within a 56-day period • Parent/guardian has a history of psychiatric disease, intellectual deficiency, substance abuse or other condition (e.g. inability to read, comprehend and write) that will limit the validity of consent to participate in this study • Unwillingness or inability of participant or parent/guardian to follow procedures outlined in the protocol • Participant who is mentally or legally incapacitated • Children who are wards of the state or government • Participant will not be eligible for this study if he/she is an immediate family member of the participating investigator, sub-investigator or study co-ordinator, or is an employee of the participating investigator |
| Interventions | <p>Sequence 1: FF 100 mcg/VI 25 mcg in period 1 and FF 100 mcg in period 2 Sequence 2: FF 100 mcg in period 1 and FF 100 mcg/VI 25 mcg in period 2 With a washout period ≥ 7 days</p> |
| Outcomes | <p>Primary outcomes</p> <ul style="list-style-type: none"> • Number of participants with AE or SAE during treatment period • Basophil, eosinophil, lymphocyte, monocyte, total neutrophil, platelet and white blood cell count values at day 14 of treatment period • Haemoglobin and MCHC values at day 14 of treatment period • Reticulocyte and RBC values at day 14 of treatment period • Haematocrit values at day 14 of treatment period • MCV value at day 14 of treatment period • MCH values at day 14 of treatment period • ALT, ALP, AST and GGT values at day 14 of treatment period • Albumin and total protein values at day 14 of treatment period • Calcium chloride, CO₂ content/bicarbonate, glucose, potassium, sodium and urea/BUN values at day 14 of treatment period • Total bilirubin, direct bilirubin, creatinine and uric acid values at day 14 of treatment period • PEF at days 1 and 14 of treatment period • Change from baseline in SBP and DBP at days 1 and 14 of treatment period • Change from baseline in heart rate at days 1 and 14 of treatment period • Maximum QTcF at days 1 and 14 of treatment period <p>Secondary outcomes</p> <ul style="list-style-type: none"> • AUC(0-t) and AUC(0-4) of FF on day 14 of treatment period • Cmax of FF at day 14 of treatment period |

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| | <ul style="list-style-type: none"> • Tmax and Tlast of FF at day 14 of treatment period • AUC(0-t) and AUC(0-4) of VI at day 14 of treatment period • Cmax of VI at day 14 of treatment period • Tmax and Tlast of VI at day 1 of treatment period • Blood glucose and potassium values at day 14 of treatment period • Serum cortisol weighted mean (0 to 12 hours) at day 14 of treatment period • Average oropharyngeal cross-sectional area at days 1 and 14 of treatment period • Distance of assessment at days 1 and 14 of treatment period • Oropharyngeal volume at days 1 and 14 of treatment period • Average flow rate and PIFR at days 1 and 14 of treatment period • Inhalation time at days 1 and 14 of treatment period • Inhaled volume at days 1 and 14 of treatment period • Peak pressure drop at days 1 and 14 of treatment period • TED at day 14 of treatment period • Ex-throat dose (ETD) and ETD < 2 microns at day 14 of treatment period | |
| Notes | <p>Data collected from 1 site in California, USA Funded by GlaxoSmithKline Study duration: 2 weeks</p> | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Central randomisation schedule was generated by the sponsor through a validated computerised system (RandAll, GlaxoSmithKline, Stevenage, UK) |
| Allocation concealment (selection bias) | Low risk | Participants were randomised via the Registration and Medication Ordering System (GlaxoSmithKline) |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Trial reported as double-blind |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Trial reported as double-blind |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Information on the 3 participants not completing the study is provided at http://clinicaltrials.gov/show/NCT01453023 |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

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| Methods | Randomised double-blind cross-over trial |
| Participants | <p>Total sample N = 52 participants, 50 completed Age: mean, 35.4 (SD 8.63) Males: 34 years (65%) Pre-bronchodilator FEV₁% predicted: mean, 89.71 (SD 8.848)</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • BMI within the range 18.5 to 35.0 kg/m² • Females of non-childbearing potential • Documented history of bronchial asthma, first diagnosed ≥ 6 months before screening visit and currently treated only with intermittent SABA therapy by inhalation • Pre-bronchodilator FEV₁ > 70% of predicted at screening • Participants who are current non-smokers • Methacholine challenge PC20 < 8 mg/mL at screening • Screening allergen challenge demonstrates that participant experiences an early asthmatic response <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Current or chronic history of liver disease, or known hepatic or biliary abnormalities • Participant hypertensive at screening • Respiratory tract infection and/or exacerbation of asthma within 4 weeks before first dose of study medication • History of life-threatening asthma • Symptomatic with hay fever at screening or predicted to have symptomatic hay fever • Unable to abstain from short-acting beta-agonists • Unable to abstain from antihistamines • Unable to abstain from other medications, including NSAIDs, antidepressant drugs and antiasthma, anti-rhinitis or hay fever medication • Participant has participated in a study with a new molecular entity during previous 3 months or has participated in 4 or more clinical studies in previous 12 months • Undergoing allergen desensitisation therapy |
| Interventions | <p>Sequence 1: placebo, FF 100 mcg, FF/VI 100/25 mcg Sequence 2: placebo, FF/VI 100/25 mcg, FF 100 mcg Sequence 3: FF 100 mcg, FF/VI 100/25 mcg, placebo Sequence 4: FF 100 mcg, placebo, FF/VI 100/25 mcg Sequence 5: FF/VI 100/25 mcg, placebo, FF 100 mcg Sequence 6: FF/VI 100/25 mcg, FF 100 mcg, placebo</p> <p>Following the run-in period, participants were randomised to 1 of 6 treatment sequences of placebo, FF 100 mcg once-daily and FF/VI 100/25 mcg once-daily. The 3 treatment periods were separated by a washout period of ≥ 21 days (from day 28 dose) and maximum of 35 days</p> |
| Outcomes | <p>Primary outcome</p> <ul style="list-style-type: none"> • Weighted mean change from baseline in FEV₁ from 0 to 2 hours, following 22 to 23-hour post-treatment allergen challenge on day 29 of each treatment period <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Maximum % decrease from baseline in FEV₁ from 0 to 2 hours, following 22 to |

Oliver 2012 (Continued)

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| | 23-hour post-treatment allergen challenge on day 29 of each treatment period <ul style="list-style-type: none"> • Minimum FEV₁ absolute change from baseline from 0 to 2 hours, following 22 to 23-hour post-treatment allergen challenge on day 29 of each treatment period • Number of participants with treatment-emergent AEs | |
| Notes | Data collected from 4 sites in Germany (1), New Zealand (1) and UK (2) Funded by GlaxoSmithKline Study duration: 4 weeks | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Randomised by RandAll (GlaxoSmithKline validated internal randomisation software) to 1 of 6 treatment sequences, each comprising 3 treatment periods |
| Allocation concealment (selection bias) | Low risk | Participants were randomised via the Registration and Medication Ordering System (GlaxoSmithKline) |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Trial reported as double-blind |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Trial reported as double-blind |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Details of attrition bias included in trial report. Two participants withdrew: 1 withdrew consent and 1 experienced an SAE |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

Oliver 2013

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| Methods | Randomised double-blind cross-over trial |
| Participants | <p>Total sample N = 27 participants Age: mean, 30.8 years (SD 7.46) Males: 19 (70%) Pre-bronchodilator FEV₁: mean % pred, 92.3 (range 71.3 to 119.8)</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • BMI within the range 18.5 to 35.0 kg/m² • Females of non-childbearing potential |

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| | <ul style="list-style-type: none"> • Documented history of bronchial asthma, first diagnosed ≥ 6 months before screening visit and currently treated only with intermittent SABA therapy by inhalation • Pre-bronchodilator FEV₁ > 70% of predicted at screening • Participants who are current non-smokers • Methacholine challenge PC20 < 8 mg/mL at screening • Screening allergen challenge demonstrates that participant experiences an early asthmatic response <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Current or chronic history of liver disease, or known hepatic or biliary abnormalities • Participant hypertensive at screening • Respiratory tract infection and/or exacerbation of asthma within 4 weeks before first dose of study medication • History of life-threatening asthma • Symptomatic with hay fever at screening or predicted to have symptomatic hay fever • Unable to abstain from short-acting beta-agonists • Unable to abstain from antihistamines • Unable to abstain from other medications, including NSAIDs, antidepressant drugs and antiasthma, antirhinitis or hay fever medication • Participant has participated in a study with a new molecular entity during previous 3 months or has participated in 4 or more clinical studies in previous 12 months • Undergoing allergen desensitisation therapy |
| Interventions | <p>Sequence 1: VI 25 mcg, placebo, FF 100 mcg, FF/VI 100/25 mcg Sequence 2: FF/VI 100/25 mcg, FF 100 mcg, placebo, VI 25 mcg Sequence 3: placebo, FF/VI 100/25 mcg, VI 25 mcg, FF 100 mcg Sequence 4: FF 100 mcg, VI 25 mcg, FF/VI 100/25 mcg, placebo</p> <p>Participants meeting all inclusion criteria and no exclusion criteria during screening visit, conducted 14 to 42 days before first dose of study medication, entered a 14-day run-in period. Participants were then randomised to 4 treatment periods, each lasting 21 days and all separated by a nominal washout period of 21 to 35 days</p> |
| Outcomes | <p>Primary outcomes</p> <ul style="list-style-type: none"> • LAR: absolute change from baseline in minimum FEV₁ between 4 and 10 hours following 1-hour post-treatment allergen challenge on day 21 of each treatment period • LAR: absolute change from saline in weighted mean FEV₁ between 4 and 10 hours following 1-hour post-treatment allergen challenge on day 21 of each treatment period • EAR: absolute change from baseline in minimum FEV₁ between 0 and 2 hours following 1-hour post-treatment allergen challenge on day 21 of each treatment period • EAR: absolute change from baseline in weighted mean FEV₁ between 0 and 2 hours following 1-hour post-treatment allergen challenge on day 21 of each treatment period <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Maximum % change from baseline in FEV₁ between 0 and 2 hours following 1-hour post-treatment allergen challenge on day 21 of each treatment period • PC20 on day 22 of each treatment period |

Oliver 2013 (Continued)

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| Notes | Data collected from 4 sites in Australia (1), New Zealand (1) and Sweden (2) Funded by GlaxoSmithKline Study duration: Each treatment period ran for 21 days with a 21 to 35-day washout period between treatment periods | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Randomisation schedule based on a Williams square generated by the sponsor through validated internal software (RandAll, GlaxoSmithKline, London, UK) |
| Allocation concealment (selection bias) | Low risk | Automated telephone-based interactive voice response system - RAMOS (GlaxoSmithKline, London, UK) - was used by investigators to register participants and obtain randomised treatment assignments in a blinded manner |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Reported as double-blind |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Reported as double-blind |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Details of attrition bias included in trial report. Twenty-seven participants were randomised, and 26 completed the study. One participant withdrew consent, and 4 protocol deviations were noted during period 1. Data for those participants were excluded from the analysis of relevant study periods |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

Woodcock 2013

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| Methods | Randomised double-blind double-dummy parallel-group multi-centre trial |
| Participants | Total sample N = 806 participants, 715 completed study FF/VI 100/25 mcg, n = 403 (358 completed study) FP/SAL 250/50 mcg twice-daily, n = 403 (357 completed study) Age |

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| | <p>FF/VI 100/25 mcg, mean 43.8 years (SD 15.86) FP/SAL 250/50 mcg twice-daily, mean 41.9 years (SD 16.90)</p> <p>Males FF/VI 100/25 mcg 159 (44%) FP/SAL 250/50 mcg twice-daily 158 (44%)</p> <p>Baseline FEV₁ (L) FF/VI 100/25 mcg, mean 2.013 (SD 0.653) FP/SAL 250/50 mcg twice-daily, mean 2.043 (SD 0.6378)</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Clinical diagnosis of asthma • Reversibility $\geq 12\%$ and ≥ 200 mL within 10 to 40 minutes following 2 to 4 inhalations of albuterol • FEV₁ 40% to 85% of predicted normal • Currently using ICS therapy <p>Exclusion criteria</p> <ul style="list-style-type: none"> • History of life-threatening asthma within previous 5 years (requiring intubation and/or associated with hypercapnia, respiratory arrest or hypoxic seizures) • Respiratory infection or oral candidiasis • Asthma exacerbation requiring OCS, or overnight hospitalisation requiring additional asthma treatment • Uncontrolled disease or clinical abnormality • Allergies • Taking another investigational medication or prohibited medication • Night shift workers • Current smokers or participants with smoking history of ≥ 10 pack-years |
| Interventions | <p>Arm 1: FF/VI 100/25 mcg once-daily Arm 2: FP/SAL 250/50 mcg twice-daily</p> |
| Outcomes | <p>Primary outcome</p> <ul style="list-style-type: none"> • Change from baseline in weighted mean 24-hour serial FEV₁ at day 168/week 24 <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Serial FEV₁ (0-24 hours) • Number of participants with indicated time to onset of bronchodilator effect at day 1 • Change from baseline in weighted mean serial FEV₁ over 0 to 4 hours post first dose (at randomisation) • Change from baseline in weighted mean serial FEV₁ over 0 to 4 hours at day 168 • Number of participants obtaining $\geq 12\%$ and ≥ 200 mL increase from baseline in FEV₁ • Change from baseline in trough FEV₁ at day 168 • Baseline FEV₁ by completion status • Change from baseline in ACT scores at day 168 • Number of healthcare contacts related to asthma or to treatment of asthma from baseline to day 168 • Change from baseline in AQLQ total score for participants ≥ 12 years of age (AQLQ + 12) • Percentage of participants with “no problems” in EQ-5D descriptive system dimensions at day 168/week 24 |

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| | • Change from baseline in EQ-5D VAS score at day 168 | |
| Notes | Data collected from 63 sites in Argentina (10), Chile (7), Republic of Korea (7), Netherlands (8), Phillipines (6) and US (25) Funded by GlaxoSmithKline Study duration: 24 weeks | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Central randomisation schedule was generated by the sponsor through a validated computerised system (RandAll, GlaxoSmithKline) |
| Allocation concealment (selection bias) | Low risk | Participants were randomised via the Registration and Medication Ordering System |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Reported as double-blind 'Neither the patients nor the investigator knew which study medication the patient was receiving' |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Reported as double-blind 'Neither the patients nor the investigator knew which study medication the patient was receiving' |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | 89% completed the study. Details of participant withdrawal included in trial report |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

AE: adverse event

ALP: alkaline phosphatase

ALT: alanine aminotransferase

AM: morning

ANC: absolute neutrophil count

AQLQ: asthma quality of life questionnaire

AST: aspartate aminotransferase

AUC: area under the curve

BMI: body mass index

BUN: blood urea nitrogen

CK: creatine kinase

Cmax: maximum serum concentration

CO: carbon monoxide

CO₂: carbon dioxide
 COPD: chronic obstructive pulmonary disease
 DBP: diastolic blood pressure
 DPI: dry powder inhaler
 EAR: early asthmatic response
 ECG: electrocardiogram
 EQ-5D: EuroQuality of Life 5D questionnaire
 ETD: ex-throat dose
 FeNO: fractional exhaled nitric oxide
 FEV₁: forced expiratory volume in one second
 FF: fluticasone furoate
 FP: fluticasone propionate
 GGT: gamma glutamyl transferase
 HIV: human immunodeficiency virus
 HRT: hormone replacement therapy
 ICS: inhaled corticosteroid
 IOP: intraocular pressure
 LABA: long-acting beta₂-agonist
 LOCS III: Lens Opacities Classification System, Version III
 LogMAR: logarithm of the minimum angle of resolution
 MCH: mean corpuscular haemoglobin
 MCHC: mean corpuscular haemoglobin concentration
 MCV: mean corpuscular volume
 NHANES: National Health and Nutrition Examination Survey
 NIOX-MINO: first point-of-care medical device for measuring fractional exhaled nitric oxide
 NSAIDs: non-steroidal anti-inflammatory drugs
 OCS: oral corticosteroid
 OM: evening
 PC20: provocative concentration of methacholine estimated to result in a 20% reduction in FEV₁
 PEF: peak expiratory flow
 PEFr: peak expiratory flow rate
 PIRf: peak inspiratory flow rate
 PK: pharmacokinetics
 ppb: parts per billion
 QTcB: QT interval using Bazett's correction
 QTcF: QT interval using Fridericia's correction
 RAMOS: Registration and Medication Ordering System
 RBC: red blood cell
 SABA: short-acting beta₂-agonist
 SAE: serious adverse event
 SAL: salmeterol
 SAS: Statistical Analysis System (a software suite developed by SAS Institute)
 SBP: systolic blood pressure
 SD: standard deviation
 TED: total emitted dose
 Tlast: time of the last point with quantifiable concentration
 Tmax: time to C_{max}
 ULN: upper limit of normal
 UMEC: umeclidinium bromide
 VAS: visual analogue scale
 VI: vilanterol
 WBC: white blood cell count
 WM: weighted mean

Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|------------------|--|
| Calverley 2014 | Study focuses on chronic obstructive pulmonary disease participants with community-acquired pneumonia |
| Gross 2013 | Pooled analysis of data from clinical trials |
| Gross 2015 | Pooled analysis of data from clinical trials |
| Hozawa 2016 | Comparison includes budesonide/formoterol maintenance <i>and</i> reliever therapy vs fluticasone furoate/vilanterol. Therefore, the comparison is not a direct evaluation of budesonide/formoterol maintenance vs fluticasone furoate/vilanterol |
| Ishiura 2015 | Participants have a diagnosis of asthma /chronic obstructive pulmonary disease overlap syndrome, rather than asthma per se. COPD is included in the review's exclusion criteria |
| Kempford 2011 | Participants did not have a diagnosis of asthma (healthy participants) |
| Kempford 2011a | Participants did not have a diagnosis of asthma (healthy participants) |
| Kempford 2012a | Participants did not have a diagnosis of asthma (healthy participants) |
| Nakahara 2013 | Report of 3 safety, pharmacokinetics and pharmacodynamics studies with healthy participants |
| NCT00603746 | VI and FF are not used together in the intervention arm |
| NCT01181895 | Inhaled steroid used in the trial was not specifically FF |
| NCT01213849 | Dose proportionality study comparing 3 doses of FF/VI without an additional comparison arm in healthy participants |
| NCT01435902 | Study was withdrawn before participants were enrolled |
| NCT01485445 | Participants did not have a diagnosis of asthma (healthy participants) |
| NCT01573767 | Trial focuses on VI and FP, not on VI and FF |
| NCT01711463 | Participants did not have a diagnosis of asthma (healthy participants) |
| NCT02712047 2016 | Study evaluating exhaled nitric oxide time profile as a biomarker of airway inflammation |
| Oliver 2014 | Inhaled steroid used in the trial was not specifically FF |
| Sterling 2012 | Inhaled steroid used in the trial was not specifically FF |

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| Woepse 2013 | Evaluation of DPI among participants with asthma and COPD |
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COPD: chronic obstructive pulmonary disease

DPI: dry powder inhaler

FF: fluticasone furoate

FP: fluticasone propionate

VI: vilanterol

Characteristics of ongoing studies [ordered by study ID]

NCT01498679

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| Trial name or title | A randomised, double-blind, placebo-controlled, parallel group, multi-centre study to evaluate the efficacy and safety of FF/VI inhalation powder delivered once-daily for 12 weeks in the treatment of asthma in adolescent and adult participants of Asian ancestry currently treated with low to mid-strength ICS or low-strength combination therapy |
| Methods | Randomised double-blind placebo-controlled parallel-group multi-centre study |
| Participants | <p>Participants of Asian ancestry with asthma. 12 years of age or older</p> <p>Inclusion criteria</p> <ul style="list-style-type: none">• Informed consent: All participants must be able and willing to give written informed consent to take part in the study• Type of participants: outpatients, of Asian ancestry, 12 years of age or older at visit 1 (or ≥ 18 years of age or older if local regulations or the regulatory status of study medication permit enrolment of adults only), with a diagnosis of asthma as defined by the Global Initiative for Asthma (GINA 2009) ≥ 12 weeks before visit 1• Gender: male or eligible female, defined as non-childbearing potential or childbearing potential using a protocol-defined acceptable method of birth control consistently and correctly. Female participants should not be enrolled if they are pregnant, lactating or plan to become pregnant during the time of study participation. A serum pregnancy test is required for females of childbearing potential at initial screening visit (visit 1) and at visit 5 or early withdrawal• Severity of disease: best FEV₁ 40% to 90% of predicted normal value at visit 1, screening visit. Predicted values will be based upon NHANES III using adjustment for Asians (Hankinson 2010)• Reversibility of disease: demonstrated $\geq 12\%$ and ≥ 200 mL reversibility of FEV₁ within 10 to 40 minutes following 2 to 4 inhalations of albuterol/salbutamol inhalation aerosol (or 1 nebulised treatment with albuterol/salbutamol solution) at screening visit• Current antiasthma therapy: All participants must be using an ICS, with or without LABA, for ≥ 12 weeks before visit 1, in accordance with protocol-defined acceptable dose ranges• SABA: All participants must be able to replace their current SABA with albuterol/salbutamol inhaler at visit 1 for use as needed for the duration of the study. Participants must be able to withhold albuterol/salbutamol for ≥ 4 hours before study visits <p>Exclusion criteria</p> <ul style="list-style-type: none">• History of life-threatening asthma: defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within the past 10 |

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| | <p>years</p> <ul style="list-style-type: none"> • Respiratory infection: culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear that was not resolved within 4 weeks of visit 1 and led to a change in asthma management or, in the opinion of the investigator, was expected to affect participant asthma status or ability of participant to participate in the study • Asthma exacerbation: any asthma exacerbation requiring OCS within 12 weeks of visit 1, or that resulted in overnight hospitalisation requiring additional treatment for asthma within 6 months before visit 1 • Concurrent respiratory disease: Participant must not have current evidence of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, bronchopulmonary dysplasia, chronic bronchitis, emphysema, COPD or respiratory abnormalities other than asthma • Other concurrent diseases/abnormalities: Participant must not have any clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the patient at risk through study participation or would confound interpretation of efficacy results if the condition/disease was exacerbated during the study • Oropharyngeal examination: Participant will not be eligible for the run-in if he/she has clinical visual evidence of candidiasis at visit 1 • Allergies: drug allergy: any adverse reaction including immediate or delayed hypersensitivity to any beta₂-agonist or sympathomimetic drug, or to any intranasal, inhaled or systemic corticosteroid therapy. Known or suspected sensitivity to constituents of the new powder inhaler (i.e. lactose or magnesium stearate). Milk protein allergy: history of severe milk protein allergy • Concomitant medications: use of protocol-defined prohibited medications before visit 1 or during the study, in accordance with the protocol • Tobacco use: current smoker or participants with smoking history of 10 pack-years (i.e. 20 cigarettes/d for 10 years). Participant may not have used inhaled tobacco products within the past 3 months (i.e. cigarettes, cigars, smokeless or pipe tobacco) • Affiliation with investigator site: Participant will not be eligible for this study if he/she is an immediate family member of the participating investigator, subinvestigator or study co-ordinator, or an employee of the participating investigator • Previous participation: Participant may not have previously been randomised to treatment in another phase III FF/VI combination product study (i.e. HZA113714, HZA106827, HZA106829, HZA106837, HZA106839, HZA106851, HZA113091) • Compliance: Participant will not be eligible if he/she or his/her parent or legal guardian has an infirmity, disability, disease or geographical location that seems likely (in the opinion of the Investigator) to impair compliance with any aspect of this study protocol, including visit schedule and completion of daily diaries |
| Interventions | FF/VI ICS/LABA combination vs placebo |
| Outcomes | <p>Primary outcome measure</p> <ul style="list-style-type: none"> • Mean change from baseline in PM PEF averaged over 12-week treatment period <p>Secondary outcome measures</p> <ul style="list-style-type: none"> • Mean change from baseline in daily AM PEF averaged over 12-week treatment period • Change from baseline in percentage of rescue-free 24-hour periods during 12-week treatment period • Change from baseline in percentage of symptom-free 24-hour periods during 12-week treatment period • Change from baseline in total AQLQ score at week 12 |
| Starting date | January 2012 |
| Contact information | GlaxoSmithKline Research and Development Limited |

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| Notes | |
| NCT01573624 | |
| Trial name or title | A multi-centree, randomised, double-blind, dose-ranging study to evaluate GSK573719 in combination with fluticasone furoate, fluticasone furoate alone and an active control of fluticasone furoate/vilanterol combination in participants with asthma |
| Methods | Randomised double-blind cross-over study |
| Participants | <p>Participants with asthma. 18 years of age or older</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> ● Outpatient ● 18 years of age or older at visit 1 ● Diagnosis of asthma ● Male or eligible female ● Pre-bronchodilator FEV₁ 40% to 80% of predicted normal value at visit 1 ● Demonstrated reversibility by $\geq 12\%$ and ≥ 200 mL of FEV₁ within 40 minutes following albuterol at visit 1 <ul style="list-style-type: none"> ● Need for regular controller therapy (i.e. ICSs alone or in combination with a LABA, or leukotriene modifier, etc.) for a minimum of 8 weeks before visit 1 <p>Exclusion criteria</p> <ul style="list-style-type: none"> ● History of life-threatening asthma ● Respiratory infection not resolved ● Asthma exacerbation ● Concurrent respiratory disease ● Current smokers ● Other uncontrolled disease or disease state that, in the opinion of the investigator, would put the safety of the patient at risk through study participation, or would confound interpretation of efficacy results if the condition/disease was exacerbated during the study <ul style="list-style-type: none"> ● Positive hepatitis B surface antigen or positive hepatitis C antibody and/or HIV ● Visual clinical evidence of oropharyngeal candidiasis ● Drug or milk protein allergies ● Concomitant medications affecting course of asthma ● Use of any other investigational medication within 30 days or 5 drug half-lives (whichever is longer) ● Previous use of GSK573719 ● Any disease preventing use of anticholinergics ● Any condition that impairs compliance with study protocol including visit schedule and completion of daily diaries <ul style="list-style-type: none"> ● Any participant with a history of alcohol or substance abuse ● Any affiliation with investigator's site |
| Interventions | FF 100 mcg vs FF/VI 100/25 mcg vs FF/GSK573719 100/15.6 to 250 mcg |
| Outcomes | <p>Primary outcome measures</p> <ul style="list-style-type: none"> ● Change from baseline in trough FEV₁ ● FEV₁ value obtained 24 hours after morning dosing on day 14 of each treatment period <p>Secondary outcome measures</p> |

NCT01573624 (Continued)

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| | <ul style="list-style-type: none"> • Mean change from baseline in daily AM/PM PEF • Mean change from baseline in rescue albuterol use |
| Starting date | April 2012 |
| Contact information | GlaxoSmithKline Research and Development Limited; GSKClinicalSupportHD@gsk.com |
| Notes | |

NCT01706198

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| Trial name or title | A 12-month, open label, randomised, effectiveness study to evaluate fluticasone furoate (GW685698)/vilanterol (GW642444) inhalation powder delivered once-daily via a novel dry powder inhaler compared with usual maintenance therapy in participants with asthma |
| Methods | Randomised parallel-group study |
| Participants | <p>Participants with asthma. 18 years of age or older</p> <p>Inclusion criteria</p> <p>Participants eligible for enrolment in the study must meet all of the following criteria</p> <ul style="list-style-type: none"> • Informed consent: Participants must be able to provide informed consent and have their consent signed and dated • Type of participants: participants with documented GP diagnosis of asthma as their primary respiratory disease • Current antiasthma therapy: All participants must be prescribed maintenance therapy and must be receiving ICS with or without LABA (fixed combination or via separate inhalers) for ≥ 4 weeks before visit 2. Other background asthma medication such as antileukotrienes are permitted • All participants receiving ICS monotherapy or ICS/LABA combination (this can be a fixed-dose combination or an ICS alone or LABA alone in separate inhalers) must have had symptoms in the past week before visit 2. Symptoms are defined by daytime symptoms more than twice per week, use of SABA bronchodilator more than twice per week, any limitation of activities or any nocturnal symptoms/awakening (Symptoms are based on participant's recall and are consistent with GINA and agree in principle with BTS/SIGN guidelines) • Participant questionnaires: Participants must be able to complete electronic participant questionnaires as well as questionnaires to be completed by phone or must provide a proxy (e.g. partner/relative/friend) who can do so on their behalf • Gender and age: male or female participants ≥ 18 years of age at visit 1. A female is eligible to enter and participate in the study if she is of: non-childbearing potential (i.e. physiologically incapable of becoming pregnant, including any female who is post-menopausal or surgically sterile). Surgically sterile females are defined as those with a documented hysterectomy and/or bilateral oophorectomy or tubal ligation. Post-menopausal females are defined as amenorrhoeic for > 1 year with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms). However, in questionable cases, a blood sample with FSH > 40 MIU/mL and estradiol < 40 pg/mL (< 147 pmol/L) is confirmatory OR childbearing potential has a negative urine pregnancy test at visit 2, and participant agrees to one of the highly effective and acceptable contraceptive methods used consistently and correctly (i.e. in accordance with approved product label and instructions of the physician for the duration of the study - visit 2 to end of study) <p>Exclusion criteria</p> <p>Participants meeting any of the following criteria must not be enrolled in the study</p> |

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| | <ul style="list-style-type: none"> • Recent history of life-threatening asthma: defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within the past 6 months • COPD: Participant must not have current evidence or GP diagnosis of COPD • Other diseases/abnormalities: participants with historical or current evidence of uncontrolled or clinically significant disease. Significant is defined as any disease that, in the opinion of the GP/investigator, would put the safety of the patient at risk through study participation, or that would affect the efficacy or safety analysis if the disease/condition was exacerbated during the study • Drug/food allergy: participants with a history of hypersensitivity to any of the study medications (e.g. beta₂-agonists, corticosteroid) or components of the inhalation powder (e.g. lactose, magnesium stearate). In addition, participants with a history of severe milk protein allergy that, in the opinion of the GP/investigator, contraindicates the participant's participation will also be excluded • Investigational medications: Participant must not have used any investigational drug within 30 days before visit 2 or within 5 half-lives (t_{1/2}) of prior investigational study (whichever is the longer of the 2) (if unsure, discuss with medical monitor before screening) • Long-term user of systemic corticosteroids: participant who, in the opinion of the GP/investigator, is considered to be a long-term user of systemic corticosteroids for respiratory or other indications (if unsure, discuss with the medical monitor before screening) • Participants who are using LABA without an ICS as asthma maintenance therapy • Participants who plan to move away from the geographical area where the study is being conducted during the study period and/or if participants have not consented to inclusion of their medical records in the electronic medical records database that is operational in the Salford area |
| Interventions | GW685698+GW642444 once-daily via a novel dry powder inhaler vs existing maintenance therapy (ICS alone or in combination with a LABA) |
| Outcomes | <p>Primary outcome measure</p> <ul style="list-style-type: none"> • Percentage of participants who have an ACT total score ≥ 20 at week 24 (6th month) assessment <p>Secondary outcome measures</p> <ul style="list-style-type: none"> • Percentage of participants with asthma control (ACT total score ≥ 20) • Mean change from baseline in ACT total score • Percentage of participants who have an increase from baseline of ≥ 3 in ACT total score • Asthma-related secondary care contacts • Asthma-related primary care contacts • All secondary care contacts • All primary care contacts • Mean annual rate of severe asthma exacerbations • Number of salbutamol inhalers (adjusted to equivalence of 200 actuations) collected by participants from study-enrolled community pharmacies over the entire treatment period <ul style="list-style-type: none"> • Time to discontinuation or modification of initial therapy • Percentage of participants who have an increase from baseline ≥ 0.5 in AQLQ(S) total score at week 52 • Percentage of participants who have an increase from baseline ≥ 0.5 in AQLQ(S) environmental stimuli domain score at week 52 |
| Starting date | November 2012 |
| Contact information | GlaxoSmithKline Research and Development Limited; GSKClinicalSupportHD@gsk.com |
| Notes | |

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| Trial name or title | A study to assess the bronchodilator effect of a single dose of fluticasone furoate (FF)/vilanterol (VI) 100/25 micrograms (mcg) combination when administered in adult participants with asthma |
| Methods | Randomised double-blind placebo-controlled cross-over study |
| Participants | <p>32 adult participants with moderately severe asthma</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> ● Asthma: a doctor diagnosis of asthma ● Age of participant: 18 to 65 years of age inclusive, at the time of signing the informed consent ● Severity of disease: screening pre-bronchodilator FEV₁ ≥ 60% of predicted ● Reversibility of disease: demonstrated presence of reversible airway disease at screening ● Current therapy: on ICS with or without a SABA for ≥ 12 weeks before screening. Able to stop current short-acting beta₂-agonists (SABAs) and replace with albuterol/salbutamol inhaler <ul style="list-style-type: none"> ● Body weight and BMI: body weight ≥ 50 kg and BMI within the range 19.0 to 29.9 kg/m² (inclusive) ● Gender: male or female. A female participant is eligible to participate if she is of: <ul style="list-style-type: none"> Non-childbearing potential. Females on HRT and whose menopausal status is in doubt will be required to use one of the contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrolment Childbearing potential and agrees to use one of the contraception methods for an appropriate period of time (as determined by product label or investigator) before the start of dosing to sufficiently minimise risk of pregnancy at that point. Female participants must agree to use contraception until completion of the follow-up visit ● Liver criteria: AST and ALT < 2 × ULN; alkaline phosphatase and bilirubin ≤ 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%) ● Consent: capable of giving written informed consent, which includes compliance with requirements and restrictions listed in the consent form <p>Exclusion criteria</p> <ul style="list-style-type: none"> ● History of life-threatening asthma ● Other significant pulmonary disease: pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, bronchopulmonary dysplasia, chronic bronchitis, emphysema, COPD, respiratory abnormalities other than asthma ● Respiratory infection: culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear that is not resolved within 4 weeks of screening that; led to a change in asthma management OR, in the opinion of the Investigator, is expected to affect the participant's asthma status, OR the participant's ability to participate in the study ● Asthma exacerbation: any asthma exacerbation requiring OCS within 12 weeks of screening or that resulted in overnight hospitalisation requiring additional treatment for asthma within 6 months before screening ● Concomitant medications: use of medications, ICS prohibited for each study period from 24 hours before dosing to 72 hours after dosing; LABA, LTRA or LAMA prohibited for 12 weeks before screening; high doses of an ICS prohibited for 8 weeks before screening; OCS prohibited for 12 weeks before screening; potent CYP3A4 inhibitors prohibited within 4 weeks before dosing. The following medications may not be used during the study from first dosing to the end of period 2 inclusive: anticonvulsants, polycyclic antidepressants, beta-adrenergic blocking agents, phenothiazines and MAO inhibitors <ul style="list-style-type: none"> ● Other concurrent diseases/abnormalities: Participant has any clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the patient at risk through study participation or would confound interpretation of study results if the condition/disease was exacerbated during the study ● Oropharyngeal examination: Participant will not be eligible if he/she has clinical visual evidence of oral |

NCT01837316 (Continued)

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| | <p>candidiasis at screening</p> <ul style="list-style-type: none"> • Pregnant and lactating females: pregnant females as determined by positive serum human chorionic gonadotropin (hCG) test at screening or by positive urine hCG test before dosing. Lactating females • Allergies: milk protein allergy: history of severe milk protein allergy. Drug allergy: any adverse reaction including immediate or delayed hypersensitivity to any beta₂-agonist or sympathomimetic drug, or to any intranasal, inhaled or systemic corticosteroid therapy. Known or suspected sensitivity to constituents of the DPI (i.e. lactose or magnesium stearate). Historical allergy: history of drug or other allergy that, in the opinion of the investigator or the GSK medical monitor, contraindicates participation • 12-Lead ECG abnormality: significant abnormality in the 12-lead ECG performed at screening • Tobacco use: current smokers or smoking history ≥ 10 pack-years. Participant may not have used any inhaled tobacco products in the 12-month period preceding the screening visit • Previous participation: exposure to more than 4 new chemical entities within 12 months before first dosing day |
| Interventions | After screening, participant will be randomised and will be assigned to 1 of 2 treatment sequences (AB or BA, where A is placebo and B is FF/VI 100/25 mcg). Between the 2 treatment periods, a washout period of 7 to 14 days will occur |
| Outcomes | Serial FEV ₁ measurements will be taken at 15 and 30 minutes, and at 1, 2, 4, 12, 24, 36, 48, 60 and 72 hours post dose. Safety assessments will include vital signs, ECGs, AE monitoring and laboratory safety tests; however, these will not constitute study endpoints. Results of the study will provide supporting information to prescribers on the bronchodilator effect of FF/VI over 72 hours |
| Starting date | Information on http://clinicaltrials.gov/ in October 2013 indicated that study was not yet recruiting. Estimated primary completion date: December 2013 |
| Contact information | GlaxoSmithKline Research and Development Limited; GSKClinicalSupportHD@gsk.com |
| Notes | |

NCT02094937

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| Trial name or title | A study to compare the efficacy and safety of fluticasone furoate (FF) 100 mcg once-daily with fluticasone propionate (FP) 250 mcg twice-daily and FP 100 mcg twice-daily in well-controlled asthmatic Japanese participants |
| Methods | Randomised double-blind multi-centre parallel-group study |
| Participants | <p>Exclusion criteria</p> <ul style="list-style-type: none"> • History of life-threatening asthma: defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within past 10 years • Respiratory infection: culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear that was not resolved within 8 weeks of visit 1 and led to a change in asthma management or, in the opinion of the investigator, is expected to affect the participant's asthma status or ability to participate in the study • Asthma exacerbation: any asthma exacerbation requiring systemic corticosteroids or injection within 12 weeks of visit 1, or that resulted in overnight hospitalisation requiring additional treatment for asthma within 6 months before visit 1 |

- Concurrent respiratory disease: Participant must not have current evidence of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, bronchopulmonary dysplasia, chronic bronchitis, emphysema, COPD or any respiratory abnormalities other than asthma
 - Other concurrent diseases/abnormalities: Participant must not have a clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the patient at risk through study participation or would confound interpretation of efficacy results if the condition/disease was exacerbated during the study. The list of additional excluded conditions/diseases includes, but is not limited to, the following: congestive heart failure, known aortic aneurysm, clinically significant coronary heart disease, clinically significant cardiac arrhythmia, stroke within 3 months of visit 1, uncontrolled hypertension (≥ 2 measurements with systolic BP > 160 mmHg, or DBP > 100 mmHg), recent or poorly controlled peptic ulcer, haematologic, hepatic or renal disease, immunologic compromise, current malignancy (history of malignancy is acceptable only if participant has been in remission for 1 year before visit 1 (remission = no current evidence of malignancy and no treatment for malignancy in the 12 months before visit 1), tuberculosis (current or untreated) (participants with a history of tuberculosis infection who have completed an appropriate course of antituberculous treatment may be suitable for study entry provided there is no clinical suspicion of active or recurrent disease), Cushing's disease, Addison's disease, uncontrolled diabetes mellitus, uncontrolled thyroid disorder, recent history of drug or alcohol abuse
 - Oropharyngeal examination: Participant will not be eligible for the run-in if he/she has clinical visual evidence of candidiasis at visit 1
 - Investigational medications: Participant must not have used any investigational drug within 30 days before visit 1 or within 5 half-lives ($t_{1/2}$) of the prior investigational study (whichever is longer of the 2)
 - Allergies: drug allergy: any adverse reaction including immediate or delayed hypersensitivity to any beta₂-agonist or sympathomimetic drug, or to any intranasal, inhaled or systemic corticosteroid therapy. Known or suspected sensitivity to constituents of the investigational product (i.e. lactose or magnesium stearate); milk protein allergy: history of severe milk protein allergy
 - Concomitant medication: administration of prescription or over-the-counter medication that would significantly affect the course of asthma, or interact with study drug, such as anticonvulsants (barbiturates, hydantoin, carbamazepine); polycyclic antidepressants; beta-adrenergic blocking agents; phenothiazines and MAO inhibitors. Immunosuppressive medications: Participant must not be using or require use of immunosuppressive medications during the study.
- Note: Immunotherapy is permitted for treatment of allergies during the study, provided it was initiated ≥ 4 weeks before visit 1 and participants remain in the maintenance phase for the duration of the study; cytochrome P450 3A4 (CYP3A4) inhibitors: participants who have received a potent CYP3A4 inhibitor within 4 weeks of visit 1 (e.g. clarithromycin, atazanavir, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleanomycin, voriconazole, mibefradil, cyclosporine)
- Compliance: Participant will not be eligible if he/she or his/her parent or legal guardian has any infirmity, disability, disease or geographical location that seems likely (in the opinion of the investigator) to impair compliance with any aspect of this study protocol, including visit schedule and completion of eDiaries and a paper medical conditions diary
 - Tobacco use: current smoker or smoking history of 10 pack-years (e.g. 20 cigarettes/d for 10 years). Participant may not have used inhaled tobacco products within the past 3 months (i.e. cigarettes, cigars or pipe tobacco)
 - Affiliation with investigator's site: Participant will not be eligible for this study if he/she is an immediate family member of the participating investigator, subinvestigator or study co-ordinator, or an employee of the participating investigator
- Other exclusion criteria at visit 2 and visit 5**
- Evidence of clinically significant abnormal laboratory tests during visit 1 that are still abnormal upon repeat analysis and are not believed to be due to disease(s) present. Each investigator will use his/her own

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| | <p>discretion in determining the clinical significance of the abnormality</p> <ul style="list-style-type: none"> • Changes in asthma medication (excluding salbutamol inhalation aerosol provided at visit 1) • Occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear during run-in and open-label treatment periods that led to a change in asthma management or, in the opinion of the investigator, is expected to affect participant's asthma status or ability of the participant to participate in the study • Any asthma exacerbation requiring systemic corticosteroids or injection or that resulted in overnight hospitalisation requiring additional treatment for asthma. Clinical visual evidence of oral candidiasis at visit 2 and visit 5 • Positive urine pregnancy test for all females of childbearing potential at visit 2 and visit 5 • Participants for whom the investigator decides that it is impossible for participant to do "switch (visit 2)" and "step-down (visit 5)" |
| Interventions | <ul style="list-style-type: none"> • Arm 1: FF/VI 100/25 mcg participants will receive FF/VI 100/25 mcg once-daily via DPI for 8 weeks in the open-label treatment period • Arm 2: FF 100 mcg participants will receive FP matching placebo twice-daily (morning and evening) and FF 100 mcg once-daily in the evening, via DPI for 12 weeks in the double-blind treatment period • Arm 3: FP 250 mcg participants will receive FP 250 mcg twice-daily (morning and evening) and FF matching placebo once-daily in the evening, via DPI for 12 weeks in the double-blind treatment period • Arm 4: FP 100 mcg participants will receive FP 100 mcg twice-daily (morning and evening) and FF matching placebo once-daily in the evening, via DPI for 12 weeks in the double-blind treatment period |
| Outcomes | <p>Primary outcome measures</p> <ul style="list-style-type: none"> • Time to withdrawal due to poorly controlled (requires step-up) asthma during period 2 • Proportion of participants with well-controlled asthma at the end of period 2 <p>Secondary outcome measures</p> <ul style="list-style-type: none"> • Mean change from baseline in clinic visit trough FEV₁ at the end of period 2 • Mean change from baseline in daily AM and PM PEF averaged during period 2 • Mean change from baseline in percentage of symptom-free 24-hour periods during period 2 • Mean change from baseline in percentage of rescue-free 24-hour periods during period 2 • Mean change from baseline in ACT score during period 2 • Proportion of participants with ACT score ≥ 20 at the end of period 2 |
| Starting date | March 2014 |
| Contact information | GlaxoSmithKline Research and Development Limited; GSKClinicalSupportHD@gsk.com |
| Notes | |

NCT02301975

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| Trial name or title | An efficacy and safety study of fluticasone furoate/vilanterol 100/25 microgram (mcg) inhalation powder, fluticasone propionate/salmeterol 250/50 mcg inhalation powder and fluticasone propionate 250 mcg inhalation powder in adults and adolescents with persistent asthma |
| Methods | Randomised double-blind double-dummy parallel-group multi-centre non-inferiority study |

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| Participants | <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Participants must give their signed and dated written informed consent to participate before commencing any study-related activities • Participants must be outpatients ≥ 12 years of age at visit 1 who have had a diagnosis of asthma, as defined by the National Institutes of Health, for ≥ 12 weeks before visit 1 (Note: Countries with local restrictions prohibiting enrolment of adolescents will enrol only participants ≥ 18 years of age) • Participants may be male or an eligible female. An eligible female is defined as having non-childbearing potential or having childbearing potential and a negative urine pregnancy test at screening and agrees to use an acceptable method of birth control consistently and correctly <ul style="list-style-type: none"> • Participants must have a best pre-bronchodilator FEV₁ $\geq 80\%$ of predicted normal value • Participants are eligible if they have received mid-dose ICS plus LABA (equivalent to FP/SAL 250/50 twice-daily or an equivalent combination via separate inhalers) for at least the 12 weeks immediately preceding visit 1 <ul style="list-style-type: none"> • All participants must be able to replace their current SABA treatment with albuterol/salbutamol aerosol inhaler at visit 1 for use, as needed, for the duration of the study. Participants must be able to withhold albuterol/salbutamol for ≥ 6 hours before study visits • If in the opinion of the investigator the participant's asthma is well controlled <p>Exclusion criteria</p> <ul style="list-style-type: none"> • History of life-threatening asthma, defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within the past 5 years <ul style="list-style-type: none"> • Culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear that is not resolved within 4 weeks of visit 1 and led to a change in asthma management or, in the opinion of the investigator, was expected to affect the participant's asthma status or the ability of the participant to participate in the study <ul style="list-style-type: none"> • Any asthma exacerbation requiring OCS within 12 weeks of visit 1 or resulting in an overnight hospitalisation requiring additional treatment for asthma within 6 months before visit 1 • Participant must not have current evidence of atelectasis, bronchopulmonary dysplasia, chronic bronchitis, chronic obstructive pulmonary disease, pneumonia, pneumothorax, interstitial lung disease or any evidence of concurrent respiratory disease other than asthma <ul style="list-style-type: none"> • Participant must not have any clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the patient at risk through study participation or would confound interpretation of results if the condition/disease was exacerbated during the study • Participant must not have used any investigational drug within 30 days before visit 1 or within 5 half-lives ($t_{1/2}$) of the prior investigational study, whichever is longer of the 2 <ul style="list-style-type: none"> • Any adverse reaction including immediate or delayed hypersensitivity to any beta₂-agonist or sympathomimetic drug, or to any intranasal, inhaled or systemic corticosteroid therapy. Known or suspected sensitivity to the constituents of RELVAR ELLIPTA inhaler, SERETIDE ACCUHALER/ DISKUS inhaler or FP 250 <ul style="list-style-type: none"> • History of severe milk protein allergy • Administration of prescription or non-prescription medication that would significantly affect the course of asthma, or interact with study drug • Participant must not be using or require the use of immunosuppressive medications during the study • Participant will not be eligible if he/she or his/her parent or legal guardian has an infirmity, disability, disease or geographical location that seems likely (in the opinion of the investigator) to impair compliance with any aspect of this study protocol, including visit schedule and completion of daily diaries <ul style="list-style-type: none"> • Current tobacco smoker or smoking history of 10 pack-years (20 cigarettes/d for 10 years). Participant |
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| | <p>may not have used inhaled tobacco products or inhaled marijuana within the past 3 months (e.g. cigarettes, cigars, electronic cigarettes, pipe tobacco)</p> <ul style="list-style-type: none"> Participant will not be eligible for this study if he/she is an immediate family member of the participating investigator, subinvestigator or study co-ordinator, or is an employee of the participating investigator |
| Interventions | <ul style="list-style-type: none"> Experimental 1: FF/VI 100/25 mcg by inhalation once-daily (PM) via ELLIPTA plus placebo by inhalation twice-daily (AM and PM) via ACCUHALER/DISKUS for 24 weeks. Interventions: drug: FF/VI 100/25 mcg via ELLIPTA inhaler; drug: placebo inhalation powder via ACCUHALER/DISKUS inhaler Experimental 2: FP/SAL 250/50 mcg by inhalation twice-daily (AM and PM) via ACCUHALER/DISKUS plus placebo by inhalation once-daily (PM) via ELLIPTA for 24 weeks. Interventions: drug: placebo inhalation powders via ELLIPTA inhaler; drug: FP/SAL 250/50 mcg via ACCUHALER/DISKUS inhaler Experimental 3: FP 250 mcg by inhalation twice-daily (AM and PM) via ACCUHALER/DISKUS plus placebo by inhalation once-daily (PM) via ELLIPTA for 24 weeks |
| Outcomes | <p>Primary outcome measures</p> <ul style="list-style-type: none"> Change from baseline in clinic visit PM FEV₁ (pre-bronchodilator and pre-dose) at the end of the 24-week treatment period <p>Secondary outcome measures</p> <ul style="list-style-type: none"> Change from baseline in percentage of rescue-free 24-hour periods during 24-week treatment period Change from baseline in percentage of symptom-free 24-hour periods during 24-week treatment period Change from baseline in AM PEF averaged over 24-week treatment period Percentage of participants controlled at the end of the 24-week treatment period Change from baseline in PM PEF averaged over 24-week treatment period |
| Starting date | February 2015 |
| Contact information | GlaxoSmithKline Research and Development Limited; GSKClinicalSupportHD@gsk.com |
| Notes | |

NCT02301975 2015

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| Trial name or title | An efficacy and safety study of fluticasone furoate/vilanterol 100/25 microgram (mcg) inhalation powder, FP/SAL 250/50 mcg inhalation powder and fluticasone propionate 250 mcg inhalation powder in adults and adolescents with persistent asthma |
| Methods | This study is a randomised double-blind double-dummy parallel-group multi-centre non-inferiority study |
| Participants | <p>Inclusion criteria</p> <ul style="list-style-type: none"> Participants must give their signed and dated written informed consent to participate before commencing any study-related activities Participants must be outpatients ≥ 12 years of age at visit 1 who have had a diagnosis of asthma, as defined by the National Institutes of Health, for ≥ 12 weeks before visit 1 (Note: Countries with local restrictions prohibiting enrolment of adolescents will enrol only participants ≥ 18 years of age) Participants may be male or an eligible female. An eligible female is defined as having non-childbearing potential or having childbearing potential and a negative urine pregnancy test at screening and agrees to use |

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| | <p>an acceptable method of birth control consistently and correctly</p> <ul style="list-style-type: none"> • Participants must have $FEV_1 \geq 80\%$ of predicted normal value • Participants are eligible if they have received mid-dose ICS plus LABA (equivalent to FP/SAL 250/50 twice-daily or an equivalent combination via separate inhalers) for at least the 12 weeks immediately preceding visit 1 • All participants must be able to replace their current SABA treatment with albuterol/salbutamol aerosol inhaler at visit 1 for use, as needed, for the duration of the study. Participants must be able to withhold albuterol/salbutamol for ≥ 6 hours before study visits • If in the opinion of the investigator, the participant's asthma is well controlled <p>Exclusion criteria</p> <ul style="list-style-type: none"> • History of life-threatening asthma, defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within the past 5 years • Culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear that is not resolved within 4 weeks of visit 1 and led to a change in asthma management or, in the opinion of the investigator, was expected to affect the participant's asthma status or the participant's ability to participate in the study • Any asthma exacerbation requiring oral corticosteroids within 12 weeks of visit 1 or resulting in an overnight hospitalisation requiring additional treatment for asthma within 6 months before visit 1 • Participant must not have current evidence of atelectasis, bronchopulmonary dysplasia, chronic bronchitis, chronic obstructive pulmonary disease, pneumonia, pneumothorax, interstitial lung disease, or any evidence of concurrent respiratory disease other than asthma • Participant must not have any clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the patient at risk through study participation or would confound interpretation of results if the condition/disease was exacerbated during the study • Participant must not have used any investigational drug within 30 days before visit 1 or within 5 half-lives ($t_{1/2}$) of the prior investigational study, whichever is longer of the 2 • Any adverse reaction including immediate or delayed hypersensitivity to any β_2-agonist or sympathomimetic drug, or any intranasal, inhaled or systemic corticosteroid therapy. Known or suspected sensitivity to the constituents of RELVAR ELLIPTA inhaler, SERETIDE ACCUHALER/DISKUS inhaler or FP 250 • History of severe milk protein allergy • Administration of prescription or non-prescription medication that would significantly affect the course of asthma, or interact with study drug • Participant must not be using or require the use of immunosuppressive medications during the study • Participant will not be eligible if he/she or his/her parent or legal guardian has an infirmity, disability, disease or geographical location that seems likely (in the opinion of the investigator) to impair compliance with any aspect of this study protocol, including visit schedule and completion of daily diaries • Current tobacco smoker or has a smoking history of 10 pack-years (20 cigarettes/d for 10 years). Participant may not have used inhaled tobacco products or inhaled marijuana within the past 3 months (e.g. cigarettes, cigars, electronic cigarettes, pipe tobacco) • Participant will not be eligible for this study if he/she is an immediate family member of the participating investigator, subinvestigator or study co-ordinator, or an employee of the participating investigator |
| Interventions | <p>The study will enrol adult and adolescent asthmatic participants who are currently receiving mid-dose inhaled corticosteroids (ICSs) plus a long-acting β_2-agonist (LABA) (equivalent to FP/SAL 250/50 microgram (mcg) twice-daily (BD)), via a fixed-dose combination product or through separate inhalers. The study consists of a LABA washout period of 5 days and a run-in period of 4 weeks, followed by a treatment period of 24</p> |

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| | <p>weeks and a follow-up contact period of 1 week. The total duration of the study is 30 weeks. Approximately 1461 participants will be randomised to 1 of the following 3 treatments (487 per treatment): FF/VI 100/25 mcg once-daily (OD) in the evening (PM) via ELLIPTA inhaler plus placebo BD via ACCUHALER/DISKUS; FP/SAL 250/50 mcg BD via ACCUHALER/DISKUS inhaler plus placebo OD (PM) via ELLIPTA inhaler; FP 250 mcg BD via ACCUHALER/DISKUS inhaler plus placebo OD (PM) via ELLIPTA inhaler. In addition, all participants will be supplied with albuterol/salbutamol inhalation aerosol for use as needed to treat acute asthma symptoms</p> |
| Outcomes | <p>Primary outcome measures</p> <ul style="list-style-type: none"> • Change from baseline in clinic visit evening (PM) forced expiratory volume in 1 second (FEV₁) (pre-bronchodilator and pre-dose) at the end of the 24-week treatment period (time frame: baseline and week 24) (designated as safety issue: no) FEV₁ is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in 1 second. Baseline will be the pre-dose value obtained at the visit 3 clinic visit. Change from baseline will be calculated as the week 24 value minus the baseline value <p>Secondary outcome measures</p> <ul style="list-style-type: none"> • Change from baseline in percentage of rescue-free 24-hour periods during 24-week treatment period (time frame: baseline and weeks 1 to 24) (designated as safety issue: no). Participants will record the number of inhalations of rescue medication used during the day and night in a daily electronic diary (eDiary). A 24-hour period in which a participant's responses to both morning and evening assessments indicated no rescue medication use will be considered to be a rescue-free 24-hour period. Baseline value will be derived from the last 7 days of the daily eDiary before randomisation of participant. Change from baseline will be calculated as the value during the 24-week treatment period minus the baseline value • Change from baseline in percentage of symptom-free 24-hour periods during 24-week treatment period (time frame: baseline and weeks 1 to 24) (designated as safety issue: no). Asthma symptoms will be recorded in a daily eDiary by participants every day morning and evening. A 24-hour period in which a participant's responses to both morning and evening assessments indicated no symptoms will be considered to be a symptom-free 24-hour period. Baseline value will be derived from the last 7 days before randomisation of the participant. Change from baseline will be calculated as the value during the 24-week treatment period minus the baseline value • Change from baseline in morning (AM) peak expiratory flow (PEF) averaged over 24-week treatment period (time frame: baseline and weeks 1 to 24) (designated as safety issue: no). PEF is defined as maximum airflow during a forced expiration beginning with the lungs fully inflated. PEF will be measured by participants using a hand-held electronic peak flow meter each morning before the dose of study medication and any rescue albuterol/salbutamol inhalation aerosol use. The best of 3 measurements will be recorded. Change from baseline (defined from the last 7 days before randomisation of the participant) will be calculated as the value of the averaged daily AM PEF over the 24-week treatment period minus the baseline value • Percentage of participants controlled at the end of the 24-week treatment period (time frame: week 24) (designated as safety issue: no). Percentage of participants controlled will be defined using an Asthma Control Test (ACT) score ≥ 20 at the end of the 24-week treatment period. The ACT is a 5-item questionnaire developed as a measure of a participant's asthma control that can be quickly and easily completed in clinical practice. The questionnaire will be self completed by participants • Change from baseline in PM PEF averaged over 24-week treatment period (time frame: baseline and weeks 1 to 24) (designated as safety issue: no). PEF is defined as maximum airflow during a forced expiration beginning with the lungs fully inflated. PEF will be measured by participants using a hand-held electronic peak flow meter each evening before the dose of study medication and any rescue albuterol/salbutamol inhalation aerosol use. Change from baseline (defined as the last 7 days before randomisation of participants) will be calculated as the value of the averaged daily PM PEF over the 24-week treatment period minus the baseline value |

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| Starting date | March 2015 |
| Contact information | US GSK Clinical Trials Call Center |
| Notes | |

NCT02446418 2015

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| Trial name or title | A study to compare the efficacy of fluticasone furoate/vilanterol inhalation powder with usual inhaled corticosteroids (ICS)/long-acting beta-agonists (LABA) in persistent asthma |
| Methods | Multi-centre open-label randomised parallel-group study |
| Participants | <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Informed consent: capable of giving signed informed consent, which includes compliance with requirements and restrictions listed in the consent form and in this protocol • Gender and age: male or female participants ≥ 18 and ≤ 75 years of age at screening visit <p>Female participant is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin (hCG) test), is not lactating and at least one of the following conditions applies:</p> <ul style="list-style-type: none"> • Non-reproductive potential defined as pre-menopausal females with 1 of the following: documented tubal ligation; documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion; hysterectomy; documented bilateral oophorectomy. Postmenopausal defined as 12 months of spontaneous amenorrhoea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone (FSH) and oestradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)); females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrolment • Reproductive potential and agrees to follow 1 of the options listed below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) requirements from 30 days before the first dose of study medication and until week 24 <p>GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP</p> <p>This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle, or for participants who are and will continue to be abstinent from penile-vaginal intercourse on a long-term and persistent basis: contraceptive subdermal implant that meets standard operating procedure (SOP) effectiveness criteria, including a < 1% rate of failure per year, as stated in the product label; intrauterine device or intrauterine system that meets SOP effectiveness criteria, including a < 1% rate of failure per year, as stated in the product label; oral contraceptive, either combined or progestogen alone; injectable progestogen; contraceptive vaginal ring; percutaneous contraceptive patches; male partner sterilisation with documentation of azoospermia before entry of female participant into the study, and this male is the sole partner for that participant; male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository). These allowed methods of contraception are effective only when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception</p> <ul style="list-style-type: none"> • Types of participants: participants with documented physician's diagnosis of asthma ≥ 1 year, unsatisfactorily controlled asthma (ACT < 20 at screening and randomisation visit) treated by ICS alone and intended to be treated by ICS/LABA maintenance therapy; participant will be eligible for inclusion in |

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| | <p>this study only if affiliated with or a beneficiary of a Social Security category</p> <ul style="list-style-type: none"> • Current asthma therapy: All participants must be prescribed maintenance therapy and receiving ICS alone without LABA for ≥ 4 weeks before randomisation visit; other background asthma medication such as anti-leukotrienes or theophylline is permitted as an alternative to ICS alone, if initiated ≥ 4 weeks before screening visit • Participant questionnaires: Participants must be able to complete the questionnaires themselves <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • History of life-threatening asthma: defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within the last 6 months before screening and randomisation visit • Participants having a severe and unstable asthma, with ACT score < 15 at screening and randomisation visit, history of repeated severe exacerbations (3/y) and/or a severe exacerbation in the previous 6 weeks before screening and randomisation visit • Chronic obstructive pulmonary disease (COPD): respiratory disease: A participant must not have current evidence or diagnosis of chronic obstructive pulmonary disease at screening visit • Current or former cigarette smokers with a history of cigarette smoking ≥ 10 pack-years at screening (number of pack-years = (number of cigarettes per day/20) \times number of years smoked (e.g. 20 cigarettes per day for 10 years, 10 cigarettes per day for 20 years)) • Other diseases/abnormalities: participants with historical or current evidence of uncontrolled or clinically significant disease at screening and randomisation visit. Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the patient at risk through study participation or would affect the efficacy or safety analysis if the disease/condition was exacerbated during the study • Participants with a history of adverse reaction, including immediate or delayed hypersensitivity to any intranasal, inhaled or systemic corticosteroid and LABA therapy and to components of the inhalation powder (e.g. lactose, magnesium stearate) at screening and randomisation visit. In addition, participants with a history of severe milk protein allergy that, in the opinion of the Investigator, contraindicates the participant's participation • Investigational medications: A participant must not have used any investigational drug within 30 days before randomisation visit or within 5 half-lives ($t_{1/2}$) of the prior investigational study (whichever is longer of the 2) (if unsure, discuss with the medical monitor before screening) • Long-term user of systemic corticosteroids: participant who, in the opinion of the Investigator, is considered to be a long-term user of systemic corticosteroids for respiratory or other indications (if unsure, discuss with the medical monitor before screening) at screening visit • Participants treated by the monoclonal antibody omalizumab at screening visit. Treatment with omalizumab is not allowed during the study • Participants involved in other clinical trials at screening visit • Affiliation with investigator site: is an investigator, sub-investigator, study co-ordinator or employee of a participating investigator or study site, or immediate family member of the aforementioned who is involved in this study • Participants who plan to move away during the study from the geographical area where the study is being conducted |
| Interventions | <p>To evaluate the efficacy and safety of FF/VI compared with 2 usual ICS/LABA fixed combinations (FP/SAL or budesonide/formoterol (BUD/F)) in participants with persistent asthma, in "close to real life" settings. FF/VI will be administered once-daily (QD) via ELLIPTA dry powder inhaler (DPI), and FP/SAL or BUD/F will be administered twice-daily (BID) via DISKUS and TURBUHALER DPI, respectively. ELLIPTA is a new powder inhaler designed to be easy to use. The total duration of individual participation will be approximately 6 months (24 weeks)</p> |

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| Outcomes | <p>Primary outcome measures</p> <ul style="list-style-type: none"> Change from baseline in Asthma Control Test (ACT) total score at week 12 (time frame: baseline and week 12) (designated as safety issue: no). ACT is a validated self administered questionnaire utilising 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5). The total score is calculated as the sum of the scores from all 5 questions. By answering all 5 questions, a participant with asthma can obtain a score that may range between 5 and 25, with higher scores indicating better control. Change from baseline was calculated as total ACT score at week 12 minus total ACT score at baseline <p>Secondary outcome measures</p> <ul style="list-style-type: none"> Change from baseline in ACT score at week 24 (time frame: baseline and week 24) (designated as safety issue: no). ACT is a validated self administered questionnaire utilising 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5). The total score is calculated as the sum of the scores from all 5 questions. By answering all 5 questions, a participant with asthma can obtain a score that may range between 5 and 25, with higher scores indicating better control. Change from baseline was calculated as total ACT score at week 24 minus total ACT score at baseline Percentage of participants making at least 1 Type A error (likely to be critical) and overall errors at week 12 and at week 24 independent of use at week 12 (time frame: week 12 and week 24) (designated as safety issue: no). Participants will be asked to read the instruction leaflet of the assigned device and will be instructed by the investigator on the proper use of inhalers. Then, participant will be asked to self administer dose of assigned study drug. Any errors (critical or non-critical) made by the participant will be recorded by the healthcare professional (HCP). A critical error is defined as an error that may impact the ability of the drug to reach the lung and hence impact efficacy. Overall errors includes non-critical errors |
| Starting date | July 2015 |
| Contact information | US GSK Clinical Trials Call Center |
| Notes | |

NCT02730351 2016

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| Trial name or title | Crossover study comparing fluticasone furoate (FF)/vilanterol (VI) once-daily versus fluticasone propionate (FP) twice-daily in participants with asthma and exercise-induced bronchoconstriction (EIB) |
| Methods | Multi-centre randomised double-blind double-dummy cross-over study with two 2-week treatment periods separated by a 2-week washout period |
| Participants | <p>Participants with asthma and exercise-induced bronchoconstriction (EIB) between 12 and 50 years of age</p> <p>Inclusion criteria</p> <p>Participants eligible for enrolment in the study must meet the following criteria</p> <ul style="list-style-type: none"> Informed consent: Participants must give their signed and dated written informed consent to participate before commencing any study-related activities Age range: 12 to 50 years of age, inclusive, at visit 1 (screening) Diagnosis: diagnosis of asthma, as defined by the National Institutes of Health for ≥ 12 weeks before visit 1 Asthma severity: Participants must have a pre-bronchodilator $FEV_1 \geq 70\%$ of predicted normal value. Predicted values will be based upon Global Lung Function Initiative equations for spirometry reference values |

- Evidence of EIB: Participants must answer “Yes” to at least 2 of the following 3 questions reflecting on the previous 12 months: Are you short of breath during exercise or other physical exertion? Do you wheeze after exercise or other physical exertion? Do you cough after exercise or other physical exertion?
 - Concurrent antiasthma therapy: Participants must be taking low- to moderate-dose inhaled steroids for 12 weeks before visit 1 to participate, with no change in dose for the 4 weeks before visit 1
 - Gender: Participants may be male or an eligible female. A female is eligible to enter and participate in the study if she is of non-childbearing potential (i.e. physiologically incapable of becoming pregnant, including any female who is post-menopausal or surgically sterile). Surgically sterile females are defined as those with a documented hysterectomy and/or bilateral oophorectomy or tubal ligation. Post-menopausal females are defined as amenorrhoeic for longer than 1 year, with an appropriate clinical profile (e.g. age appropriate, > 45 years), in the absence of hormone replacement therapy
- OR
- Childbearing potential: has a negative pregnancy test at screening, and agrees to acceptable contraceptive methods approved in local country, when used consistently and correctly (i.e. in accordance with the approved product label and instructions of the physician for the duration of the study - screening to follow-up contact)
 - Albuterol/salbutamol use: All participants must be able to replace their current short-acting beta₂-agonist with albuterol/salbutamol, to be used only on an as-needed basis for the duration of the study. Each participant must be judged capable of withholding albuterol/salbutamol for ≥ 6 hours before performing spirometric evaluations
 - Physical capacity: Each participant must be physically able to perform exercise challenges on a treadmill when bronchodilators have been withheld

Exclusion criteria

Participants are not eligible for enrolment in the study if they meet the following criteria

- Intermittent asthma, seasonal asthma or exercise-induced bronchoconstriction only: Participants with only intermittent or seasonal asthma or only exercise-induced asthma are excluded from participation in this study
- History of life-threatening asthma: defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within the past 10 years
- Asthma exacerbation: any asthma exacerbation requiring oral corticosteroids within 12 weeks of visit 1, or that resulted in an overnight hospitalisation requiring additional treatment for asthma within 6 months before visit 1
- Symptomatic allergic rhinitis: Participants with symptomatic allergic rhinitis at visit 1 may be treated for up to 4 weeks with intranasal corticosteroids, followed by a repeat screening visit to determine eligibility before entry into the study. Participants who continue to be symptomatic after up to 4 weeks of treatment will be excluded
- 12-Lead electrocardiogram (ECG): A participant is not eligible if he/she has an abnormal, clinically significant ECG as determined by investigator at the screening visit.
- Pregnancy: women who are pregnant or lactating or are planning on becoming pregnant during the study
- Respiratory infection: culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear that is not resolved within 4 weeks of visit 1 and led to a change in asthma management or, in the opinion of the investigator, is expected to affect participant’s asthma status or ability of participant to participate in the study
- Concurrent respiratory disease: A participant must not have current evidence of atelectasis, bronchopulmonary dysplasia, chronic bronchitis, chronic obstructive pulmonary disease (COPD) (current or past diagnosis including asthma/COPD overlap), pneumonia, pneumothorax, interstitial lung disease or

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| | <p>any evidence of concurrent respiratory disease other than asthma</p> <ul style="list-style-type: none"> • Other concurrent diseases/abnormalities: A participant must not have any clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the patient at risk through study participation or would confound interpretation of efficacy results if the condition/disease was exacerbated during the study • Investigational medications: A participant must not have used any investigational drug within 30 days before visit 1 or within 5 half-lives ($t_{1/2}$) of the prior investigational study, whichever is longer of the 2 periods • Allergies: drug allergy: any adverse reaction including immediate or delayed hypersensitivity to any beta₂-agonist or sympathomimetic drug, or to any intranasal, inhaled or systemic corticosteroid therapy, or excipients used with FF/VI 100/25 or FP 250 (i.e. drug, lactose or magnesium stearate); milk protein allergy: history of severe milk protein allergy latex allergy: history of allergy or sensitivity to latex that, in the opinion of the investigator, contraindicates participation of the patient in the study • Concomitant medication: administration of prescription or non-prescription medication that would significantly affect the course of asthma, or interact with study drug • Immunosuppressive medication: A participant must not be using or require the use of immunosuppressive medications during the study • Compliance: A participant will not be eligible if he/she or his/her parent or legal guardian has an infirmity, disability, disease or geographical location that seems likely (in the opinion of the investigator) to impair compliance with any aspect of this study protocol • Tobacco/Marijuana use: current tobacco smoker or has a smoking history of ≥ 10 pack-years (20 cigarettes/d for 10 years). Participant may not have used inhaled tobacco products or inhaled marijuana within the past 3 months (e.g. cigarettes, cigars, electronic cigarettes, pipe tobacco) • Affiliation with investigator's site: Participant will not be eligible for this study if he/she is an immediate family member of the participating investigator, subinvestigator or study co-ordinator, or an employee of the participating investigator |
| Interventions | This study is designed to compare fluticasone furoate (FF)/vilanterol (VI) once-daily vs fluticasone propionate (FP) twice-daily in participants with asthma and exercise-induced bronchoconstriction (EIB) |
| Outcomes | <p>Primary outcome measures</p> <ul style="list-style-type: none"> • Maximal percent decrease from pre-exercise forced expiratory volume in 1 second (FEV₁) following exercise challenge at 12 hours post evening dose at the end of 2-week treatment period • Maximal percent decrease will be defined as percent change from pre-exercise FEV₁ to minimum FEV₁ collected within 1 hour following exercise challenge at 12 hours post dose <p>Secondary outcome measures</p> <ul style="list-style-type: none"> • Maximal percent decrease from pre-exercise FEV₁ following exercise challenge at 23 hours post evening dose at the end of 2-week treatment period • Maximal percent decrease will be defined as percent change from pre-exercise FEV₁ to minimum FEV₁ collected within 1 hour following exercise challenge at 23 hours post dose. Pre-exercise FEV₁ will be defined as FEV₁ value collected before the exercise challenge test at 23 hours post dose. Serial spirometry will be performed at time points 5, 10, 15, 30, 45 and 60 minutes post exercise challenges • Proportion of participants with a 30-minute post-challenge FEV₁ that was no more than 5% lower than their pre-exercise FEV₁ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of 2-week treatment period • Serial spirometry will be performed at time points 5, 10, 15, 30, 45 and 60 minutes post exercise challenges • Weighted mean for percent decrease from pre-exercise FEV₁ following exercise challenge at 12 hours and 23 hours post evening dose at the end of 2-week treatment period |

NCT02730351 2016 (Continued)

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| | <ul style="list-style-type: none"> Serial spirometry will be performed at time points 5, 10, 15, 30, 45 and 60 minutes post exercise challenges |
| Starting date | March 2016 |
| Contact information | GlaxoSmithKline |
| Notes | |

NCT02753712 2016

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| Trial name or title | A study to evaluate the effect of fluticasone/formoterol breath actuated inhaler (BAI) or Relvar Ellipta DPI on ventilation heterogeneity in asthma |
| Methods | A randomised assessor-blinded parallel-group trial |
| Participants | <p>Inclusion criteria for participants on Seretide Accuhaler 250/50 µg at screening</p> <ul style="list-style-type: none"> Male and female participants ≥ 18 years old Adequate contraception Documented clinical history of asthma for ≥ 6 months before screening visit Using Seretide Accuhaler at a stable dose of 250/50 µg twice-daily at screening for ≥ 8 weeks Uncontrolled asthma as defined by Asthma Control Questionnaire (ACQ-6) score ≥ 1.0 R5-R20 ≥ 0.10 kPa/L/s as measured on impulse oscillometry during screening visit Historical evidence (within 24 months) of eosinophilic airways disease evidenced by sputum eosinophil count ≥ 3% and/or FeNO 35 ppb <p>Inclusion criteria for participants on equivalent /higher dose or other ICS-LABAs or higher dose of Seretide at screening</p> <ul style="list-style-type: none"> Male and female participants ≥ 18 years old Adequate contraception Documented clinical history of asthma for ≥ 6 months before screening visit R5-R20 ≥ 0.07 kPa/L/s as measured on impulse oscillometry during screening visit 5. Historical evidence (within past 24 months) of eosinophilic airways disease, evidenced by sputum eosinophil count ≥ 3% and/or FeNo ≥ 35 ppb <p>Exclusion criteria for all participants</p> <ul style="list-style-type: none"> Any severe chronic respiratory disease other than asthma Participant has a smoking history ≥ 10 “pack-years” (i.e. ≥ 1 pack of 20 cigarettes/d for 10 years or 10 packs/d for 1 year, etc) <ul style="list-style-type: none"> Current smoking history within 12 months before screening visit Near fatal or life-threatening (including intubation) asthma within the past year Known history of systemic (injectable or oral) corticosteroid medication within 1 month of visit 1 Evidence of clinically unstable disease as determined by medical history or physical examination that, in the investigator’s opinion, precludes entry into the study. ‘Clinically unstable’ is defined as any disease that, in the opinion of the Investigator, would put the patient at risk through study participation, or would affect the outcome of the study <ul style="list-style-type: none"> In the investigator’s opinion, a clinically significant upper or lower respiratory infection within 4 weeks before visit 1 Current evidence or known history of alcohol and/or substance abuse within 12 months pbefore screening visit |

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| | <ul style="list-style-type: none"> Participant has taken β-blocking agents, tricyclic antidepressants, monoamine oxidase inhibitors, astemizole, quinidine type antiarrhythmics or potent CYP 3A4 inhibitors such as ketoconazole within 1 week before screening visit Current use of bronchodilators/anti-inflammatory agents other than those specified in the protocol Known or suspected sensitivity to study drug or excipients Participation in a clinical drug study within 30 days of screening visit Current participation in a clinical study <p>Exclusion criteria for participant or participants undergoing OR-MRI and HD-CT</p> <ul style="list-style-type: none"> Contraindication for MRI scanning (as assessed by local MRI safety questionnaire), which includes but is not limited to presence of non-MRI compatible artificial heart valves, hydrocephalus shunts, intracranial aneurysm clips, joint replacements or metal implants, pacemakers or other cardiac rhythm management devices, claustrophobia, history of metal in the eye, presence of shrapnel from a war injury, callipers or braces, dentures, dental plates or hearing aids that include metal and cannot be removed, history of epilepsy or blackouts, ear implants, piercings that cannot be removed, intrauterine contraceptive device or coil Inability to stay in the supine position for the duration of the scanning procedure Obesity (body weight > 140 kg) |
| Interventions | Comparison between fluticasone/formoterol BAI vs fluticasone/vilanterol DPI (Relvar Ellipta DPI) |
| Outcomes | <p>Primary outcome measures</p> <ul style="list-style-type: none"> Measurement of peripheral airway resistance (R5-R20) Measurement of peripheral airway resistance (R5-R20) <p>Secondary outcome measures</p> <ul style="list-style-type: none"> Ventilation heterogeneity (using functional respiratory imaging) Distal airway volume and resistance (using impulse oscillometry) Evaluation of asthma control (using ACQ-6) Evaluation of health status (using AQLQ) |
| Starting date | April 2016 |
| Contact information | Mundipharma Research Limited |
| Notes | |

New 2014 (NCT01551758)

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| Trial name or title | A randomised effectiveness study comparing fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) with standard treatment in chronic obstructive pulmonary disease (COPD) |
| Methods | This is a phase III multi-centre randomised open-label study |
| Participants | <p>Inclusion criteria</p> <p>Participants eligible for enrolment in the study must meet all of the following criteria</p> <ul style="list-style-type: none"> Types of participants: participants with documented GP diagnosis of COPD, and currently receiving maintenance therapy Informed consent: Participants must be able to provide informed consent, have their consent signed and dated. Participants must be able to complete the electronic participant questionnaires or allow a proxy to do so on their behalf |

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| | <ul style="list-style-type: none"> • Gender and age: male or female participants ≥ 40 years of age at visit 1. A female is eligible to enter and participate in the study if she is of non-childbearing potential (i.e. physiologically incapable of becoming pregnant, including any female who is post-menopausal or surgically sterile). Surgically sterile females are defined as those with a documented hysterectomy and/or bilateral oophorectomy or tubal ligation. Post-menopausal females are defined as amenorrhoeic for longer than 1 year with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms). However, in questionable cases, a blood sample with FSH > 40 MIU/mL and oestradiol < 40 pg/mL (< 140 pmol/L) is confirmatory. Or with childbearing potential has a negative urine pregnancy test at visit 2, and agrees to 1 of the highly effective and acceptable contraceptive methods used consistently and correctly (i.e. in accordance with the approved product label and instructions of the physician for the duration of the study - visit 2 to the end of the study) • Participants with exacerbation history • Current COPD maintenance therapy <p>Exclusion criteria</p> <p>Participants meeting any of the following criteria must not be enrolled in the study</p> <ul style="list-style-type: none"> • Participants with any life-threatening condition (e.g. low probability (in the opinion of the GP/ Investigator) of 12-month survival due to severity of COPD or co-morbid condition) at point of entry into the study • Other diseases/abnormalities: participants with historical or current evidence of uncontrolled or clinically significant disease. Significant is defined as any disease that, in the opinion of the GP/ Investigator, would put the safety of the patient at risk through participation or would affect the efficacy or safety analysis if the disease/condition was exacerbated during the study • Participants with unstable COPD, defined as the occurrence of the following in the 2 weeks before visit 2: acute worsening of COPD that is managed by the participant with corticosteroids or antibiotics or that requires treatment prescribed by a physician • Long-term user of oral corticosteroids: participants who, in the opinion of the GP/Investigator, are considered to be long-term users of oral corticosteroids for respiratory or other indications (if unsure, discuss with the medical monitor before screening) • Drug/food allergy: participants with a history of hypersensitivity to any of the study medications (e.g. beta-agonists, corticosteroids) or components of the inhalation powder (e.g. lactose, magnesium stearate). In addition, participants with a history of severe milk protein allergy that, in the opinion of the GP/ investigator, contraindicates the patient's participation • Investigational medications: A participant must not have used any investigational drug treatment within 30 days before visit 2 or within 5 half-lives ($t_{1/2}$) of the prior investigational study (whichever is the longer of the 2) • Participants who plan to move away during the study period from the geographical area where the study is being conducted and/or participants who have not consented to inclusion of their medical records in the electronic medical records database that is operational in the Salford area |
| Interventions | <p>This study is designed to compare the effectiveness and safety of FF/VI. Inhalation powder (100 mcg FF, GW685698)/25 mcg VI, GW642444) delivered once-daily via a novel dry powder inhaler (NDPI) compared with existing COPD maintenance therapy over 12 months in participants diagnosed with COPD. Participants who meet eligibility criteria are randomised and will enter a 12-month treatment period</p> |
| Outcomes | <p>Primary outcome measures</p> <ul style="list-style-type: none"> • Mean annual rate of moderate and severe exacerbations (time frame: 12 months) (designated as safety issue: no). A moderate exacerbation is defined by the participant receiving an exacerbation-related prescription of oral corticosteroids and/or antibiotic (with NHS contact) not requiring hospitalisation. A severe exacerbation is defined as an exacerbation-related hospitalisation <p>Secondary outcome measures</p> |

New 2014 (NCT01551758) (Continued)

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| | <ul style="list-style-type: none"> • Variety of healthcare utilisation endpoints (time frame: 12 months). (designated as safety issue: no). Healthcare utilisation • Serious adverse events and non-serious adverse drug reactions (time frame: 12 months). (designated as safety issue: no). Frequency and types of serious adverse events and non-serious adverse drug reactions • Patient-reported outcomes (time frame: 12 months). (designated as safety issue: no). Patient-reported outcomes |
| Starting date | January 2012 |
| Contact information | GlaxoSmithKline |
| Notes | |

Woodcock 2014 (NCT01706198)

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| Trial name or title | An effectiveness study comparing fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) with standard treatment in asthma |
| Methods | Multi-centre randomised open-label study |
| Participants | <p>Inclusion criteria</p> <p>Participants eligible for enrolment in the study must meet all of the following criteria</p> <ul style="list-style-type: none"> • Informed consent: Participants must be able to provide informed consent, have their consent signed and dated • Types of participants: participants with documented GP diagnosis of asthma as their primary respiratory disease • Current antiasthma therapy: All participants must be prescribed maintenance therapy and must be receiving ICS with or without LABA (fixed combination or via separate inhalers) and for at least 4 weeks before visit 2. Other background asthma medications such as anti-leukotrienes are permitted • All participants receiving ICS monotherapy or ICS/LABA combination (this can be a fixed-dose combination or an ICS alone or LABA alone in separate inhalers) must have had symptoms in the past week before visit 2. Symptoms are defined by daytime symptoms more than twice per week, use of a short-acting beta₂-agonist bronchodilator more than twice per week, any limitation of activities or any nocturnal symptoms/awakening (Symptoms are based on participant's recall and are consistent with the GINA and in principle with BTS/SIGN guidelines) • Participant questionnaires: Participants must be able to complete the electronic participant questionnaires as well as those questionnaires completed by phone or provide a proxy (e.g. partner/relative/friend who can do so on their behalf) • Gender and age: male or female participants \geq 18 years of age at visit 1. A female is eligible to enter and participate in the study if she is of: non-childbearing potential (i.e. physiologically incapable of becoming pregnant, including any female who is post-menopausal or surgically sterile). Surgically sterile females are defined as those with a documented hysterectomy and/or bilateral oophorectomy or tubal ligation. Post-menopausal females are defined as amenorrhoeic for longer than 1 year with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms). However, in questionable cases, a blood sample with FSH $>$ 40 MIU/mL and oestradiol $<$ 40 pg/mL ($<$ 147 pmol/L) is confirmatory <p>OR</p> <p>Childbearing potential with a negative urine pregnancy test at visit 2, and agrees to one of the highly effective and acceptable contraceptive methods used consistently and correctly (i.e. in accordance with the approved</p> |

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| | <p>product label and instructions of the physician for the duration of the study - visit 2 to the end of the study)</p> <p>Exclusion criteria</p> <p>Participants meeting any of the following criteria must not be enrolled in the study</p> <ul style="list-style-type: none"> ● Recent history of life-threatening asthma: defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within the past 6 months ● COPD: respiratory disease: Participant must not have current evidence or GP diagnosis of chronic obstructive pulmonary disease ● Other diseases/abnormalities: participants with historical or current evidence of uncontrolled or clinically significant disease. Significant is defined as any disease that, in the opinion of the GP/investigator, would put the safety of the patient at risk through study participation or would affect the efficacy or safety analysis if the disease/condition was exacerbated during the study ● Drug/food allergy: participants with a history of hypersensitivity to any of the study medications (e.g. beta₂-agonists, corticosteroid) or components of the inhalation powder (e.g. lactose, magnesium stearate). In addition, participants with a history of severe milk protein allergy that, in the opinion of the GP/ Investigator, contraindicates the patient's participation ● Investigational medications: Participant must not have used any investigational drug within 30 days before visit 2 or within 5 half-lives (t_{1/2}) of the prior investigational study (whichever is longer of the 2) (if unsure, discuss with the medical monitor before screening) ● Long-term user of systemic corticosteroids: participant who, in the opinion of the GP/investigator, is considered to be a long-term user of systemic corticosteroids for respiratory or other indications (if unsure, discuss with the medical monitor before screening) <ul style="list-style-type: none"> ● Participants who are using LABA without an ICS as asthma maintenance therapy ● Participants who plan to move away during the study period from the geographical area where the study is being conducted and/or participants who have not consented to inclusion of their medical records in the electronic medical records database that is operational in the Salford area |
| Interventions | <p>This study is designed to compare the effectiveness and safety of FF/VI inhalation powder ((100 mcg FF , GW685698)/25 mcg VI, GW642444) or 200 mcg FF, GW685698)/25 mcg VI, GW642444) delivered once-daily via a novel dry powder inhaler (NDPI) compared with the existing asthma maintenance therapy over 12 months in participants diagnosed with asthma. Participants who meet the eligibility criteria are randomised and will enter a 12-month treatment period</p> |
| Outcomes | <p>Primary outcome measures</p> <ul style="list-style-type: none"> ● Percentage of participants who have an ACT total score ≥ 20 at week 24 (6th month) assessment (time frame: week 24) (designated as safety issue: no) ● Percentage of participants who have an ACT total score ≥ 20 at week 24 (6th month) assessment <p>Secondary outcome measures</p> <ul style="list-style-type: none"> ● Percentage of participants with asthma control (ACT total score ≥ 20) (time frame: weeks 12, 40 and 52) (designated as safety issue: no). Percentage of participants with asthma control (ACT total score ≥ 20) ● Mean change from baseline in ACT total score (time frame: weeks 12, 24, 40 and 52) (designated as safety issue: no). Mean change from baseline in ACT total score ● Percentage of participants who have an increase from baseline ≥ 3 in ACT total score (time frame: weeks 12, 24, 40 and 52) (designated as safety issue: no). Percentage of participants who have an increase from baseline ≥ 3 in ACT total score ● Asthma-related secondary care contacts (time frame: 12 months) (designated as safety issue: no). Asthma-related secondary care contacts ● Asthma-related primary care contacts (time frame: 12 months) (designated as safety issue: no). Asthma-related primary care contacts |

Woodcock 2014 (NCT01706198) (Continued)

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| | <ul style="list-style-type: none"> • All secondary care contacts (time frame: 12 months) (designated as safety issue: no). All secondary care contacts • All primary care contacts (time frame: 12 months) (designated as safety issue: no). All primary care contacts • Mean annual rate of severe asthma exacerbations (time frame: 12 months) (designated as safety issue: no). Mean annual rate of severe asthma exacerbations • Number of salbutamol inhalers (adjusted to equivalence of 200 actuations) collected by participants from study-enrolled community pharmacies over the entire treatment period (time frame: 12 months) (designated as safety issue: no). Number of salbutamol inhalers (adjusted to equivalence of 200 actuations) collected by participants from study-enrolled community pharmacies over the entire treatment period • Time to discontinuation or modification of initial therapy (time frame: 12 months) (designated as safety issue: no). Time to discontinuation or modification of initial therapy • Percentage of participants who have an increase from baseline ≥ 0.5 in AQLQ(S) total score at week 52 (time frame: week 52) (designated as safety issue: no). Percentage of participants who have an increase from baseline ≥ 0.5 in AQLQ(S) total score at week 52 • Percentage of participants who have an increase from baseline ≥ 0.5 in AQLQ(S) environmental stimuli domain score at week 52 (time frame: week 52) (designated as safety issue: no). Percentage of participants who have an increase from baseline ≥ 0.5 in AQLQ(S) environmental stimuli domain score at week 52 |
| Starting date | November 2012 |
| Contact information | US GSK Clinical Trials Call Center |
| Notes | |

ACT: Asthma Control Test
 AE: adverse event
 AM: morning
 AQLQ: Asthma Quality of Life Questionnaire
 BTS: British Thoracic Society
 COPD: chronic obstructive pulmonary disease
 DPI: dry powder inhaler
 ECG: electrocardiogram
 FEV₁: forced expiratory volume in one second
 FF: fluticasone furoate
 FP: fluticasone propionate
 FRP: female reproductive potential
 FSH: follicle-stimulating hormone
 GINA: Global Initiative for Asthma
 GP: general practitioner
 HCP: healthcare practitioner
 HRT: hormone replacement therapy
 ICS: inhaled corticosteroid
 LABA: long-acting beta₂-agonist
 LAMA: long-acting muscarinic agonist
 LTRA: leukotriene receptor antagonist
 MAO: monoamine oxidase
 NHANES: National Health and Nutrition Examination Survey

OCS: oral corticosteroid
PEF: peak expiratory flow
PM: afternoon
SABA: short-acting beta₂-agonist
SAL: salmeterol
SIGN: Scottish Intercollegiate Guidelines Network
SOP: standard operating procedure

DATA AND ANALYSES

Comparison 1. FF/VI 100/25 versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|----------------|---------------------|---------------------------------|---------------------|
| 1 Change in quality of life (measured by AQLQ at 12 wk) | 1 | 329 | Mean Difference (Fixed, 95% CI) | 0.3 [0.14, 0.46] |
| 2 Exacerbations | 2 | 161 | Odds Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Serious adverse events | 5 | 721 | Odds Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4 FEV ₁ Litres | 1 | | Mean Difference (Fixed, 95% CI) | 0.17 [0.09, 0.26] |
| 5 PEFR AM L/min (change from baseline at 12 wk) | 1 | | Mean Difference (Fixed, 95% CI) | 33.3 [26.59, 40.01] |
| 6 PEFR PM L/min (change from baseline at 12 wk) | 1 | | Mean Difference (Fixed, 95% CI) | 28.2 [21.67, 34.73] |
| 7 Change in asthma symptoms (measured by ACT) | 1 | 339 | Mean Difference (Fixed, 95% CI) | 1.9 [1.22, 2.58] |

Comparison 2. FF/VI 100/25 versus same dose of FF

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|----------------|---------------------|---------------------------------|----------------------|
| 1 Change in quality of life (measured by AQLQ at 12 wk) | 1 | | Mean Difference (Fixed, 95% CI) | 0.15 [-0.00, 0.30] |
| 2 Exacerbations | 2 | 2425 | Odds Ratio (M-H, Fixed, 95% CI) | 1.38 [0.86, 2.22] |
| 3 Serious adverse events | 5 | 1258 | Odds Ratio (M-H, Fixed, 95% CI) | 1.61 [0.42, 6.17] |
| 4 Trough FEV ₁ (L) | 1 | | Mean Difference (Fixed, 95% CI) | 0.08 [0.02, 0.14] |
| 5 PEFR AM (change from baseline at 12 wk) | 2 | | Mean Difference (Fixed, 95% CI) | 20.29 [15.72, 24.85] |
| 6 PEFR PM (change from baseline at 12 wk) | 2 | | Mean Difference (Fixed, 95% CI) | 18.52 [14.03, 23.01] |
| 7 Change in asthma symptoms (measured by ACT) | 1 | | Mean Difference (Fixed, 95% CI) | 0.6 [-0.04, 1.24] |

Comparison 3. FF/VI 100/25 versus same dose VI

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---------------------------|----------------|---------------------|---------------------------------|----------------|
| 1 Serious adverse events | 1 | 53 | Odds Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |

Comparison 4. FF/VI 100/25 versus FP 500 µg

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---------------------------|----------------|---------------------|---------------------------------|-------------------|
| 1 Exacerbations | 1 | 301 | Odds Ratio (M-H, Fixed, 95% CI) | 0.49 [0.10, 2.47] |
| 2 Serious adverse events | 1 | 301 | Odds Ratio (M-H, Fixed, 95% CI) | 0.20 [0.05, 0.80] |

Comparison 5. FF/VI 100/25 versus FPS 250/50 bd

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|----------------|---------------------|---------------------------------|---------------------|
| 1 Change in quality of life (measured by AQLQ at 24 wk) | 1 | 677 | Mean Difference (Fixed, 95% CI) | 0.09 [-0.03, 0.21] |
| 2 Exacerbations | 1 | 806 | Odds Ratio (M-H, Fixed, 95% CI) | 0.50 [0.05, 5.52] |
| 3 Serious adverse events | 1 | 806 | Odds Ratio (M-H, Fixed, 95% CI) | 0.80 [0.21, 2.99] |
| 4 FEV ₁ | 1 | | Mean Difference (Fixed, 95% CI) | -0.02 [-0.07, 0.03] |
| 5 Change in asthma symptoms (measured by ACT) | 1 | | Mean Difference (Fixed, 95% CI) | 0.24 [-0.20, 0.68] |

Comparison 6. FF/VI 100/25 µg versus FF/VI 200/25 µg

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---------------------------|----------------|---------------------|---------------------------------|-------------------|
| 1 Exacerbations | 2 | 515 | Odds Ratio (M-H, Fixed, 95% CI) | 2.02 [0.50, 8.19] |
| 2 Serious adverse events | 2 | 515 | Odds Ratio (M-H, Fixed, 95% CI) | 0.33 [0.03, 3.18] |

Comparison 7. FF/VI 200/25 versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|----------------|---------------------|---------------------------------|-------------------|
| 1 Exacerbations | 1 | 114 | Odds Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Serious adverse events | 1 | 114 | Odds Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3 FEV ₁ Litres | 1 | | Mean Difference (Fixed, 95% CI) | 0.21 [0.13, 0.29] |
| 4 Change in asthma symptoms (measured by ACT) | 1 | | Mean Difference (Fixed, 95% CI) | 0.9 [0.12, 1.68] |

Comparison 8. FF/VI 200/25 µg versus FP 500 µg

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|----------------|---------------------|-------------------------------------|---------------------|
| 1 Change in quality of life (measured by AQLQ at 12 wk) | 2 | 606 | Mean Difference (Fixed, 95% CI) | 0.05 [-0.08, 0.17] |
| 2 Change in quality of life (measured by AQLQ at 24 wk) | 1 | | Mean Difference (Fixed, 95% CI) | 0.03 [-0.15, 0.21] |
| 3 OLD***Health-related quality of life | 2 | 606 | Mean Difference (IV, Fixed, 95% CI) | 0.04 [-0.08, 0.17] |
| 4 Exacerbations | 2 | 611 | Odds Ratio (M-H, Fixed, 95% CI) | 0.70 [0.22, 2.20] |
| 5 Serious adverse events | 3 | 1003 | Odds Ratio (M-H, Fixed, 95% CI) | 0.61 [0.25, 1.49] |
| 6 PEFR | 1 | | Mean Difference (Fixed, 95% CI) | 28.6 [20.23, 36.97] |
| 7 PEFR AM | 1 | | Mean Difference (Fixed, 95% CI) | 33.0 [24.84, 41.16] |
| 8 PEFR PM | 1 | | Mean Difference (Fixed, 95% CI) | 26.2 [18.04, 34.36] |
| 9 % symptom-free days | 1 | | Mean Difference (Fixed, 95% CI) | 4.8 [-2.84, 12.44] |
| 10 Change in asthma symptoms (measured by ACT) | 1 | 332 | Mean Difference (Fixed, 95% CI) | 0.8 [0.01, 1.59] |

Comparison 9. FF/VI 200/25 versus same dose of FF

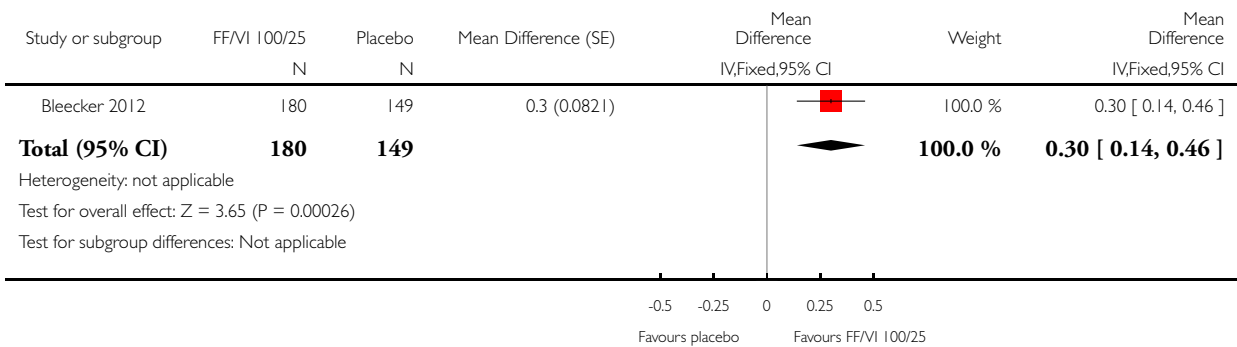
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|----------------|---------------------|---------------------------------|---------------------|
| 1 Change in quality of life (measured by AQLQ at 12 wk) | 1 | | Mean Difference (Fixed, 95% CI) | 0.08 [-0.08, 0.24] |
| 2 Change in quality of life (measured by AQLQ at 24 wk) | 1 | 307 | Mean Difference (Fixed, 95% CI) | 0.05 [-0.14, 0.24] |
| 3 Serious adverse events | 1 | 391 | Odds Ratio (M-H, Fixed, 95% CI) | 6.06 [0.72, 50.84] |
| 4 FEV ₁ Litres | 1 | | Mean Difference (Fixed, 95% CI) | 0.19 [0.10, 0.28] |
| 5 PEFR AM | 1 | | Mean Difference (Fixed, 95% CI) | 33.6 [25.41, 41.79] |
| 6 PEFR PM | 1 | | Mean Difference (Fixed, 95% CI) | 30.7 [22.51, 38.89] |
| 7 Change in asthma symptoms (measured by ACT) | 1 | 317 | Mean Difference (Fixed, 95% CI) | 0.3 [-0.50, 1.10] |

Analysis 1.1. Comparison 1 FF/VI 100/25 versus placebo, Outcome 1 Change in quality of life (measured by AQLQ at 12 wk).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 1 FF/VI 100/25 versus placebo

Outcome: 1 Change in quality of life (measured by AQLQ at 12 wk)

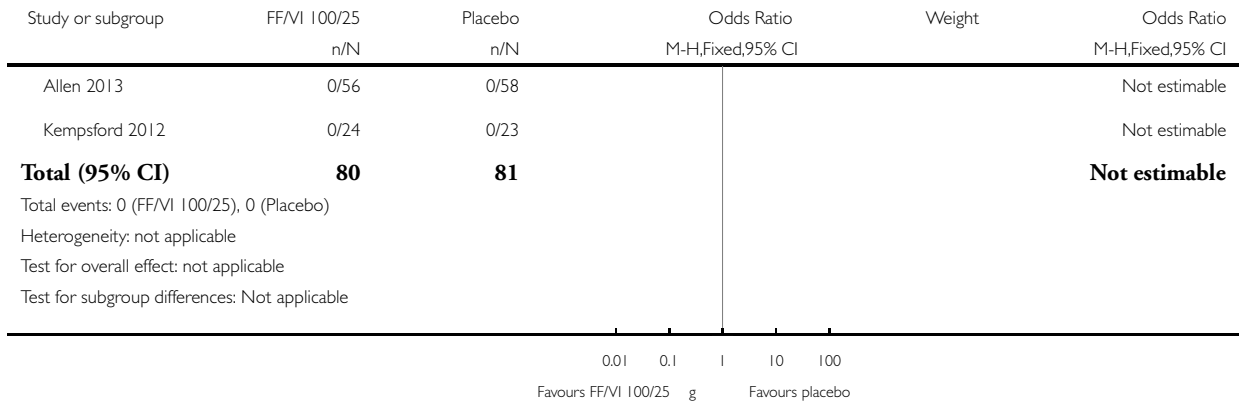


Analysis 1.2. Comparison 1 FF/VI 100/25 versus placebo, Outcome 2 Exacerbations.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 1 FF/VI 100/25 versus placebo

Outcome: 2 Exacerbations

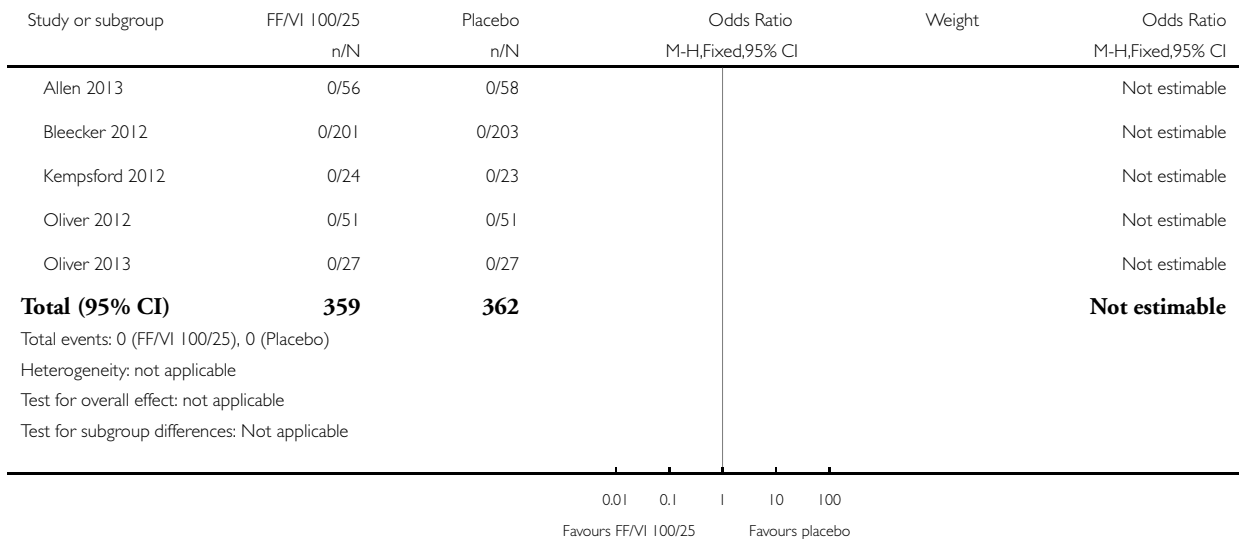


Analysis 1.3. Comparison 1 FF/VI 100/25 versus placebo, Outcome 3 Serious adverse events.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 1 FF/VI 100/25 versus placebo

Outcome: 3 Serious adverse events

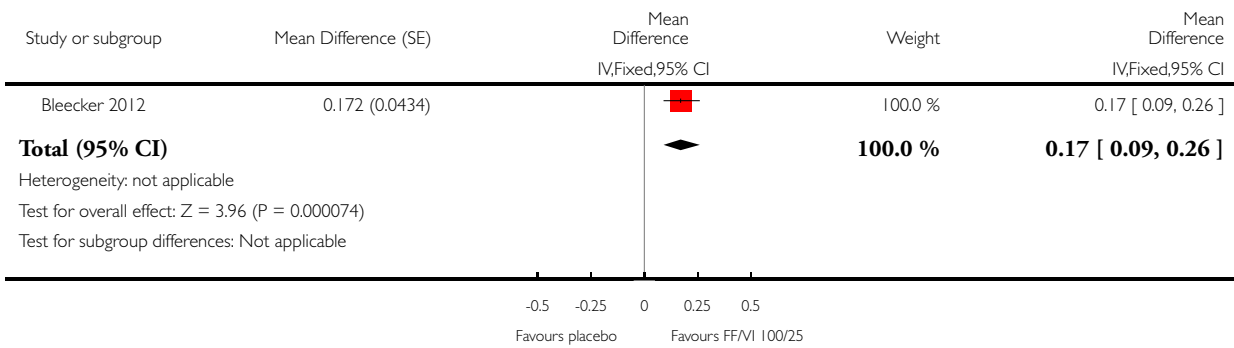


Analysis 1.4. Comparison 1 FF/VI 100/25 versus placebo, Outcome 4 FEV1 Litres.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 1 FF/VI 100/25 versus placebo

Outcome: 4 FEV₁ Litres

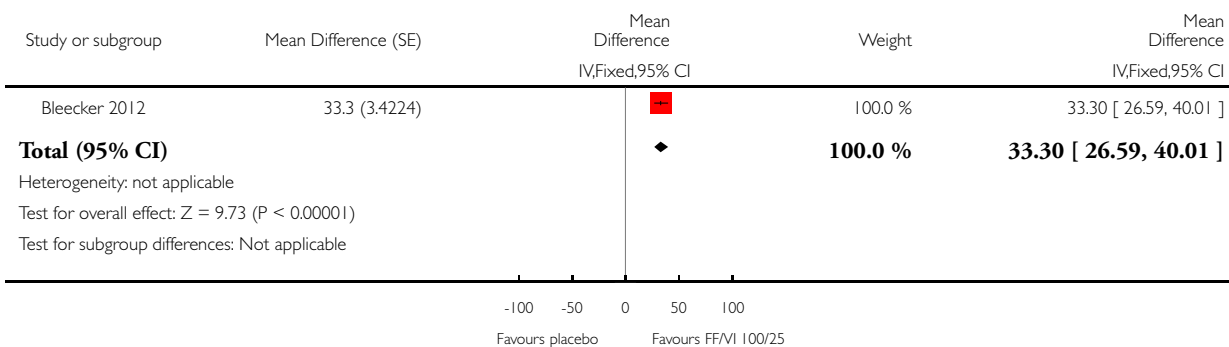


Analysis 1.5. Comparison 1 FF/VI 100/25 versus placebo, Outcome 5 PEFR AM L/min (change from baseline at 12 wk).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 1 FF/VI 100/25 versus placebo

Outcome: 5 PEFR AM L/min (change from baseline at 12 wk)

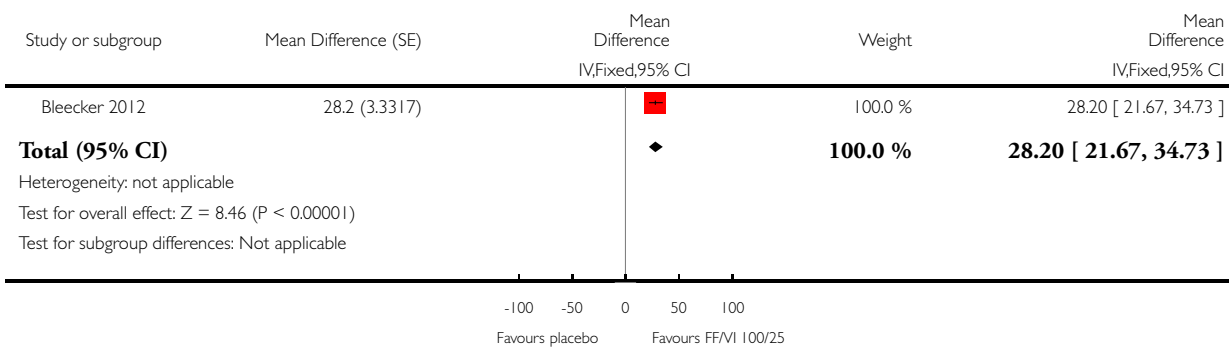


Analysis 1.6. Comparison 1 FF/VI 100/25 versus placebo, Outcome 6 PEFR PM L/min (change from baseline at 12 wk).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 1 FF/VI 100/25 versus placebo

Outcome: 6 PEFR PM L/min (change from baseline at 12 wk)

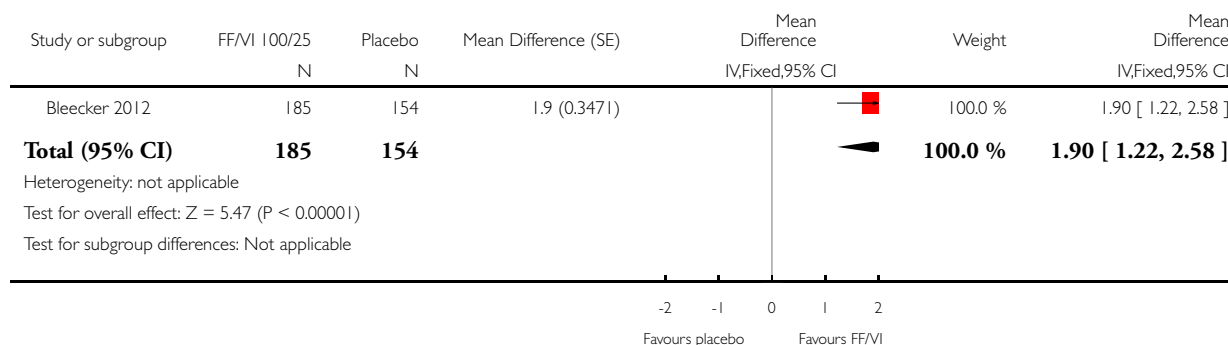


Analysis 1.7. Comparison 1 FF/VI 100/25 versus placebo, Outcome 7 Change in asthma symptoms (measured by ACT).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 1 FF/VI 100/25 versus placebo

Outcome: 7 Change in asthma symptoms (measured by ACT)

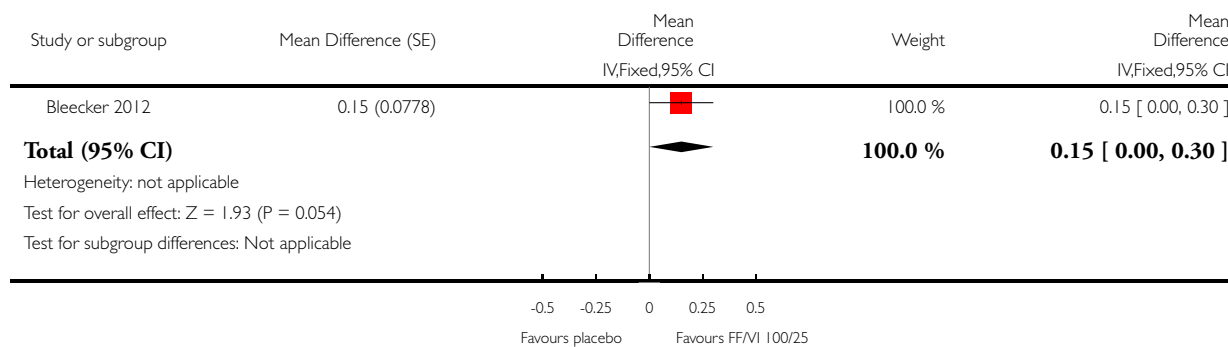


Analysis 2.1. Comparison 2 FF/VI 100/25 versus same dose of FF, Outcome 1 Change in quality of life (measured by AQLQ at 12 wk).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 2 FF/VI 100/25 versus same dose of FF

Outcome: 1 Change in quality of life (measured by AQLQ at 12 wk)

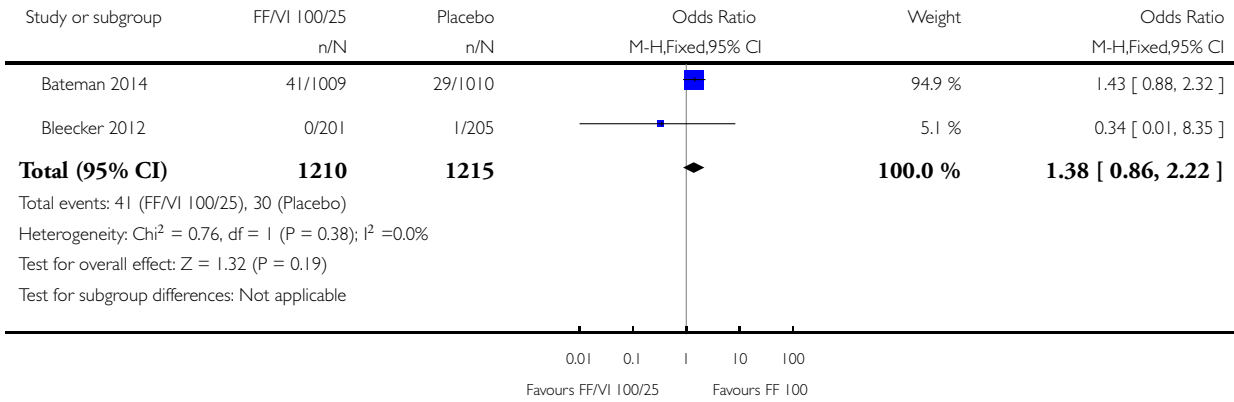


Analysis 2.2. Comparison 2 FF/VI 100/25 versus same dose of FF, Outcome 2 Exacerbations.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 2 FF/VI 100/25 versus same dose of FF

Outcome: 2 Exacerbations

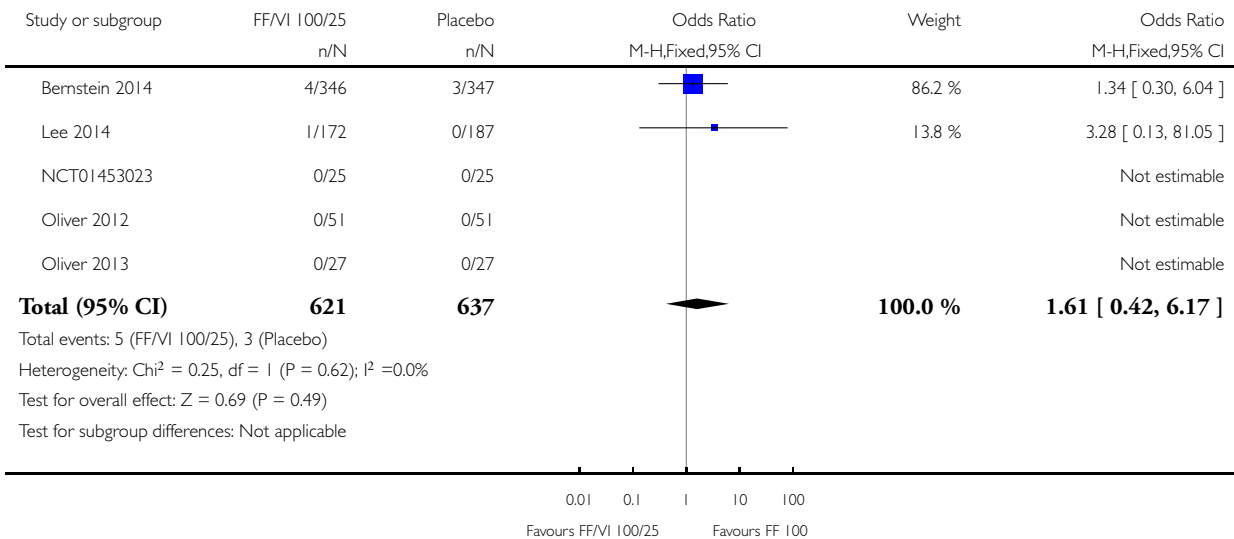


Analysis 2.3. Comparison 2 FF/VI 100/25 versus same dose of FF, Outcome 3 Serious adverse events.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 2 FF/VI 100/25 versus same dose of FF

Outcome: 3 Serious adverse events

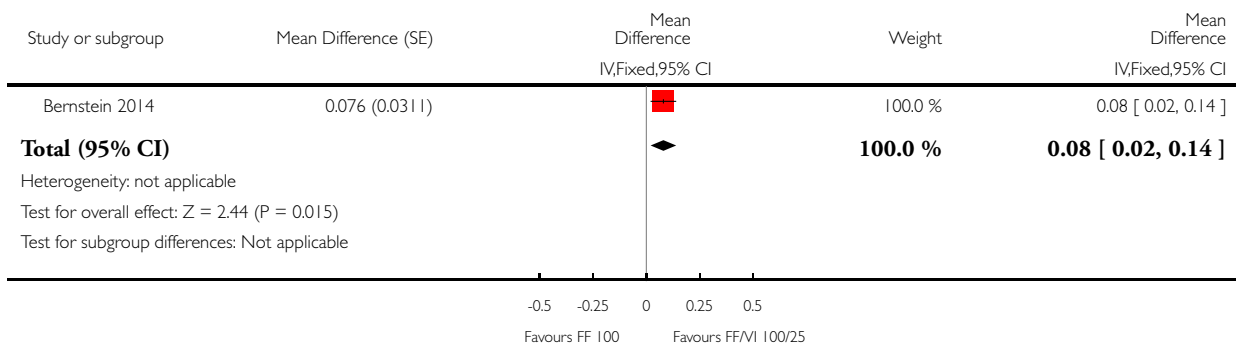


Analysis 2.4. Comparison 2 FF/VI 100/25 versus same dose of FF, Outcome 4 Trough FEV₁ (L).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 2 FF/VI 100/25 versus same dose of FF

Outcome: 4 Trough FEV₁ (L)

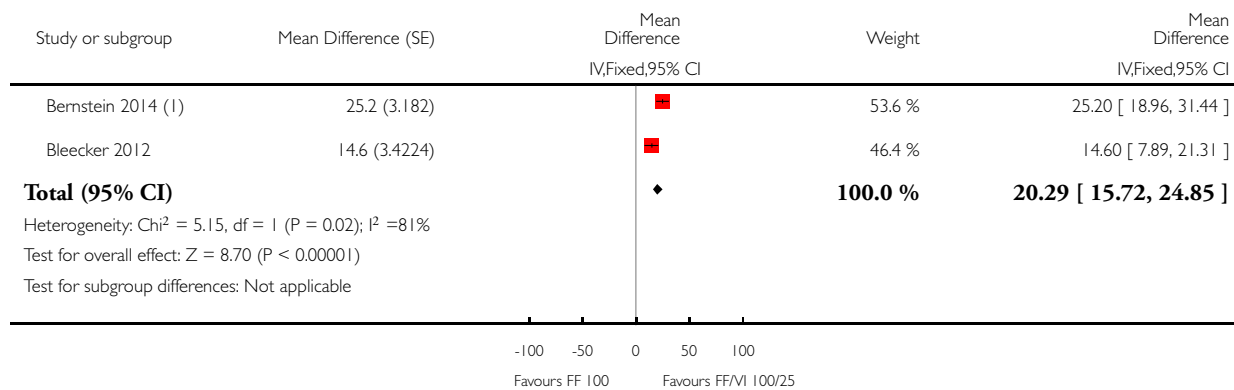


Analysis 2.5. Comparison 2 FF/VI 100/25 versus same dose of FF, Outcome 5 PEFR AM (change from baseline at 12 wk).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 2 FF/VI 100/25 versus same dose of FF

Outcome: 5 PEFR AM (change from baseline at 12 wk)



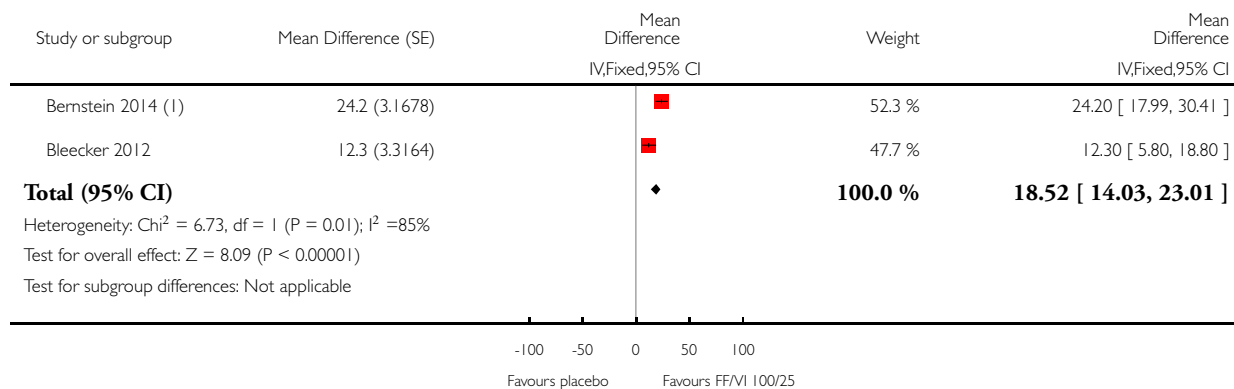
(1) Change from baseline averaged over 12 weeks

Analysis 2.6. Comparison 2 FF/VI 100/25 versus same dose of FF, Outcome 6 PEFR PM (change from baseline at 12 wk).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 2 FF/VI 100/25 versus same dose of FF

Outcome: 6 PEFR PM (change from baseline at 12 wk)



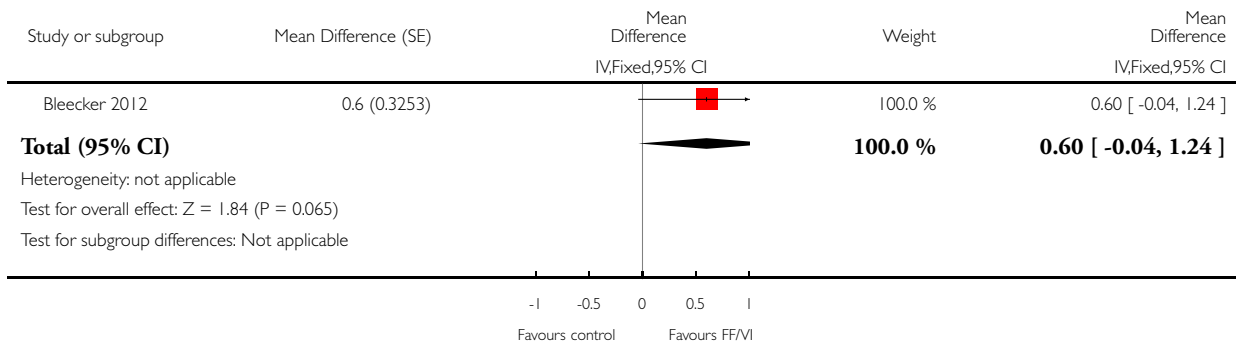
(I) Change from baseline averaged over 12 weeks

Analysis 2.7. Comparison 2 FF/VI 100/25 versus same dose of FF, Outcome 7 Change in asthma symptoms (measured by ACT).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 2 FF/VI 100/25 versus same dose of FF

Outcome: 7 Change in asthma symptoms (measured by ACT)

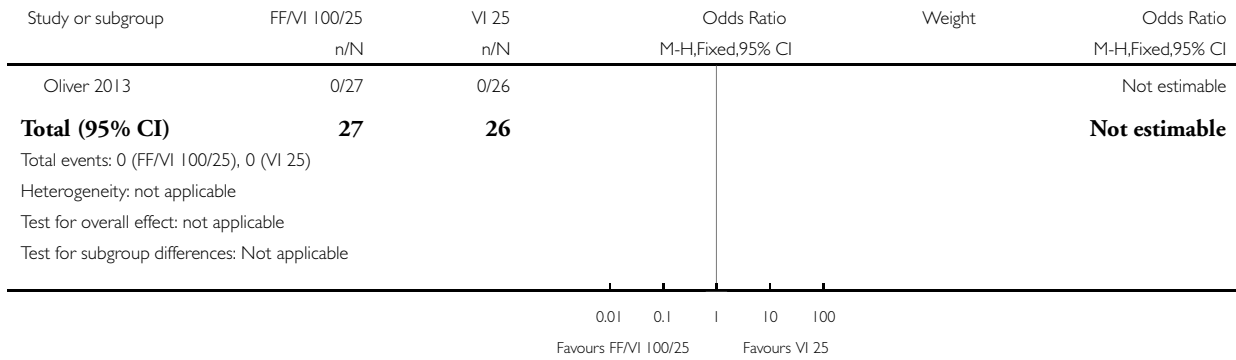


Analysis 3.1. Comparison 3 FF/VI 100/25 versus same dose VI, Outcome 1 Serious adverse events.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 3 FF/VI 100/25 versus same dose VI

Outcome: 1 Serious adverse events

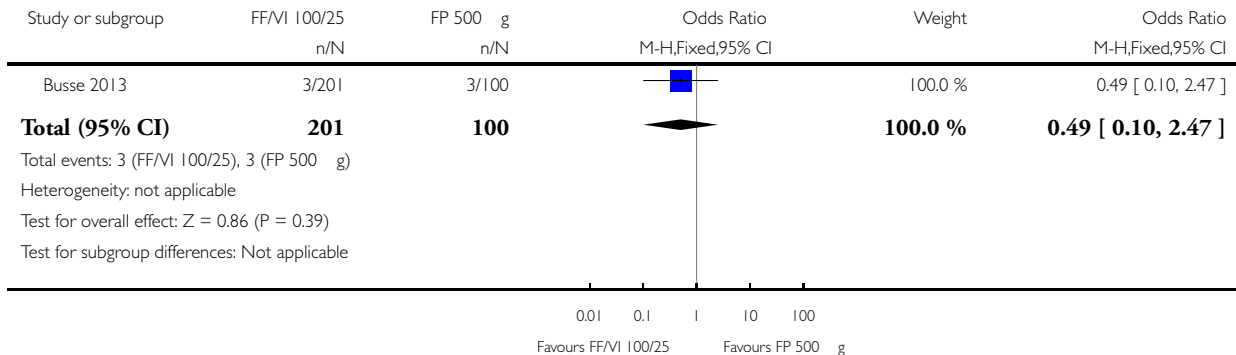


Analysis 4.1. Comparison 4 FF/VI 100/25 versus FP 500 µg, Outcome 1 Exacerbations.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 4 FF/VI 100/25 versus FP 500 µg

Outcome: 1 Exacerbations

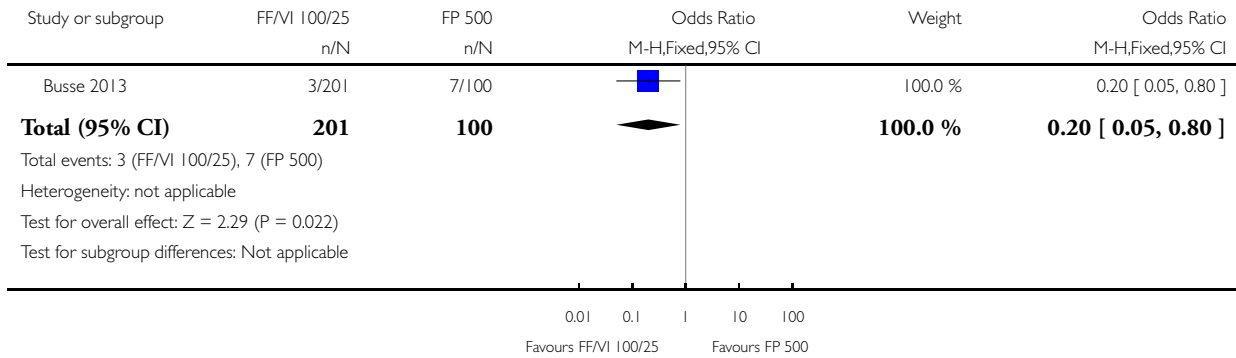


Analysis 4.2. Comparison 4 FF/VI 100/25 versus FP 500 µg, Outcome 2 Serious adverse events.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 4 FF/VI 100/25 versus FP 500 µg

Outcome: 2 Serious adverse events

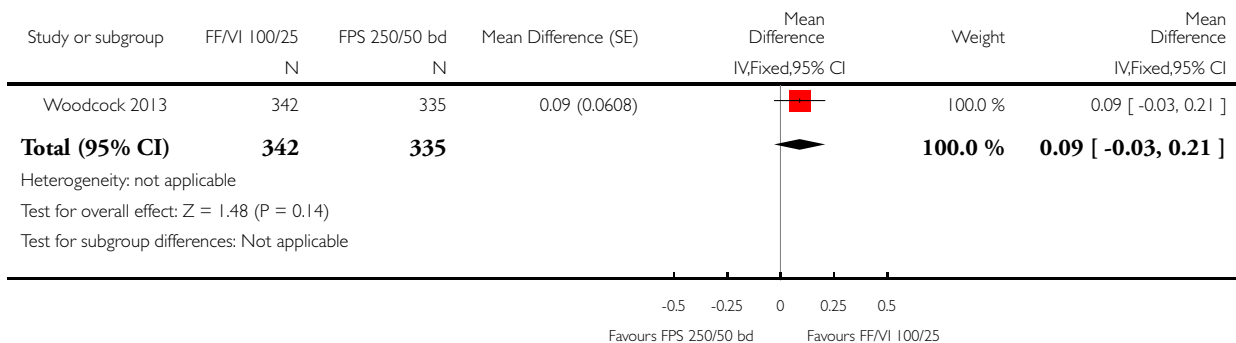


Analysis 5.1. Comparison 5 FF/VI 100/25 versus FPS 250/50 bd, Outcome 1 Change in quality of life (measured by AQLQ at 24 wk).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 5 FF/VI 100/25 versus FPS 250/50 bd

Outcome: 1 Change in quality of life (measured by AQLQ at 24 wk)

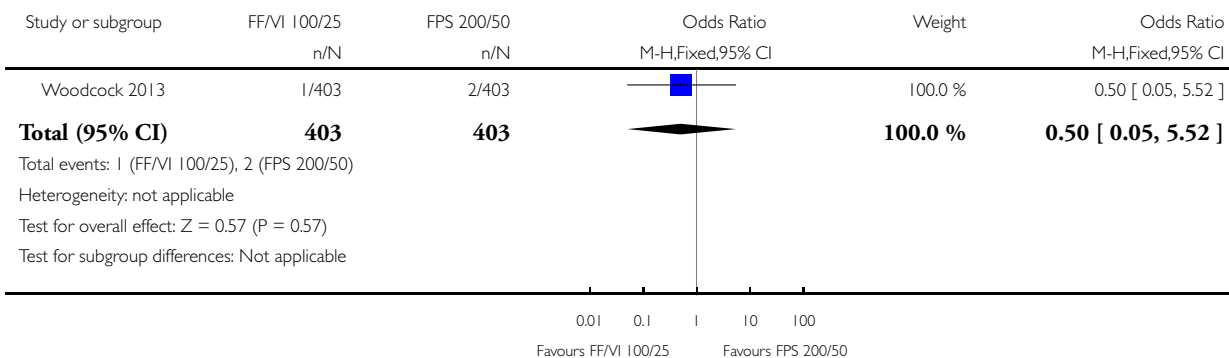


Analysis 5.2. Comparison 5 FF/VI 100/25 versus FPS 250/50 bd, Outcome 2 Exacerbations.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 5 FF/VI 100/25 versus FPS 250/50 bd

Outcome: 2 Exacerbations

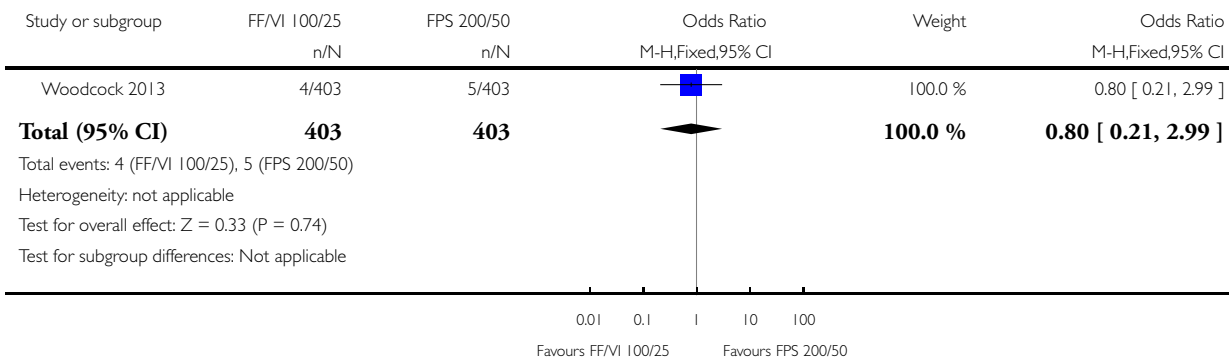


Analysis 5.3. Comparison 5 FF/VI 100/25 versus FPS 250/50 bd, Outcome 3 Serious adverse events.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 5 FF/VI 100/25 versus FPS 250/50 bd

Outcome: 3 Serious adverse events

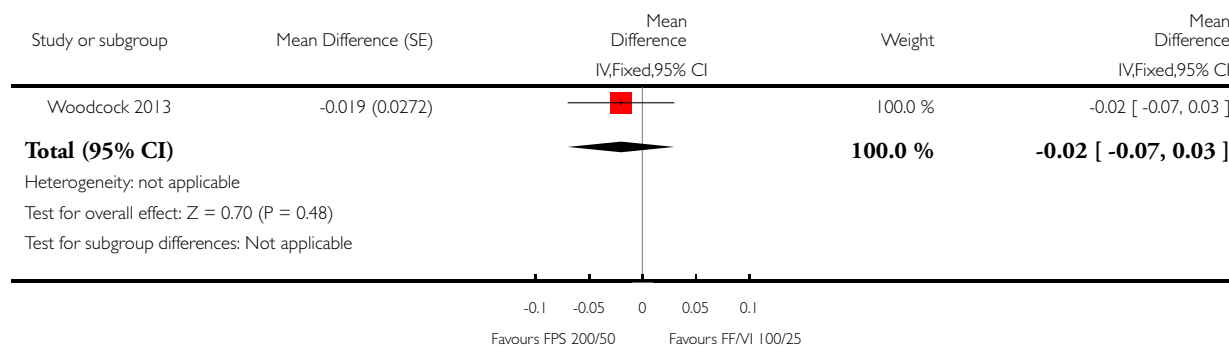


Analysis 5.4. Comparison 5 FF/VI 100/25 versus FPS 250/50 bd, Outcome 4 FEV₁.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 5 FF/VI 100/25 versus FPS 250/50 bd

Outcome: 4 FEV₁

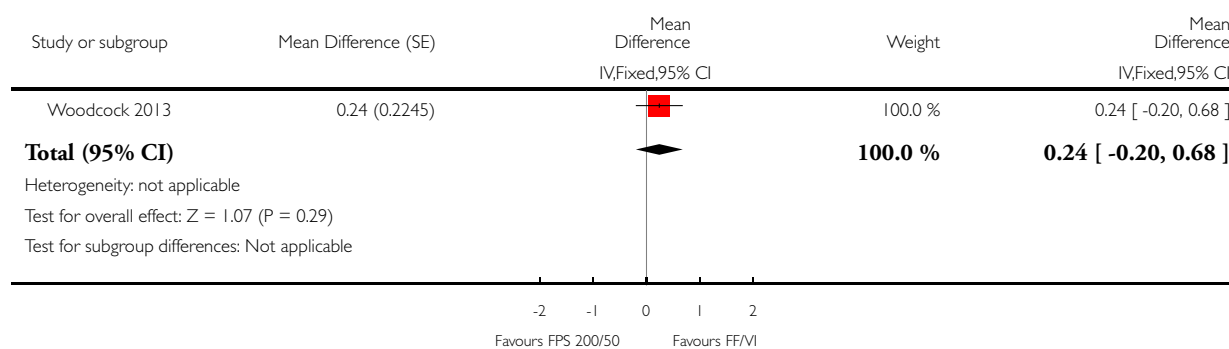


Analysis 5.5. Comparison 5 FF/VI 100/25 versus FPS 250/50 bd, Outcome 5 Change in asthma symptoms (measured by ACT).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 5 FF/VI 100/25 versus FPS 250/50 bd

Outcome: 5 Change in asthma symptoms (measured by ACT)

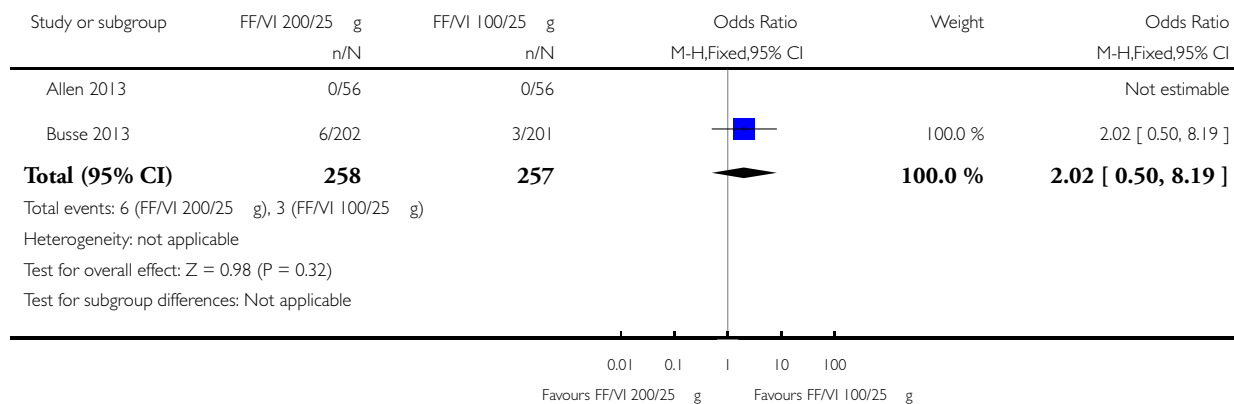


Analysis 6.1. Comparison 6 FF/VI 100/25 µg versus FF/VI 200/25 µg, Outcome 1 Exacerbations.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 6 FF/VI 100/25 g versus FF/VI 200/25 g

Outcome: 1 Exacerbations

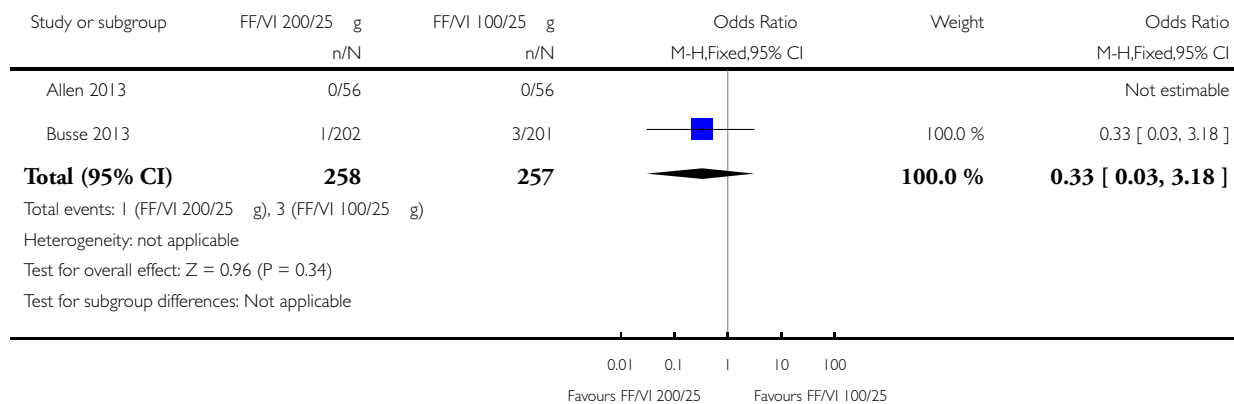


Analysis 6.2. Comparison 6 FF/VI 100/25 µg versus FF/VI 200/25 µg, Outcome 2 Serious adverse events.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 6 FF/VI 100/25 g versus FF/VI 200/25 g

Outcome: 2 Serious adverse events

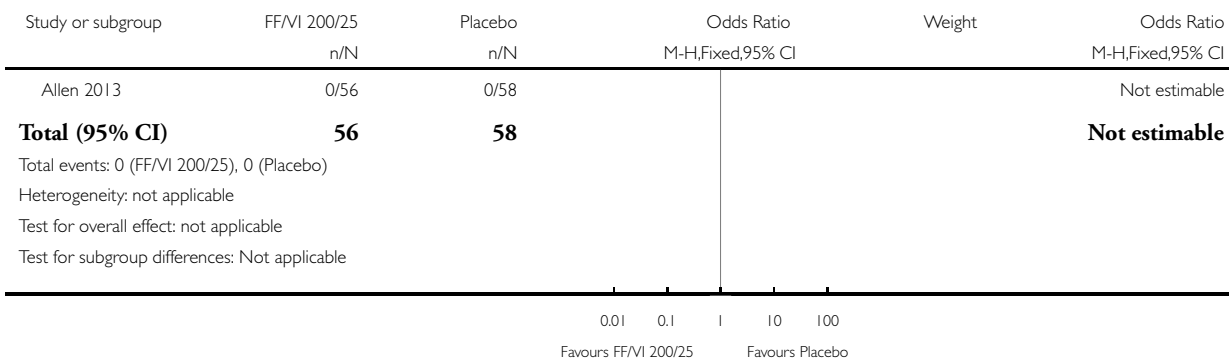


Analysis 7.1. Comparison 7 FF/VI 200/25 versus placebo, Outcome 1 Exacerbations.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 7 FF/VI 200/25 versus placebo

Outcome: 1 Exacerbations

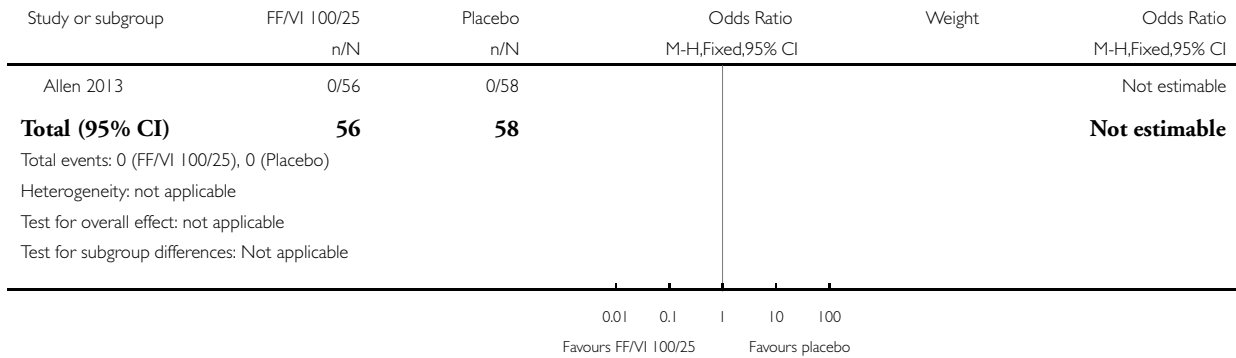


Analysis 7.2. Comparison 7 FF/VI 200/25 versus placebo, Outcome 2 Serious adverse events.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 7 FF/VI 200/25 versus placebo

Outcome: 2 Serious adverse events

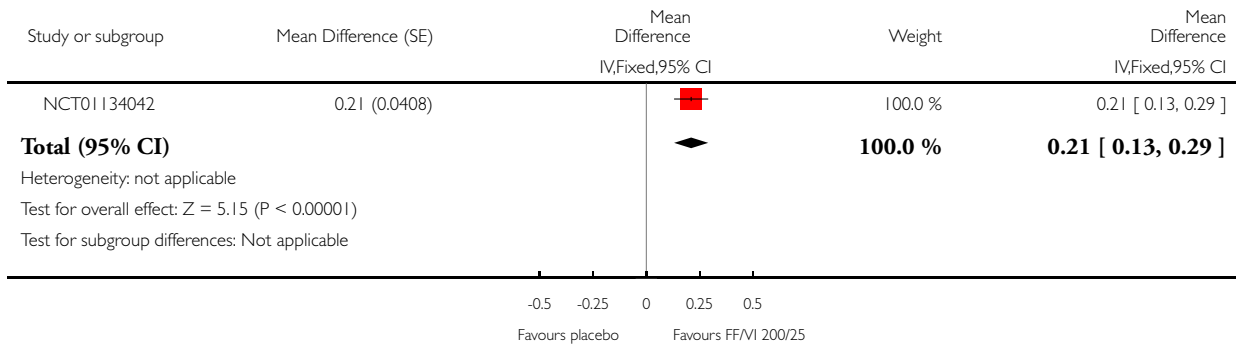


Analysis 7.3. Comparison 7 FF/VI 200/25 versus placebo, Outcome 3 FEV₁ Litres.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 7 FF/VI 200/25 versus placebo

Outcome: 3 FEV₁ Litres

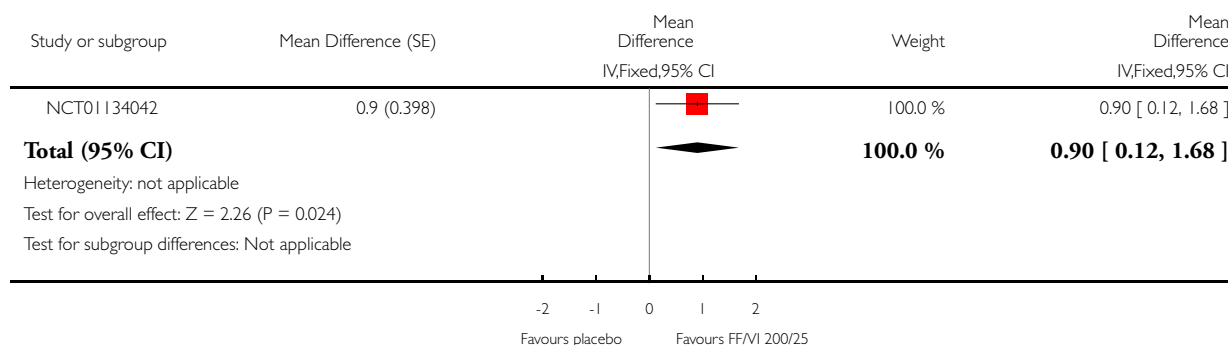


Analysis 7.4. Comparison 7 FF/VI 200/25 versus placebo, Outcome 4 Change in asthma symptoms (measured by ACT).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 7 FF/VI 200/25 versus placebo

Outcome: 4 Change in asthma symptoms (measured by ACT)

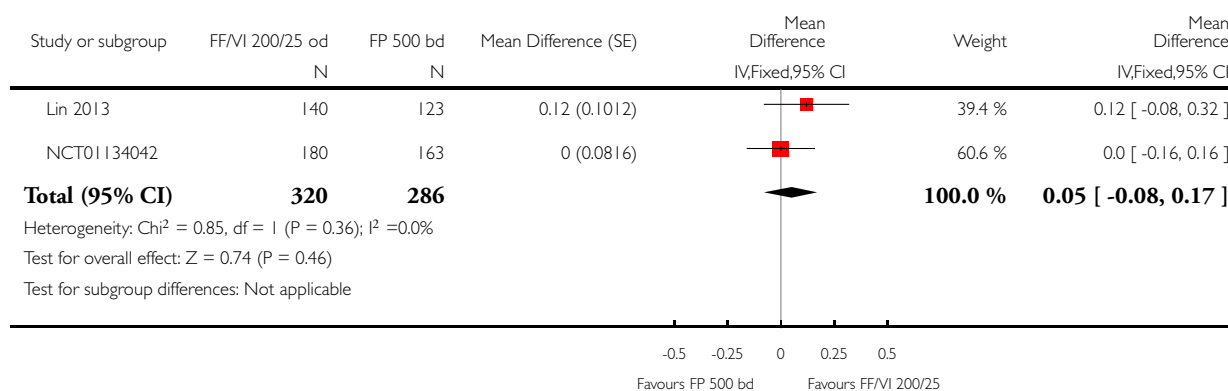


Analysis 8.1. Comparison 8 FF/VI 200/25 µg versus FP 500 µg, Outcome 1 Change in quality of life (measured by AQLQ at 12 wk).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 8 FF/VI 200/25 g versus FP 500 g

Outcome: 1 Change in quality of life (measured by AQLQ at 12 wk)

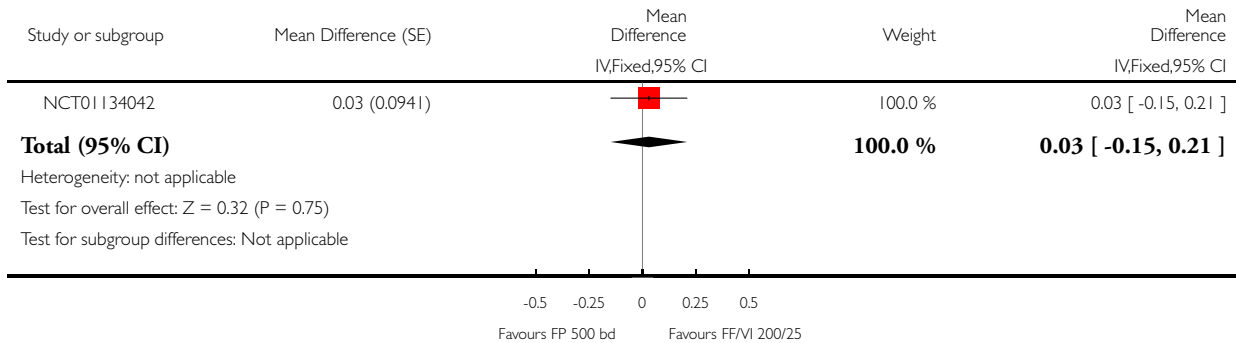


Analysis 8.2. Comparison 8 FF/VI 200/25 µg versus FP 500 µg, Outcome 2 Change in quality of life (measured by AQLQ at 24 wk).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 8 FF/VI 200/25 g versus FP 500 g

Outcome: 2 Change in quality of life (measured by AQLQ at 24 wk)

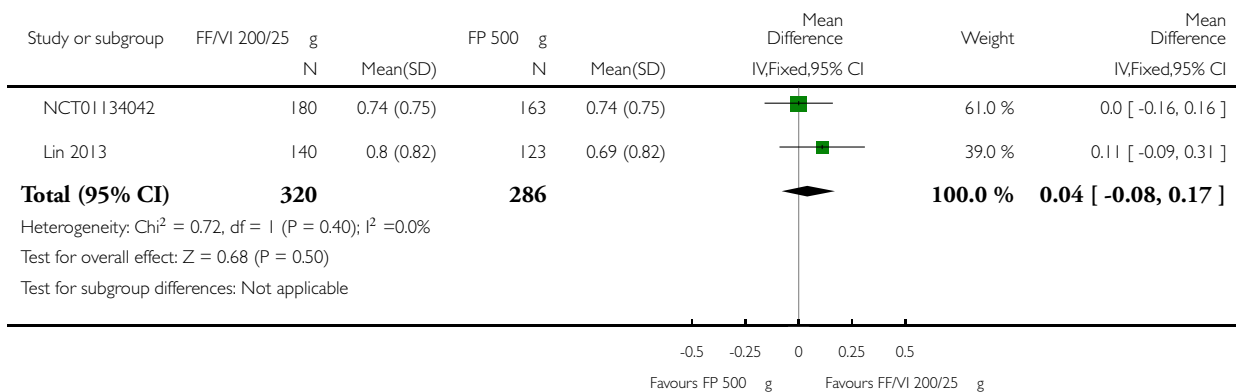


Analysis 8.3. Comparison 8 FF/VI 200/25 µg versus FP 500 µg, Outcome 3 OLD*Health-related quality of life.**

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 8 FF/VI 200/25 g versus FP 500 g

Outcome: 3 OLD***Health-related quality of life

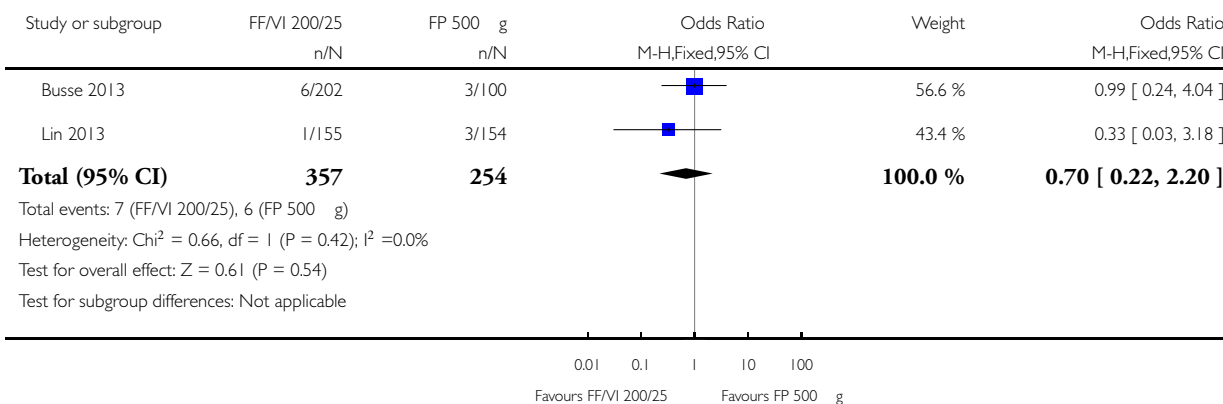


Analysis 8.4. Comparison 8 FF/VI 200/25 µg versus FP 500 µg, Outcome 4 Exacerbations.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 8 FF/VI 200/25 µg versus FP 500 µg

Outcome: 4 Exacerbations

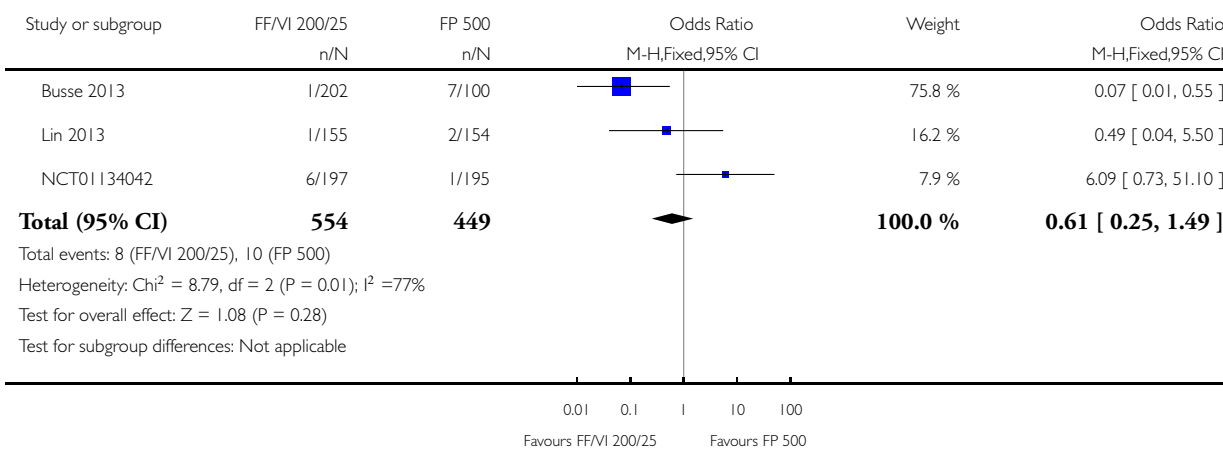


Analysis 8.5. Comparison 8 FF/VI 200/25 µg versus FP 500 µg, Outcome 5 Serious adverse events.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 8 FF/VI 200/25 µg versus FP 500 µg

Outcome: 5 Serious adverse events

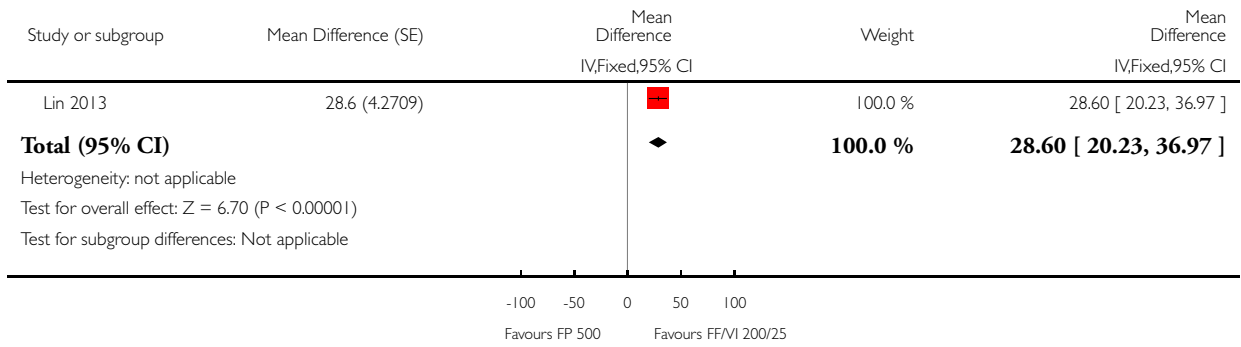


Analysis 8.6. Comparison 8 FF/VI 200/25 µg versus FP 500 µg, Outcome 6 PEFR.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 8 FF/VI 200/25 g versus FP 500 g

Outcome: 6 PEFR

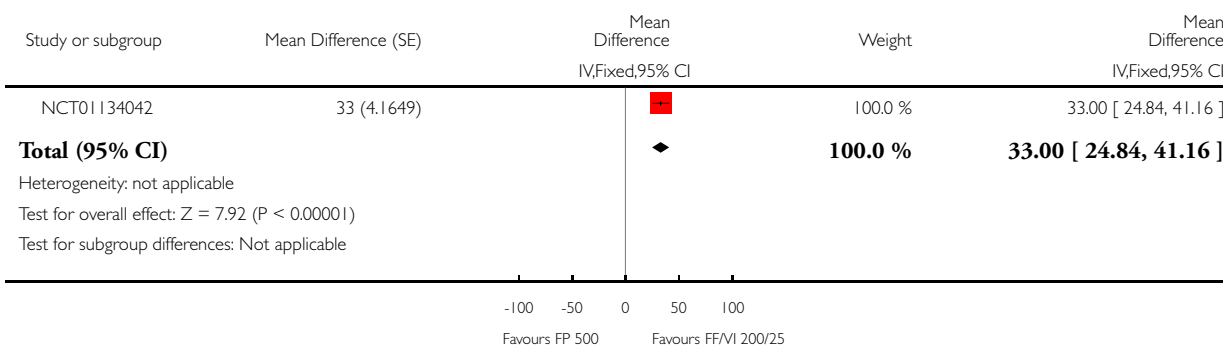


Analysis 8.7. Comparison 8 FF/VI 200/25 µg versus FP 500 µg, Outcome 7 PEFR AM.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 8 FF/VI 200/25 g versus FP 500 g

Outcome: 7 PEFR AM

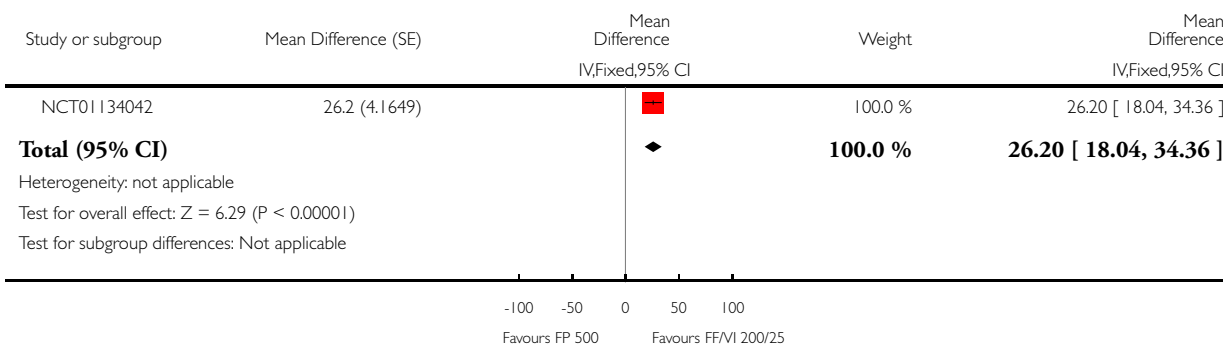


Analysis 8.8. Comparison 8 FF/VI 200/25 µg versus FP 500 µg, Outcome 8 PEFR PM.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 8 FF/VI 200/25 g versus FP 500 g

Outcome: 8 PEFR PM

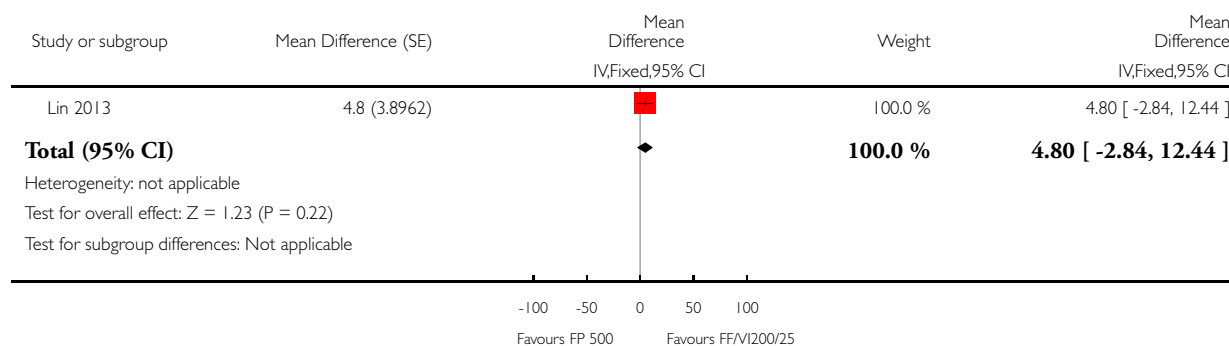


Analysis 8.9. Comparison 8 FF/VI 200/25 µg versus FP 500 µg, Outcome 9 % symptom-free days.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 8 FF/VI 200/25 g versus FP 500 g

Outcome: 9 % symptom-free days

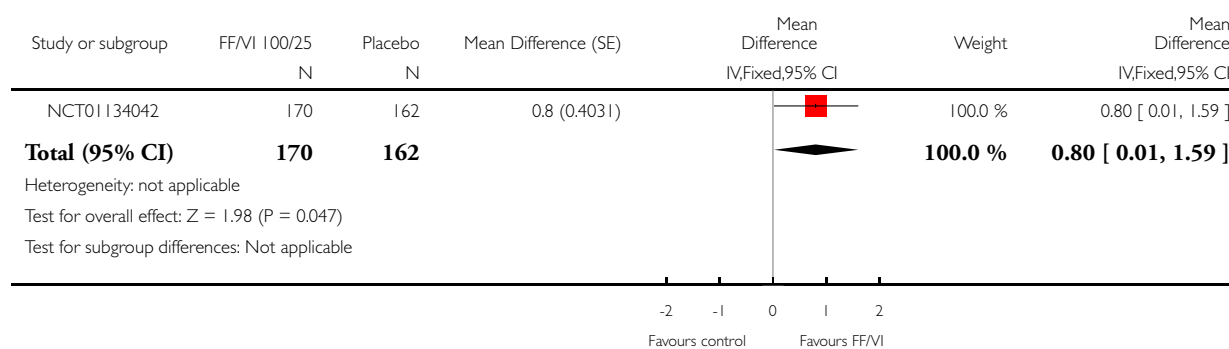


Analysis 8.10. Comparison 8 FF/VI 200/25 µg versus FP 500 µg, Outcome 10 Change in asthma symptoms (measured by ACT).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 8 FF/VI 200/25 g versus FP 500 g

Outcome: 10 Change in asthma symptoms (measured by ACT)

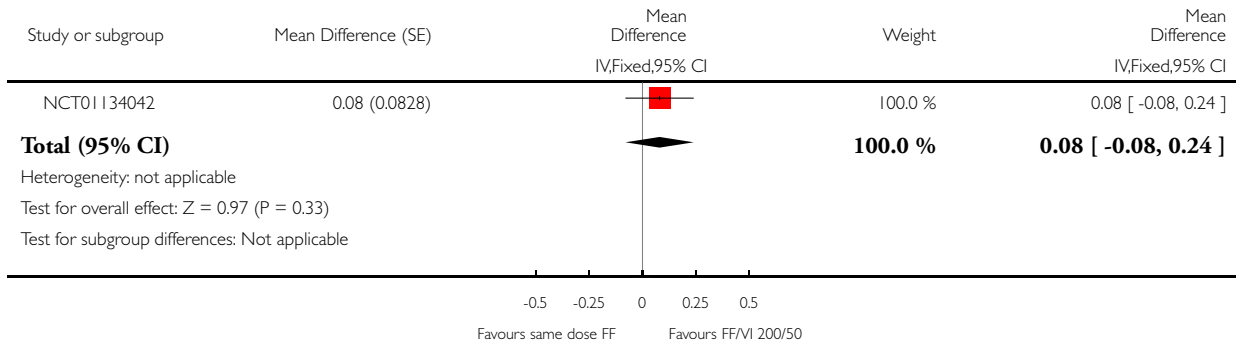


Analysis 9.1. Comparison 9 FF/VI 200/25 versus same dose of FF, Outcome 1 Change in quality of life (measured by AQLQ at 12 wk).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 9 FF/VI 200/25 versus same dose of FF

Outcome: 1 Change in quality of life (measured by AQLQ at 12 wk)

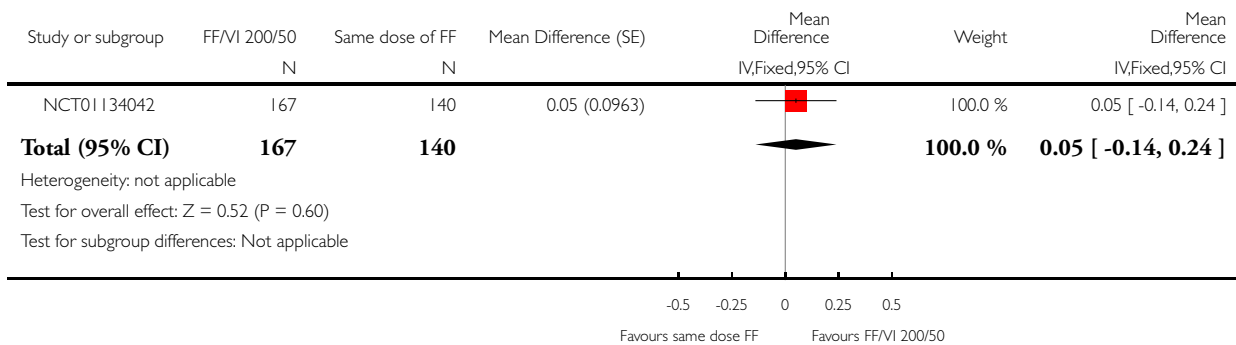


Analysis 9.2. Comparison 9 FF/VI 200/25 versus same dose of FF, Outcome 2 Change in quality of life (measured by AQLQ at 24 wk).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 9 FF/VI 200/25 versus same dose of FF

Outcome: 2 Change in quality of life (measured by AQLQ at 24 wk)

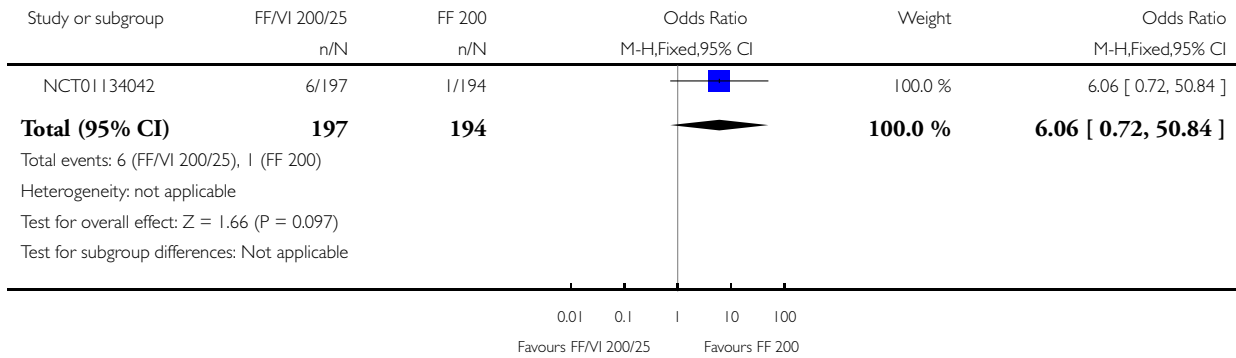


Analysis 9.3. Comparison 9 FF/VI 200/25 versus same dose of FF, Outcome 3 Serious adverse events.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 9 FF/VI 200/25 versus same dose of FF

Outcome: 3 Serious adverse events

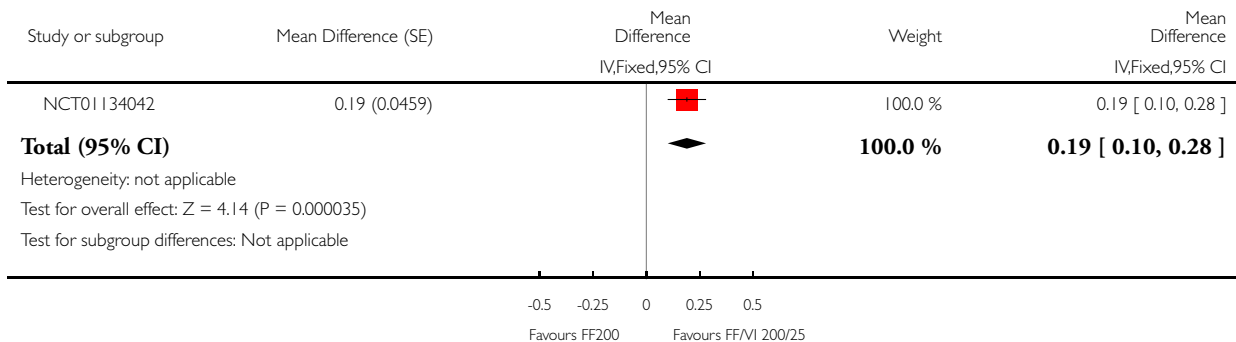


Analysis 9.4. Comparison 9 FF/VI 200/25 versus same dose of FF, Outcome 4 FEV₁ Litres.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 9 FF/VI 200/25 versus same dose of FF

Outcome: 4 FEV₁ Litres

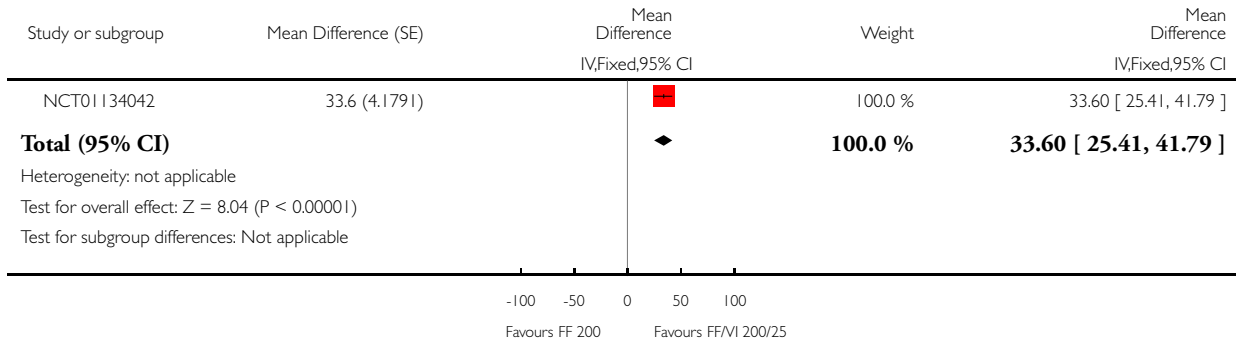


Analysis 9.5. Comparison 9 FF/VI 200/25 versus same dose of FF, Outcome 5 PEFR AM.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 9 FF/VI 200/25 versus same dose of FF

Outcome: 5 PEFR AM

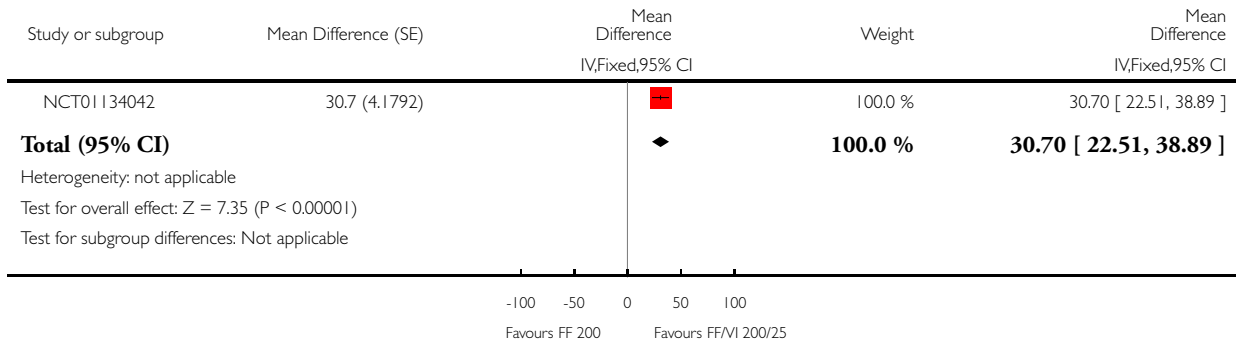


Analysis 9.6. Comparison 9 FF/VI 200/25 versus same dose of FF, Outcome 6 PEFR PM.

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 9 FF/VI 200/25 versus same dose of FF

Outcome: 6 PEFR PM

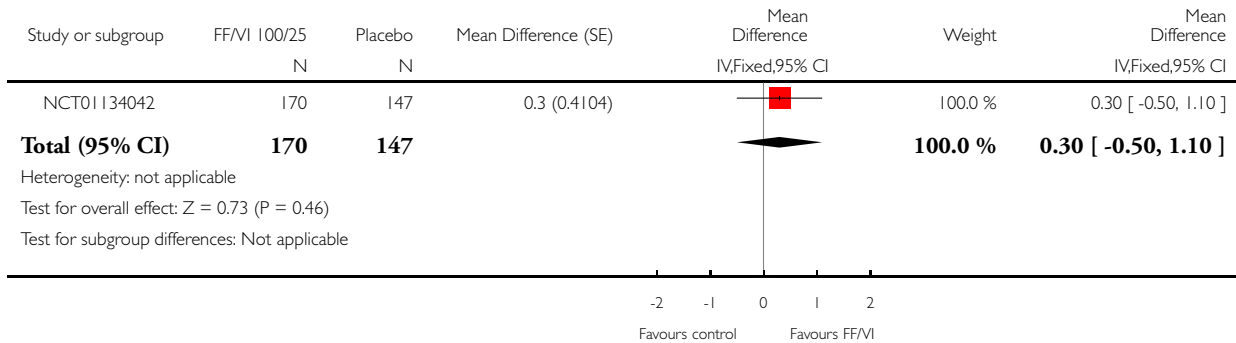


Analysis 9.7. Comparison 9 FF/VI 200/25 versus same dose of FF, Outcome 7 Change in asthma symptoms (measured by ACT).

Review: Vilanterol and fluticasone furoate for asthma

Comparison: 9 FF/VI 200/25 versus same dose of FF

Outcome: 7 Change in asthma symptoms (measured by ACT)



ADDITIONAL TABLES

Table 1. Summary of study characteristics

| Study | Duration (weeks) | Severity at baseline | Inclusion criteria | Adverse events |
|--------------------------------|------------------|---|---|--|
| Allen 2013 | 6 | Reversibility > 12% FEV ₁ > 50% of predicted | Adults Comply with treatment Clinical diagnosis of asthma for ≥ 12 weeks | Cortisol urinary excretion, serum AUC and trough |
| Bateman 2014 | 24 to 78 | Reversibility > 12% FEV ₁ > 50% to 90% of predicted | Adults Using ICS History of ≥ 1 exacerbation requiring hospitalisation or steroids in the past year | None |
| Bernstein 2014 | 12 | Reversibility > 12% FEV ₁ 50% to 80% of predicted | ICS for > 12 weeks before study > 12 years of age | Yes, not clear |

Table 1. Summary of study characteristics (Continued)

| | | | | |
|---------------|--------|--|---|------------------------------|
| Bleecker 2012 | 12 | Pre-bronchodilator FEV ₁ 40% to 90% of predicted normal Reversibility FEV ₁ ≥ 12% | ICS for 12 weeks before study > 12 years of age | Details not stated |
| Busse 2013 | 52 | Pre-bronchodilator FEV ₁ 40% to 90% of predicted normal Reversibility FEV ₁ ≥ 12% | Adults Clinical diagnosis of asthma ICS at high dose | Details not stated |
| Hojo 2015 | 4 | ACT suggesting poor control and FEV ₁ mean 70% (SD 11%) | Asthma ≥ 20 years of age | No, conference abstract only |
| Lee 2014 | 4 | Pre-bronchodilator FEV ₁ 40% to 80% of predicted Demonstrated reversibility by ≥ 12% | Need for regular controller therapy for minimum of 8 weeks Stable dose of ICS for ≥ 4 weeks ≥ 18 years of age Diagnosis of asthma for ≥ 6 months | No |
| Lin 2013 | 12 | Reversibility of disease: demonstrated ≥ 12% and FEV ₁ 40% to 90% | ICS, with or without LABA, for ≥ 12 weeks Clinical diagnosis of asthma for 12 weeks Adults | No |
| Kempford 2012 | 6 to 8 | Pre-bronchodilator FEV ₁ ≥ 60% of predicted. | 18 and 70 years of age inclusive Using an ICS, with or without a SABA, for ≥ 12 weeks before screening Participants who are current non-smokers, who have not used inhaled tobacco products in the 12-month period preceding screening visit Body weight ≥ 50 kg and BMI within the range 19.0 to 29.9 kg/m ² | Yes, details not stated |

Table 1. Summary of study characteristics (Continued)

| | | | | |
|---------------|-------------------------|---|---|---|
| NCT01134042 | 24 | Pre-bronchodilator FEV ₁ 40% to 90% of predicted Reversibility FEV ₁ ≥ 12% | Current asthma therapy that includes an ICS for ≥ 12 weeks before first visit Adults | Cor-tisol, ECG, mouth swabs, various blood parameters |
| NCT01453023 | 14 | Mild to moderate (GINA) | Stable asthma therapy (FP, total daily dose ≤ 400 mcg or equivalent) and SABA inhaler for ≥ 4 weeks before screening 5 to 12 years of age Clinical diagnosis of asthma 6 months before Controlled asthma (Child-hood ACT > 19) | Not stated |
| Oliver 2012 | 8 | Pre-bronchodilator FEV ₁ > 70% of predicted at screening Methacholine chal-lenge PC20 < 8 mg/mL at screening | Adults Stable asthma therapy (FP, total daily dose ≤ 400 mcg or equivalent) and SABA inhaler for ≥ 4 weeks before screening BMI within the range 18.5 to 35.0 kg/m ² | Not stated |
| Oliver 2013 | 3 with 3 weeks' washout | Pre-bronchodilator FEV ₁ > 70% of predicted at screening Methacholine chal-lenge PC20 < 8 mg/mL at screening | Stable asthma therapy (FP, total daily dose ≤ 400 mcg or equivalent) and SABA inhaler for ≥ 4 weeks before screening BMI within the range 18.5 to 35.0 kg/m ² Adults | Not stated |
| Woodcock 2013 | 24 | Reversibility ≥ 12% and 200 mL within 10 to 40 minutes following 2 to 4 inhalations of albuterol FEV ₁ 40% to 85% pre-dicted normal | Currently using ICS ther-apy Clinical diagnosis of asthma Adults | Not stated |

ACT: Asthma Control Test

AUC: area under the curve

BMI: body mass index

ECG: electrocardiogram

FEV₁: forced expiratory volume in one second

FP: fluticasone propionate

GINA: Global Initiative for Asthma

ICS: inhaled corticosteroid

LABA: long-acting beta₂-agonist

PC20: provocative concentration of methacholine estimated to result in a 20% reduction in FEV₁

SABA: short-acting beta₂-agonist

Table 2. Health-related quality of life

| Study score (change from baseline) | FF/VI 100/25 mcg Mean (SE), N | FF 100 mcg Mean (SE), N | FF 200 mcg Mean (SE), N | FF/VI 200/25 mcg Mean (SE), N | FP/SAL 250/50 mcg twice-daily | FP 500 mcg | Placebo | MD (95% CI) |
|---|-------------------------------|-------------------------|-------------------------|-------------------------------|-------------------------------|-----------------------|-----------------------|--|
| Bleecker 2012 AQLQ change from baseline at 12 weeks | 0.91 (0.055), n = 180 | 0.76 (0.055), n = 184 | - | - | - | - | 0.61 (0.061), n = 149 | 0.15 (0.00 to 0.30), 0.30 (0.14 to 0.46), 0.15 (-0.01 to 0.31) |
| Lin 2013 AQLQ change from baseline at 12 weeks | - | - | - | 0.80 (0.069), n = 140 | - | 0.69 (0.074), n = 123 | - | 0.12 (-0.08 to 0.32) |
| NCT0113404 AQLQ change from baseline at 12 weeks | - | - | 0.66 (0.061), n = 154 | 0.74 (0.056), n = 180 | - | 0.74 (0.059), n = 163 | - | -0.08 (-0.24 to 0.08), -0.08 (-0.25 to 0.09), 0.00 (-0.16 to 0.16) |
| NCT0113404 AQLQ change from baseline at 24 weeks | - | - | 0.88 (0.071), n = 140 | 0.93 (0.065), n = 167 | - | 0.90 (0.068), n = 156 | - | -0.05 (-0.24 to 0.14), -0.02 (-0.21 to 0.17), 0.03 (-0.15 to 0.21) |
| Woodcock 2013 AQLQ change from baseline at 168 days | 0.46 (0.043), n = 342 | - | - | - | 0.37 (0.043), n = 335 | - | - | 0.09 (-0.03 to 0.21) |
| Woodcock 2013 EQ-5D | 5.5 (0.60), n = 343 | - | - | - | 4.1 (0.60), n = 349 | - | - | 1.4 (-0.3 to 3.0) |

Table 2. Health-related quality of life (Continued)

| | | | | | | | | | |
|----------------------------------|--|--|--|--|--|--|--|--|--|
| change from baseline at 168 days | | | | | | | | | |
|----------------------------------|--|--|--|--|--|--|--|--|--|

AQLQ: asthma quality of life questionnaire; CI: confidence interval; EQ-5D: EuroQuality of Life-5D questionnaire; FF: fluticasone furoate; FP: fluticasone propionate; MD: mean difference; SAL: salmeterol; SE: standard error; VI: vilanterol

Table 3. Asthma exacerbation

| Study | FF/VI 100/25 mcg | FF 100 mcg | FF 200 mcg | FF/VI 200/25 mcg | FP/SAL 250/50 mcg twice-daily | FP 500 mcg | Pred- nisolone 10 mg | Placebo |
|---|---------------------------------|-------------------|---------------|---------------------|-------------------------------------|---------------|----------------------------|--------------|
| Allen 2013 ^a 6 weeks' duration | 0/56 (0.00%) | - | - | 0/56 (0.00%) | - | - | 0/15 (0.00%) | 0/58 (0.00%) |
| Bateman 2014 ≥ 24 to 78 weeks' duration Time to first severe exacerbation (HR 0.80, 95% CI 0.64 to 0.99). Annualised rate of severe exacerbation 25% reduction (95% CI 5% to 40%) | 154/1009 (15.26%) | 186/1010 (18.42%) | - | - | - | - | - | - |
| Busse 2013 52 weeks' duration | 3/201 (1.49%) | - | - | 6/202 (2.97%) | - | 3/100 (3.00%) | - | - |
| Lin 2013 12 weeks' duration | - | - | - | 1/155 (0.65%) | - | 3/154 (1.95%) | - | - |
| Kempsford 2012 Cross-over | 0/24 (0.00%) AM 0/25 (0.00%) | - | - | - | - | - | - | 0/23 (0.00%) |

Table 3. Asthma exacerbation (Continued)

| | | | | | | | | | | |
|--|---------------|-------|---|---|---|---------------|-------|---|---|---|
| trial. Each period lasted 14 days with a 14 to 21-day washout period between periods | 00%) PM | | | | | | | | | |
| Woodcock 2013 ^b 24 weeks' duration | 1/403 (0.25%) | (0. - | - | - | - | 2/403 (0.50%) | (0. - | - | - | - |

^a One participant in the FF/VI 100/25 mcg group experienced a severe asthma exacerbation concurrent with sinusitis and was withdrawn owing to lack of efficacy. The participant did not require hospitalisation, and the event, which was not classified as an AE, resolved following treatment with prednisone

^bThe incidence of asthma exacerbations was low, and no difference was noted between groups (3% vs 2% on FP/SAL vs FF/VI, respectively (on-treatment events)). Eight (2%) participants in the FF/VI group and seven (2%) in the FP/SAL group withdrew because of exacerbation. One patient in the FF/VI group and two in the FP/SAL group were hospitalised because of exacerbation

AM: morning; CI: confidence interval; FF: fluticasone furoate; FP: fluticasone propionate; HR: hazard ratio; PM: afternoon; SAL: salmeterol; VI: vilanterol

Table 4. Serious adverse events

| Study | FF/VI 100/25 mcg | FF 100 mcg | FF 200 mcg | FF/VI 200/25 mcg | VI 25 mcg | FP/SAL 250/50 mcg twice-daily | FP 500 mcg | Prednisolone 10 mg | Placebo |
|--|------------------|-----------------|------------|------------------|-----------|-------------------------------|------------|--------------------|--------------|
| Allen 2013 6 weeks' duration. Post-treatment period SAEs | 0/56 (0.00%) | - | - | 0/56 (0.00%) | - | - | - | 0/15 (0.00%) | 0/58 (0.00%) |
| Bateman 2014 ≥ 24 to 78 weeks' duration. On-treatment SAEs | 41/1009 (4.06%) | 29/1010 (2.87%) | - | - | - | - | - | - | - |
| Bernstein 2014 12 weeks' | 4/346 (1.16%) | 3/347 (0.86%) | - | 1/346 (0.29%) | - | - | - | - | - |

Table 4. Serious adverse events (Continued)

| | | | | | | | | | | |
|---|--------------------------------------|---------------|---------------|---------------|---|---|---|---------------|---|---------------|
| duration | | | | | | | | | | |
| Bleecker 2012 12 weeks' duration | 0/201 (0.00%) | 0/205 (0.49%) | - | - | - | - | - | - | - | 0/203 (0.00%) |
| Busse 2013 52 weeks' duration. On-treatment SAEs | 3/201 (1.49%) | - | - | 1/202 (0.50%) | - | - | - | 7/100 (7.00%) | - | - |
| Lee 2014 Cross-over trial. Three of 7 treatments (2 weeks) separated by 12 to 14-day washout periods | 1/172 (0.006%) | 0/187 (0%) | - | - | - | - | - | - | - | - |
| Lin 2013 12 weeks' duration | - | - | - | 1/155 (0.65%) | - | - | - | 2/154 (1.30%) | - | - |
| Kempford 2012 Cross-over trial. Each period lasted 14 days with a 14 to 21-day washout period | 0/24 (0.00%) AM. 0/25 (0.00%) PM. | - | - | - | - | - | - | - | - | 0/23 (0.00%) |
| NCT011340 24 weeks' duration | - | - | 1/194 (0.52%) | 6/197 (3.05%) | - | - | - | 2/195 (1.03%) | - | - |
| NCT014530 Cross-over | 0/25 (0.00%) | 0/25 (0.00%) | - | - | - | - | - | - | - | - |

Table 4. Serious adverse events (Continued)

| | | | | | | | | | | | |
|---|----------------------|---------------------|---|---|---|---------------------|----------------------|---|---|---|---------------------|
| trial. 11 weeks (for a single period) | | | | | | | | | | | |
| Oliver 2012^a Cross-over trial. 28 days for each period | 0/51 (0.00%) | 0/51 (0.00%) | - | - | - | - | - | - | - | - | 0/51 (0.00%) |
| Oliver 2013 Cross-over trial. 21 days | 0/27 (0.00%) | 0/27 (0.00%) | - | - | - | 0/26 (0.00%) | - | - | - | - | 0/27 (0.00%) |
| Woodcock 2013 24 weeks' duration | 4/403 (0.99%) | - | - | - | - | - | 5/403 (1.24%) | - | - | - | - |

^aThe main paper reports that 1 of the 52 withdrew during the study owing to an SAE, which occurred 4 days after the last dose in the FF 100 treatment period. This participant was provisionally diagnosed with moderate (grade 2) Still's disease. Six weeks later, the participant was hospitalised. A diagnosis of histiocytic necrotising lymphadenitis (Kikuchi's disease) was made on the basis of histology of an excised lymph node. Tapered prednisolone treatment, initiated at 60 mg per day, has been successful
FF: fluticasone furoate; FP: fluticasone propionate; SAE: serious adverse event; SAL: salmeterol; VI: vilanterol

Table 5. Forced expiratory flow in one second (FEV₁)

| Study measure time point/duration | FF/VI 100/25 mcg Mean (SE), N, of MD (95% CI) | FF 100 mcg Mean (SE), N | FF 200 mcg Mean (SE), N | FF/VI 200/25 mcg Mean (SE), N | VI 25 mcg Mean (SE), N | FP/SAL250/50 mcg twice-daily Mean (SE), N | FP 500 mcg Mean (SE), N | Placebo Mean (SE), N | MD (95% CI, unless otherwise stated) |
|---|---|-------------------------|-------------------------|-------------------------------|------------------------|---|-------------------------|----------------------|--------------------------------------|
| Bernstein 2014 Trough FEV ₁ At 0 to 12 weeks Change in base- | 0.441 L (0.022) | 0.365 L (0.022) | - | 0.457 L (0.022) | - | - | - | - | - |

Table 5. Forced expiratory flow in one second (FEV₁) (Continued)

| | | | | | | | | | |
|---|--|--|---|---|---|---|---|--|--|
| line trough FEV ₁ from baseline to week 12 | | | | | | | | | |
| Bleecker 2012 Trough FEV ₁ At 0 to 12 weeks Mean change in trough FEV ₁ (pre- bron- chodilator and pre- dose) from baseline to week 12 | 0.368 L (0.0304), n = 200 | 0.332 L (0.0302), n = 203 | - | - | - | - | - | 0.196 L (0.0310), n = 193 | 0.04 L (-0. 05 to 0.12) 0.17 L (0. 09 to 0.26) 0.14 L (0. 05 to 0.22) |
| Lee 2014 Trough FEV ₁ combining all treat- ment peri- ods At 0 to 2 weeks 3 of 7 treat- ments (2 weeks) sep- a- rated by 12 to 14-day washout periods | 0.200 L, n = 158 | 0.087 L, n = 158 | - | - | - | - | - | - | - |
| Lin 2013 12 weeks' duration | - | - | - | - | - | - | - | - | Adjusted treat- ment dif- ference 0. 108 L (0. 040 to 0. 176) |

Table 5. Forced expiratory flow in one second (FEV₁) (Continued)

| | | | | | | | | | |
|--|--|---|---|---|---|---|---|---|---|
| <p>Kemp- ford 2012</p> <p>Weighted mean FEV₁ over the day At day 14 Weighted mean FEV₁, over 0 to 24 hours post dose at day 14 Cross-over trial. Each pe- riod lasted 14 days with a 14 to 21-day washout period</p> | <p>AM dose: 3.188 L (3.112 to 3.265), n = 24 PM dose: 3.233 L (3.159 to 3.306), n = 25</p> | - | - | - | - | - | - | <p>2.811 L (2.729 to 2.893), n = 20</p> | <p>AM vs placebo 0.377 L (90% CI 0.293 to 0. 462) PM vs placebo 0.422 L (90% CI 0.337 to 0. 507) AM vs PM -0.44 L (90% CI - 0.125 to 0. 36)</p> |
| <p>(Kemp- ford 2012)</p> <p>Day 14 pre- treatment (trough) AM FEV₁ At day 14</p> | <p>AM dose: 3.191 L (3.087 to 3.295), n = 24 PM dose: 3.285 L (3.187 to 3.383), n = 25</p> | - | - | - | - | - | - | <p>2.788 L (2.684 to 2.892), n = 22</p> | <p>AM vs placebo 0.403 L (90% CI 0.272 to 0. 533) PM vs placebo 0.496 L (90% CI 0.369 to 0. 624) AM vs PM -0.094 L (90% CI - 0.221 to 0. 034)</p> |
| <p>(Kemp- ford 2012)</p> <p>Day 14 pre-</p> | <p>AM dose: 3.153 L (3.049 to 3.258), n = 24 PM dose:</p> | - | - | - | - | - | - | <p>2.879 L (2.775 to 2.982), n = 23</p> | <p>AM vs placebo 0.275 L (90% CI 0.169 to 0.</p> |

Table 5. Forced expiratory flow in one second (FEV₁) (Continued)

| | | | | | | | | | |
|--|---|---|----------------------------------|----------------------------------|---|---|----------------------------------|---|---|
| treatment (trough) PM FEV ₁ At day 14 | 3.188 L (3.088 to 3.288), n = 25 | | | | | | | | 380) PM vs placebo 0.309 L (90% CI 0.205 to 0.413) AM vs PM -0.034 (90% CI -0.138 to 0.070) |
| NCT011340 Change in base-line trough FEV ₁ At 24 weeks Change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV ₁ at end of 24-week treatment period | - | - | 0.201 L (0.0303), n = 186 | 0.394 L (0.0302), n = 187 | - | - | 0.183 L (0.0300), n = 190 | - | -0.19 L (-0.28 to -0.11) 0.02 L (-0.06 to 0.10) 0.21 L (0.13 to 0.29) |
| (NCT011340 Change from baseline in weighted mean serial FEV ₁ over 24 hours At 24 weeks Change from | - | - | 0.328 L (0.0493), n = 83 | 0.464 L (0.0470), n = 89 | - | - | 0.258 L (0.0483), n = 86 | - | -0.14 L (-0.27 to -0.00) 0.07 L (-0.07 to 0.21) 0.21 L (0.07, 0.34) |

Table 5. Forced expiratory flow in one second (FEV₁) (Continued)

| | | | | | | | | | |
|--|---------------------------------|---------------------------------|---|---|---|---|---|---------------------------------|---|
| baseline in weighted mean serial FEV ₁ over 0 to 24 hours post dose at week 24 | | | | | | | | | |
| Oliver 2012 23 hours post challenge At day 29 Cross-over trial - 28 days for each period Weighted mean change from baseline in FEV ₁ between 0 and 2 hours following 22 to 23-hour post-treatment allergen challenge at day 29 of each treatment period | -0.227 L (0.0550), n = 46 | -0.210 L (0.0549), n = 49 | - | - | - | - | - | -0.372 L (0.0557), n = 45 | FF vs placebo 0.162 L (0.087 to 0.237) FF/VI vs placebo 0.145 L (0.069 to 0.222) FF/VI vs FF - 0.017 L (-0.091 to 0.057) |
| (Oliver 2012) Decrease from baseline 23 hours post challenge At day 29 Maximum % decrease | -13.206% (2.0491), n = 46 | -14.040% (2.0435), n = 49 | - | - | - | - | - | -24.991% (2.0736), n = 45 | FF vs placebo 10.951% (8.053 to 13.848) FF/VI vs placebo |

Table 5. Forced expiratory flow in one second (FEV₁) (Continued)

| | | | | | | | | | |
|---|---------------------------|---------------------------|---|---|---|---|---|---------------------------|---|
| from base-line FEV ₁ between 0 and 2 hours following 22 to 23-hour post-treatment allergen challenge at day 29 of each treatment period (time frame: base-line and at day 29 of each treatment period (up to study day 197)) | | | | | | | | | 11.785% (8.849 to 14.721) FF/VI vs FF 0.834% (-2.010 to 3.678) |
| (Oliver 2012) Change from base-line FEV ₁ 23 hours post challenge Minimum FEV ₁ absolute change from base-line between 0 and 2 hours following 22 to 23-hour post-treatment allergen challenge at day 29 of | -0.478 L (0.0767), n = 46 | -0.479 L (0.0765), n = 49 | - | - | - | - | - | -0.809 L (0.0775), n = 45 | FF vs placebo 0.330 L (0.232 to 0.429) FF/VI vs placebo 0.331 L (0.231 to 0.43) FF/VI vs FF 0.001 L (-0.096 to 0.097) |

Table 5. Forced expiratory flow in one second (FEV₁) (Continued)

| | | | | | | | | | |
|--|--|--|---|---|--|---|---|--|---|
| each treatment period | | | | | | | | | |
| Oliver 2013 Change from baseline 4 to 10 hours post challenge At day 21 Cross-over trial - 21 days LAR: absolute change from baseline in minimum FEV ₁ between 4 and 10 hours following 1-hour post-treatment allergen challenge at day 21 of each treatment period | -0.216 L (-0.343 to -0.088), n = 26 | -0.188 L (-0.315 to -0.061), n = 27 | - | - | -0.536 L (-0.676 to -0.396), n = 22 | - | - | -0.731 L (-0.878 to -0.584), n = 20 | - |
| (Oliver 2013) Change from baseline 4 to 10 hours post challenge At day 21 LAR: absolute change from baseline in weighted | 0.018 L (-0.089 to 0.125), n = 26 | 0.018 L (-0.089 to 0.124), n = 27 | - | - | -0.298 L (-0.415 to -0.181), n = 22 | - | - | -0.466 L (-0.589 to -0.343), n = 20 | - |

Table 5. Forced expiratory flow in one second (FEV₁) (Continued)

| | | | | | | | | | |
|--|---------------------------|---|---|---|---|---------------------------|---|---|----------------------------|
| mean FEV ₁ between 4 and 10 hours following 1-hour post-treatment allergen challenge at day 21 of each treatment period | | | | | | | | | |
| Woodcock 2013 Change from baseline trough FEV ₁ At day 168 24 weeks' duration | 0.281 L (0.0191), n = 397 | - | - | - | - | 0.300 L (0.0193), n = 389 | - | - | -0.019 L (-0.073 to 0.034) |

AM: morning; CI: confidence interval; FEV₁: forced expiratory volume in one second; FF: fluticasone furoate; FP: fluticasone propionate; h: hour; LAR: late asthmatic response; MD: mean difference; PM: afternoon; SAL: salmeterol; SE: standard error; VI: vilanterol

Table 6. Peak expiratory flow

| Study | Duration (weeks) | Measure of PEF | FF/VI 100/25 mcg Mean (SD, unless otherwise stated), N | FF 100 mcg Mean (SD, unless otherwise stated), N | FF 200 mcg Mean (SE), N | FF/VI 200/25 mcg Mean (SE), N | FP 500 mcg Mean (SE), N | Placebo Mean (SE, unless otherwise stated), N | MD (95% CI, unless otherwise stated) |
|----------------|------------------|--|--|--|-------------------------|-------------------------------|-------------------------|---|--|
| Bernstein 2014 | 12 | Change from baseline, AM Change from baseline in AM PEF Averaged over | 44.3 L/min (2.25) | 19.1 L/min (2.25) | - | 47.7 L/min (2.25) | - | | 25.20 L/min (18.96 to 31.44), 100/25 vs 100 FF |

Table 6. Peak expiratory flow (Continued)

| | | | | | | | | | |
|---------------|--------------------|---|--|--|---|---|--------------------------|---|--|
| | | 12-week treatment period | | | | | | | |
| | 12 | Change from baseline, PM Change from baseline in AM PEF Averaged over 12-week treatment period | 39.7 L/min (2.24) | 15.5 L/min (2.24) | - | | 41.7 L/min (2.24) | - | 24.20 L/min (17.99 to 30.41), 100/25 vs 100 FF |
| Bleecker 2012 | 12 | Change from baseline, PM Mean change from baseline in daily PM PEF averaged over 12-week treatment period | 26.4 L/min (SE 2.35), n = 201 | 14.1 L/min (SE 2.34), n = 204 | - | - | - | - | 1.8 L/min (2.36), n = 202 12.30 L/min (5.80 to 18.80), 28.20 L/min (21.67 to 34.73), 15.90 L/min (9.39 to 22.41) |
| Hojo 2015 | 4 | Change from baseline, AM Only 1 (FF/VI) condition reported. Trial reported as conference abstract with limited information | | | | | | | |
| Lee 2014 | Baseline to day 15 | Least squares mean change cal- | 24.1 (2.46) AM 21.4 (2. | -2.9 (2.44) AM -5.2 (2. | - | - | - | - | - |

Table 6. Peak expiratory flow (Continued)

| | | culated from base-line to day 15 Least squares mean change in last 7 days, mean PEF | 58) PM n = 172 | 51) PM n = 187 | | | | | |
|--------------|---------|---|---|---------------------------------|---|---|---|--|--|
| Lin 2013 | 12 | 12 weeks' duration. | - | - | - | 39.1 L/min (3.01), n = 155 | 10.5 L/min (3.03), n = 154 | - | Adjusted treatment difference 28.5 L/min (20.1 to 36.9) |
| Kempson 2012 | 12 days | Pre-treatment Pre-treatment PEF at days 1 to 12 Cross-over trial. Each period lasted 14 days with a 14 to 21-day washout period | AM dose: 510.4 L/min (95% CI 492.9 to 527.8), n = 24 PM dose: 535.3 L/min (95%CI 518.1 to 552.5), n = 25 | - | - | - | - | 466.3 L/min (95% CI 448.8 to 483.9), n = 24 | AM vs placebo 44.0 L/min (90% CI 31.2 to 56.9) PM vs placebo 69.0 L/min (90% CI 55.9 to 82.1) AM vs PM -25.0 L/min (90% CI -37.9 to -12.0) |
| | 12 days | Pre-treatment Pre-treatment PEF (PM) at days 1 to 12 | AM dose: 517.6 L/min (95% CI 503.0 to 532.2), n = 24 PM dose: 521.4 L/min (95% CI 507.1 to 535.7), | - | - | - | - | 453.2 L/min (95% CI 438.5 to 467.9), n = 24 | AM vs placebo 64.4 L/min (90% CI 52.9 to 76.0) PM vs placebo 68.2 L/min (90% CI 56.5 to 79.8) |

Table 6. Peak expiratory flow (Continued)

| | | | n = 26 | | | | | | AM vs PM -3.7 L/min (90% CI - 15.2 to 7. 7) |
|-----------|----|--|--------|---|----------------------------|----------------------------|----------------------------|---|---|
| NCT011340 | 24 | Change from baseline, AM 4 weeks Mean change from baseline in daily trough (AM) PEF averaged over 24-week treatment period | - | - | 18.2 L/min (2.97), n = 193 | 51.8L/min (2.94), n = 197 | 18.8L/min (2.95), n = 195 | - | -33.60 L/min (-41.79 to -25.41), -0.60 L/min (-8.80 to 7.60), 33.00 L/min (24.84 to 41.16) |
| | 24 | Change from baseline, PM Mean change from baseline in daily trough (PM) PEF averaged over 24-week treatment period | - | - | 9.1 L/min (2.98), n = 192 | 39.8 L/min (2.93), n = 197 | 13.6 L/min (2.96), n = 194 | - | -30.70 L/min (-38.89 to -22.51), -4.50 L/min (-12.73 to 3.73), 26.20 L/min (18.04 to 34.36) |

AM: morning; CI: confidence interval; FF: fluticasone furoate; PEF: peak expiratory flow; PM: evening; SD: standard deviation; SE: standard error; VI: vilanterol

Table 7. Asthma symptoms

| Study | Measure | FF/ VI 100/25 mcg Mean (SE) | FF 100 mcg Mean (SE) | FF 200 mcg Mean (SE) | FF/ VI 200/25 mcg Mean (SE) | FP/ SAL250/ 50 mcg twice- daily Mean (SE) | FP 500 mcg Mean (SE) | Placebo Mean (SE) | MD (95% CI) |
|--|--|--------------------------------------|-----------------------------|----------------------------|--------------------------------------|--|----------------------------|----------------------------|---|
| Bateman 2014 | ACQ7 mean dif- ference and responder analysis | NR | NR | - | - | - | - | - | - |
| ≥ 24 to 78 weeks' du- ration Responder analysis re- sults: ORs for FF/ VI vs FF at week 12 (1.49, 95% CI 1. 20 to 1.84) , week 36 (1.49, 95% CI 1. 21 to 1.83) and at end- point (1. 50, 95% CI 1. 23 to 1.82) | | | | | | | | | |
| Bernstein 2014 | Change from baseline % Change from base- line in per- centage of symptom- free 24- hour peri- ods during 12-week treatment | 27.2 (1. 74) n = 345 | 19.4 (1. 74) n = 346 | - | 29.0 (1. 74) n = 346 | - | - | -- | |
| Bleecker 2012 | Change from baseline % Change from base- line in % of symptom- free days | 32.5 (2. 14), n = 201 | 20.4 (2. 13), n = 204 | - | - | - | - | 14.6 (2.15), n = 202 | 12.10 (6. 18 to 18. 02), 17.90 (11.95 to |

Table 7. Asthma symptoms (Continued)

| | | | | | | | | | | |
|---|--|-----------------------|-----------------------|------------------------|-------------------------|---|-------------------------|---|---|---|
| symptom-free 24-hour periods during 12-week treatment period | | | | | | | | | | 23.85), 5.80 (-0.13 to 11.73) |
| Hojo 2015 Trial Change from baseline ACT score reported as conference abstract with limited information | | | | | | | | | | |
| Lee 2014 LS mean change in symptom-free days during 2-week treatment period | LS mean change in symptom-free days (SE) | 7.3 (1.67) n = 172 | 5.8 (1.64) n = 187 | - | - | - | - | - | - | - |
| Lin 2013 % of symptom-free 24-hour periods, weeks 1 to 12 | % of symptom-free days | - | - | - | 25.4 (2.74), n = 155 | - | 20.6 (2.77), n = 152 | - | - | 4.9 (-2.8 to 12.5) |
| NCT011340 Change from baseline in ACT scores at week 12 | Change from baseline ACT score | - | - | 3.9 (0.29), n = 164 | 4.8 (0.27), n = 183 | - | 3.9 (0.28), n = 169 | - | - | -0.90 (-1.68 to -0.12), 0.00 (-0.79 to 0.79), 0.90 (0.14 to 1.66) |
| (NCT011340 Change from baseline in | Change from baseline ACT score | - | - | 5.2 (0.30), n = 147 | 5.5 (0.28), n = 170 | - | 4.7 (0.29), n = 162 | - | - | -0.30 (-1.10 to 0.50), 0.50 (-0.32 to 1.32) |

Table 7. Asthma symptoms (Continued)

| | | | | | | | | | | |
|--|--------------------------------|---------------------|---|---|---|---------------------|---|---|---|--------------------------|
| ACT scores at week 24 | | | | | | | | | | 32), 0.80 (0.01 to 1.59) |
| Woodcock 2013 Change from baseline in ACT scores at day 168 and at 24 weeks | Change from baseline ACT score | 2.3 (0.16), n = 354 | - | - | - | 2.0 (0.16), n = 348 | - | - | - | 0.2 (-0.2 to 0.7) |

ACT: asthma control test; CI: confidence interval; FF: fluticasone furoate; FP: fluticasone propionate; LS: least squares; MD: mean difference; NR: not reported; OR: odds ratio; SAL: salmeterol; SE: standard error; VI: vilanterol

Table 8. Adverse events

| Study | FF/VI 100/25 mcg | FF 100 mcg | FF 200 mcg | FF/VI 200/25 mcg | VI 25 mcg | FP/SAL 250/50 mcg twice-daily | FP 500 mcg | Pred-nisolone 10 mg | Placebo |
|---|-------------------|-------------------|------------|------------------|-----------|-------------------------------|------------|---------------------|-----------------|
| Allen 2013 6 weeks' duration. On-treatment AEs | 23/56 (41.00%) | - | - | 21/56 (38.00%) | - | - | - | 5/15 (33.00%) | 16/58 (28.00%) |
| Bateman 2014 ≥24 to 78 weeks' duration. On-treatment AEs | 636/1009 (63.00%) | 652/1010 (65.00%) | - | - | - | - | - | - | - |
| Bernstein 2014 12 weeks' duration | 54/346 (15.61%) | 67/347 (19.31%) | - | 52/346 (15.03%) | -- | - | - | - | - |
| Bleecker 2012 12 weeks' | 29/201 (14.43%) | 20/205 (9.76%) | - | - | - | - | - | - | 22/203 (10.84%) |

Table 8. Adverse events (Continued)

| | | | | | | | | | |
|---|--|-------------------------------|----------------------------------|-----------------------------------|---|---|----------------------------------|---|----------------------|
| duration | | | | | | | | | |
| Busse 2013 52 weeks' duration. On-treatment AEs | 139/201 (69.15%) | - | - | 134/202 (66.34%) | - | - | 73/100 (73.00%) | - | - |
| Lee 2014 Cross-over trial. 3 of 7 treatments (2 weeks) separated by 12 to 14-day washout periods | 43/172 (25%) | 25/187 (13%) | - | - | - | - | - | - | - |
| Lin 2013 12 weeks' duration. Any AE | - | - | - | 40/155 (26.00%) | - | - | 41/154 (27.00%) | - | - |
| Kempford 2012 Cross-over trial. Each period lasted 14 days with a 14 to 21-day washout period between periods | 11/24 (45.83%) AM 12/25 (48.00%) PM | - | - | - | - | - | - | - | 8/23 (34.78%) |
| NCT011340 24 weeks' duration | - | - | 66/194 (34.02%) | 62/197 (31.47%) | - | - | 73/195 (37.44%) | - | - |
| NCT014530 Cross-over trial. 11 weeks (for | 4/25 (16.00%) | 1/25 (4.00%) | - | - | - | - | - | - | - |

Table 8. Adverse events (Continued)

| | | | | | | | | | |
|--|-----------------------------|----------------------------|---|---|----------------------------|-----------------------------|---|---|----------------------------|
| a single pe- riod) | | | | | | | | | |
| Oliver 2012 Cross- over trial. 28 days for each period | 11/51 (21. 57%) | 18/51 (35. 29%) | - | - | - | - | - | - | 15/51 (29. 41%) |
| Oliver 2013 Cross- over trial. 21 days | 20/27 (74. 07%) | 19/27 (70. 37%) | - | - | 22/26 (84. 62%) | - | - | - | 19/27 (70. 37%) |
| Woodcock 2013 24 weeks' duration | 110/403 (27.30%) | - | - | - | - | 106/403 (26.30%) | - | - | - |

Fractions shown in the table indicate the proportions of people who suffered one or more adverse events of any cause in each treatment arm

AE: adverse event; F: fluticasone furoate; FP: fluticasone propionate; SAL: salmeterol; VI: vilanterol

APPENDICES

Appendix I. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

| Database | Frequency of search |
|---|---------------------|
| CENTRAL (<i>The Cochrane Library</i>) | Monthly |
| MEDLINE (Ovid) | Weekly |
| Embase (Ovid) | Weekly |

(Continued)

| | |
|-----------------|---------|
| PsycINFO (Ovid) | Monthly |
| CINAHL (EBSCO) | Monthly |
| AMED (EBSCO) | Monthly |

Handsearches: core respiratory conference abstracts

| Conference | Years searched |
|---|--------------------------|
| American Academy of Allergy, Asthma and Immunology (AAAAI) | 2001 onwards |
| American Thoracic Society (ATS) | 2001 onwards |
| Asia Pacific Society of Respiriology (APSR) | 2004 onwards |
| British Thoracic Society Winter Meeting (BTS) | 2000 onwards |
| Chest Meeting | 2003 onwards |
| European Respiratory Society (ERS) | 1992, 1994, 2000 onwards |
| International Primary Care Respiratory Group Congress (IPCRG) | 2002 onwards |
| Thoracic Society of Australia and New Zealand (TSANZ) | 1999 onwards |

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma\$.mp.
3. (antiasthma\$ or anti-asthma\$).mp.
4. Respiratory Sounds/
5. wheez\$.mp.
6. Bronchial Spasm/
7. bronchospas\$.mp.
8. (bronch\$ adj3 spasm\$).mp.
9. bronchoconstrict\$.mp.
10. exp Bronchoconstriction/
11. (bronch\$ adj3 constrict\$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/

14. ((bronchial\$ or respiratory or airway\$ or lung\$) adj3 (hypersensitiv\$ or hyperreactiv\$ or allerg\$ or insufficiency)).mp.
15. ((dust or mite\$) adj3 (allerg\$ or hypersensitiv\$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy for Cochrane Airways Group Register

- #1 AST:MISC1
- #2 MeSH DESCRIPTOR Asthma Explode All
- #3 asthma*:ti,ab
- #4 #1 or #2 or #3
- #5 fluticasone*
- #6 GW685698
- #7 FF:TI,AB
- #8 #5 OR #6 OR #7
- #9 vilanterol*
- #10 GW642444
- #11 VI:TI,AB
- #12 #9 OR #10 OR #11
- #13 #8 AND #12
- #14 FF/VI:TI,AB
- #15 #13 or #14
- #16 #4 and #15

[In search line #1, MISC1 denotes the field in which the reference has been coded for condition, in this case, asthma]

CONTRIBUTIONS OF AUTHORS

All review authors contributed to writing of the protocol. NW and LB independently selected studies for inclusion in the review, CP and SJM extracted data and KD entered the data into the RevMan file with cross-checking by SJM. KD wrote the Results section, and NW, LB, CP, KD and SJM co-authored the Discussion and Conclusions sections.

DECLARATIONS OF INTEREST

The review authors have no declarations of interest to report.

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- The authors declare that no internal source funding was received for this systematic review, Other.

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- The authors declare that no external source funding was received for this systematic review, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We conducted this review in accordance with the protocol. However, we removed content from the section detailing measures of treatment effect: If two comparisons (e.g. drug A vs placebo and drug B vs placebo) were combined in the same meta-analysis, we halved the control group to avoid double-counting. We changed the wording, but not the intent, of the objectives.