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Efficacy and Safety of Fluticasone Furoate/Vilanterol Compared with Fluticasone Propionate/Salmeterol Combination in Adult and Adolescent Patients with Persistent Asthma: a Randomized Trial

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Running header: Efficacy and safety of FF/VI vs FP/SAL in asthma

Summary of conflicts of interest: Dr Woodcock has served as consultant to Almirall, AstraZeneca, Chiesi, Cytos, GlaxoSmithKline, Merck Sharpe and Dohme and Novartis; and has received lecture fees and research grants from Chiesi and GlaxoSmithKline. Dr Bleecker has served as a consultant to AstraZeneca, Boehringer Ingelheim, Cephalon, Forest, Genentech, GlaxoSmithKline, MedImmune, Novartis, Pfizer and Sanofi-Aventis; has received reimbursement for travel from GlaxoSmithKline; and has performed clinical trials for AstraZeneca, Boehringer Ingelheim, Centocor, Genentech, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis and Pfizer, which have been administered by his employer Wake Forest School of Medicine. Dr Lötvald has served as a consultant to and received lecture fees from AstraZeneca, GlaxoSmithKline, Merck Sharpe and Dohme, Novartis, and UCB Pharma; has been partly covered by some of these companies to attend previous scientific meetings including the ERS and the AAAAI; has provided expert testimony for Barr Pharmaceuticals, and has participated in clinical research studies sponsored by AstraZeneca, GlaxoSmithKline, Merck Sharpe and Dohme, and Novartis. Dr O'Byrne has served as a consultant to AstraZeneca, Almirall, Boehringer Ingelheim, GlaxoSmithKline, and Merck; has served on advisory boards for AIM, Altair, Boehringer, GlaxoSmithKline, Medimmune and Merck; has received lecture fees from Chiesi; and has received research funding from Amgen, AstraZeneca, Asmacure, Genentech and Ono. Dr Bateman has served as a consultant to AlkAbello, Almirall, Cephalon, Hoffman la Roche, ICON and MS Consulting Group; been on advisory boards for Almirall, AstraZeneca, Boehringer Ingelheim, Elevation Pharma, Forest, GlaxoSmithKline, Merck, Napp, Novartis and Nycomed; and received lecture fees from AlkAbello, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer and Takeda; and his institution has received remuneration for participation in clinical trials sponsored by Actelion, Aeras, Almirall, AstraZeneca, Boehringer Ingelheim, Forest, GlaxoSmithKline, Hoffman La Roche, Merck, Novartis, Takeda and TEVA. Dr Busse has served as a consultant to Amgen, AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, MedImmune, Novartis and TEVA; served on advisory boards for Altair, Amgen, Centocor, GlaxoSmithKline, Johnson & Johnson, Merck Sharpe and Dohme and Pfizer; received lecture fees from Merck Sharpe and Dohme; and received research funding from AstraZeneca, Ception, GlaxoSmithKline, MedImmune and Novartis. Dr Medley, Ms Ellsworth and Dr Jacques are employees of and hold stock in GlaxoSmithKline.

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ABSTRACT

Background: The combination of fluticasone furoate (FF), a novel inhaled corticosteroid (ICS) and vilanterol (VI), a long-acting beta₂ agonist, is under development as a once-daily treatment for asthma and chronic obstructive pulmonary disease. The aim of this study was to compare the efficacy of FF/VI with fluticasone propionate (FP)/salmeterol (SAL) in patients with persistent asthma uncontrolled on medium-dose ICS.

Methods: In a randomized, double-blind, double-dummy, parallel-group study, 806 patients received FF/VI (100/25 µg, n = 403) once daily in the evening via dry powder inhaler, or FP/SAL (250/50 µg, n = 403) twice daily via DiskusTM/AccuhalerTM. The primary efficacy measure was 0–24 h serial weighted mean forced expiratory volume in 1 second (wmFEV₁) after 24 weeks of treatment.

Results: Improvements from baseline in 0–24 h wmFEV₁ were observed with both FF/VI (341 ml) and FP/SAL (377 ml); the adjusted mean treatment difference was not statistically significant (–37 ml [95% confidence interval: –88, 15], *p* = 0.162). There were no differences between the 0–4 h serial wmFEV₁, trough FEV₁, and asthma control and quality of life questionnaire scores. There was no difference in reported exacerbations between treatments. Both treatments were well tolerated, with no clinically relevant effect on urinary cortisol excretion or vital signs, and no treatment-related serious adverse events.

Conclusions: The efficacy of once-daily FF/VI was similar to twice-daily FP/SAL in improving lung function in patients with persistent asthma. No safety issues were identified.

Trial registry: ClinicalTrials.gov; No.: NCT01147848; funded by GSK (HZA113091).

Abbreviations list: AE = adverse event; AQLQ+12 = Asthma Quality of Life +12 Questionnaire; CI = confidence interval; EQ-5D = European Quality of Life-5 Dimensions; FEV₁ = forced expiratory volume in 1 second; FF = fluticasone furoate; FP = fluticasone propionate; ICS = inhaled corticosteroid; LABA = long-acting beta₂ agonist; SAE = serious adverse event; SAL = salmeterol; UC = urinary cortisol; VI = vilanterol; wm = weighted mean.

INTRODUCTION

For patients with asthma who remain uncontrolled despite inhaled corticosteroid (ICS) therapy, a long-acting inhaled beta₂ agonist (LABA) may be added.^{1,2} Combination therapy improves symptoms, reduces severe exacerbation rate and achieves better asthma control in more patients than ICS monotherapy.^{1, 3-5} However, poor adherence to twice-daily therapy may account for poor asthma control in some patients. For these patients once-daily therapy could offer them greater convenience, thereby improving adherence.⁶

Vilanterol (VI; GW642444M) is a LABA with inherent 24-h activity in development as a once-daily treatment in combination with the novel ICS, fluticasone furoate (FF), for asthma and chronic obstructive pulmonary disease. Three dose-ranging FF studies in patients with persistent asthma showed significant improvements from baseline in lung function relative to placebo with the 100 µg and 200 µg doses of FF (over 8 weeks) providing optimal efficacy with an acceptable tolerability profile.⁷⁻⁹ A VI dose-ranging study with concurrent ICS, also in persistent asthma, showed that the 25 µg dose of VI administered once daily over 4 weeks provided the most beneficial therapeutic ratio.¹⁰

The main aim of this study was to compare the efficacy of FF/VI 100/25 µg administered once daily in the evening with fluticasone propionate (FP)/salmeterol (SAL) 250/50 µg administered twice daily over a 24-week treatment period in patients ≥12 years of age with persistent asthma uncontrolled on medium-dose ICS. The dose of FP/SAL selected was considered suitable for the patient population to be studied.

MATERIALS AND METHODS

Patients

Eligible patients were ≥ 12 years old with a diagnosis of asthma,¹ could demonstrate a $\geq 12\%$ and ≥ 200 ml reversibility of forced expiratory volume in 1 second (FEV₁) following albuterol inhalation at screening, and had a best evening FEV₁ of 40–85% of the predicted normal value at screening and at randomization.¹¹ Prior to screening, patients had been taking ICS for ≥ 12 weeks, with a stable medium dose of ICS (FP 250 μ g twice daily or equivalent) for ≥ 4 weeks. Key exclusion criteria are shown in e-Appendix-1. The study was approved by local ethics review committees (e-Appendix-2) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients gave written informed consent.

Study Design and Treatments

This was a phase III, multicenter, randomized, double-blind, double-dummy, parallel group study conducted between 16 June 2010 and 27 July 2011 (GlaxoSmithKline study number HZA113091; www.clinicaltrials.gov registration number NCT011478489). After screening, eligible patients entered a 4-week run-in period during which they replaced their current asthma medication with FP 250 μ g twice daily, and their short-acting bronchodilator with albuterol via metered dose inhaler. After the run-in period, patients received (1:1) either FF/VI 100/25 μ g (emitted dose 92/22 μ g) once daily administered via ELLIPTA™ dry powder inhaler or FP/SAL 250/50 μ g twice daily (morning and evening) via Diskus™/Accuhaler™ for 24 weeks (ELLIPTA™ is a trademark of the GlaxoSmithKline group of companies). The central randomization schedule was generated by the sponsor using a validated computerized system (RandAll; GlaxoSmithKline, London, UK) and patients were randomized using Registration and Medication Ordering System. Neither the patients nor the investigator knew which study medication the patient was receiving. A summary of permitted/prohibited medications is provided in e-Appendix-3. Compliance with study medication was measured by reviewing the dose counter on the dry powder inhaler and Diskus/Accuhaler.

Outcome Measurements

The primary endpoint was change from baseline in 0–24 h serial weighted mean (wm) FEV₁ after 24 weeks of treatment. Secondary endpoints were: individual serial FEV₁ assessments at Week 24 (FEV₁ at each time point on Day 168); time to onset of bronchodilator effect (the time point when FEV₁ first exceeded 12% and 200 ml increase over baseline [taken from serial measurements]) at randomization visit only; 0–4 h serial wmFEV₁ post-dose at randomization visit and at Week 24; percentage of patients obtaining $\geq 12\%$ and ≥ 200 ml increase from baseline in FEV₁ at 12 h and at 24 h at Week 24; and change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV₁ at Week 24.

Other efficacy endpoints of the study included: the Asthma Quality of Life +12 Questionnaire (AQLQ+12), the Asthma Control Test™, the European Quality of Life-5 Dimensions (EQ-5D) test, and unscheduled healthcare resource utilization. Patients were asked to complete questionnaires at baseline and end of treatment. A post-hoc analysis of the individual AQLQ+12 domains and also minimally important difference (≥ 0.5 -point improvement in score) on AQLQ+12 was also performed. Results from this post-hoc analysis are provided in e-Appendix-4.

Safety Evaluations

Adverse events (AEs) could be reported throughout the study. Other safety assessments included: 24-h urinary cortisol (UC) excretion at baseline and at the end of the 24-week treatment period (subset of patients), vital signs (diastolic and systolic blood pressure, pulse rate), incidence of severe asthma exacerbations, liver safety, and screening assessments of electrocardiography, clinical chemistry and hematology.

Patients were withdrawn from the study due to lack of efficacy if they experienced a severe exacerbation, worsening asthma, or at the investigator's discretion. A severe exacerbation was defined as deterioration of asthma requiring treatment with systemic or oral corticosteroids for ≥ 3 days, or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. Worsening asthma was defined as a requirement for any treatment other than study medication or use of rescue albuterol. Severe asthma exacerbations were not recorded as an AE unless they met the definition of a serious AE (SAE).

Statistical Analysis

Sample size calculations were based on the primary endpoint, 0–24 h serial wmFEV_1 at the end of the 24-week treatment period, for the treatment comparison of FF/VI 100/25 μg once daily vs FP/SAL 250/50 μg twice daily. It was estimated that ~348 patients with evaluable data per treatment group would provide 90% power to detect a difference of 80 ml between FF/VI 100/25 μg and FP/SAL 250/50 μg ; this assumed a standard deviation of 325 ml. Details regarding the analysis populations and the power calculation are provided in e-Appendix-5.

The primary analysis was performed on the intent-to-treat population using an Analysis of Covariance model allowing for the effects due to baseline FEV_1 , region, sex, age, and treatment group. A two-sided 5% risk (significance level) associated with incorrectly rejecting the null hypothesis was considered acceptable for this study. For the secondary and other efficacy endpoints, if the statistical test for the primary endpoint failed to reject the null hypothesis of no treatment difference at the 0.05 significance level, the tests for the secondary and other efficacy endpoints were to be interpreted as descriptive only.

As a consequence of site audits conducted by the study sponsor GlaxoSmithKline, concerns regarding the quality of data supplied were identified for 2 study centers. These centers contributed 57 patients (7% of enrolled patients) to the study. Because of these concerns, analysis of the primary endpoint was repeated excluding the data from these two centers. Results were entirely consistent with the primary analysis. The authors and study sponsor are satisfied that the exclusion of data derived from these centers did not materially change any findings of the study. We have therefore presented a complete dataset from all of the centers.

RESULTS

Study Population

Patient disposition is shown in Figure 1. Most patients (89%) in both treatment groups completed the 24-week treatment period (Fig 1). Patient demographics and baseline lung function are shown in Table 1.

Efficacy Assessments

Lung function: Improvements from baseline in 0–24 h serial wmFEV_1 were seen with both FF/VI (341 ml) and FP/SAL (377 ml); however, the adjusted mean treatment difference was not statistically significant (–37 ml [95% confidence interval (CI): –88, 15], $p = 0.162$; Figure 2).

There were no differences in key secondary endpoints including the change from baseline in individual serial FEV_1 assessments over time at Week 24 – these showed sustained 24-h duration of action for both once-daily FF/VI and twice-daily FP/SAL at all time points (Fig 3). The adjusted mean treatment differences between FF/VI and FP/SAL ranged from 2 ml to 58 ml. No important differences were seen between FF/VI vs FP/SAL for the secondary endpoints of time to onset of bronchodilator effect, 0–4 h serial wmFEV_1 post-dose at randomization and at Week 24, percentage of patients obtaining $\geq 12\%$ and ≥ 200 ml increase from baseline in FEV_1 at 12 h and at 24 h at Week 24, and change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV_1 at Week 24 (Table 2). Change from baseline in pre-dose FEV_1 over the 24-week treatment period is shown in e-Figure 1.

Health Outcomes

Improvements from baseline in the asthma health outcomes assessments of AQLQ+12, Asthma Control Test and the EQ-5D were observed for both FF/VI and FP/SAL, with no difference between treatments (Table 3).

Safety Assessments

The overall incidence of AEs and SAEs reported while on-treatment are presented in Table 4. The most frequently occurring AEs reported by both groups were nasopharyngitis and headache; treatment-related AEs were similar between groups (Table 4). A total of nine patients reported on-treatment SAEs: four on FF/VI and five on FP/SAL (Table 4). SAEs were single events with the exception of asthma exacerbation and pneumonia (one pre-treatment and one on-treatment [FP/SAL]). None of the SAEs were considered treatment related. No deaths were reported during the study.

There was no statistically significant difference between FF/VI and FP/SAL in 24-h UC excretion at Week 24 (adjusted treatment ratio: 0.85; 95% CI, 0.72, 1.02; $p = 0.075$). However, 24-h UC excretion did increase in both groups from baseline to Week 24 (ratio to baseline: 1.11 FF/VI and 1.21 FP/SAL; Fig 4).

The incidence of asthma exacerbations was low and there was no difference between groups (3% on FP/SAL vs 2% on FF/VI [on-treatment events]). Eight (2%) patients in the FF/VI group and seven (2%) in the FP/SAL group withdrew due to their exacerbation. One patient in the FF/VI group and two in the FP/SAL group were hospitalized due to their asthma exacerbations. None of the exacerbations were considered treatment related.

No clinically relevant treatment effects on vital signs (e-Appendix-6) or liver function parameters were found, with the exception of one patient (on FP/SAL) who met liver stopping criteria of alanine aminotransferase levels >8 times the upper limit of normal, which was reported as an AE but was not considered treatment related.

DISCUSSION

In this study of patients aged ≥ 12 years with persistent asthma uncontrolled on medium-dose ICS, FF/VI 100/25 μg dosed once daily in the evening was not significantly different to twice-daily FP/SAL 250/50 μg for the primary endpoint of 0–24 h serial wmFEV_1 at Week 24, or for any of the secondary endpoints. The AE profiles for both treatments were similar and those AEs reported with FP/SAL were consistent with those previously reported with this drug combination.^{12,13}

Patients in our study were symptomatic on medium-dose ICS at baseline. According to current asthma guidelines, these patients would require a step up in their asthma treatment from Step 3 to Step 4.² Lack of asthma control in the patient population at baseline was evident by an FEV_1 of approximately 68% of the predicted normal value for both groups and also by the fact that $\geq 50\%$ of patients had an Asthma Control Test score of < 20 . The goal of asthma treatment is to control asthma symptoms.² A number of studies have shown that non-adherence to asthma therapy is an important reason for loss of asthma control in some patients.^{14–16} Adherence to the treatment schedule was high during the study ($> 94\%$ in both groups), although the artificial setting of a clinical trial may have encouraged normally ‘non-adherers’ to take their medication. If poor adherence to the dosing schedule is an important factor in loss of asthma control, then once-daily dosing (as opposed to twice-daily dosing) such as that provided by FF/VI may represent a more convenient treatment option for patients in a ‘real-world’ setting.¹⁷

No differences in asthma control test scores or in measures of quality of life (AQLQ+12 and EQ-5D) were shown in this study. A difference of 1.4 was observed between groups with the EQ-5D test, however, this difference was not statistically significant. The outcomes of the post-hoc analysis (e-Appendix-4) suggest that FF/VI may provide clinically relevant improvements in certain patient-reported quality of life measures (in this study it was in the environmental domain of the AQLQ+12), as well as in the percentage of patients who improved by at least the minimally important difference of 0.5,¹⁸ that were not reported with FP/SAL. However, this statement is speculative and requires further evaluation in real-world studies that are outside the environment of a clinical trial.

FF/VI and FP/SAL were well tolerated and FF/VI had a similar AE profile to FP/SAL. The AE profile with FF/VI reported in our study is consistent with that seen in the two FF dose-ranging studies that included the 100 µg once-daily dose^{7,8} and the two VI (25 µg) plus concurrent ICS studies.^{10,19} Most of the SAEs reported in this study were single events and none were considered treatment related. Asthma exacerbations requiring hospitalization occurred in one patient on FF/VI and two patients on FP/SAL.

A potential effect of ICS treatment is reduction in UC levels as a result of suppression of the hypothalamic-pituitary-adrenal axis, although this usually only occurs at higher doses of ICS.^{9,20,21} In earlier phase dose-ranging studies, once-daily FF at doses of 100 µg or 200 µg did not significantly inhibit 24-h UC levels relative to placebo.^{7,8} In the current study, clinically insignificant increases in UC levels from baseline were reported and no statistically significant differences were observed between the groups at Week 24. LABAs have occasional side effects such as headache, tremor and hypertension.²² In this study, no clinically relevant effects of FF/VI or FP/SAL were found in measures of blood pressure or pulse rate.

It may be considered a limitation that the study duration was too short to reliably collect information on important endpoints such as exacerbations. Also, while a once-daily dosing schedule could provide greater convenience to the patient and may therefore increase compliance to treatment,²³ the double-blind, double dummy nature of the study, together with the very high compliance levels during the study, means that the full benefit of once-daily dosing compared with twice-daily dosing could not be realized in this study. This can only be investigated in a real-world effectiveness study such as the Salford Lung Study, which is now underway.²⁴ It is possible that pre-study ICS adherence was lower than anticipated by the protocol, as suggested by the high degree of FEV₁ reversibility seen at screening. Patient compliance with run-in medication was not formally assessed. Once-daily FF/VI had similar treatment effects to twice-daily FP/SAL in improving lung function and health status in this double-blind randomized study. It remains to be seen whether it will be superior in a real-world setting.

In conclusion, there was no difference in efficacy or safety between FF/VI 100/25 µg administered once daily in the evening and FP/SAL 250/50 µg administered twice daily.

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Dr. Woodcock: contributed to study design, to the interpretation of data and to the critical review of the manuscript, including review and approval of the final version to be published.

Dr. Bleecker: contributed to study design, to the interpretation of data and to the critical review of the manuscript, including review and approval of the final version.

Dr. Lötvall: contributed to study design, to the interpretation of data and to the critical review of the manuscript, including review and approval of the final version.

Dr. O'Byrne: contributed to study design, to the interpretation of data and to the critical review of the manuscript, including review and approval of the final version.

Dr. Bateman: contributed to study design, to the interpretation of data and to the critical review of the manuscript, including review and approval of the final version.

Dr. Medley: contributed to study conception and design, to the collection of data and to the critical review of the manuscript, including review and approval of the final version.

Ms. Ellsworth: contributed to study design, to the analysis and interpretation of data and to the critical review of the manuscript, including review and approval of the final version.

Dr. Jacques: contributed to study design, to the collection, analysis and interpretation of data and to the critical review of the manuscript, including review and approval of the final version.

Dr. Busse: contributed to study design, to the interpretation of data and to the critical review of the manuscript, including review and approval of the final version.

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has received reimbursement for travel from GlaxoSmithKline; and has performed clinical trials for AstraZeneca, Boehringer Ingelheim, Centocor, Genentech, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis and Pfizer, which have been administered by his employer Wake Forest School of Medicine. Dr Lötvald has served as a consultant to and received lecture fees from AstraZeneca, GlaxoSmithKline, Merck Sharpe and Dohme, Novartis, and UCB Pharma; has been partly covered by some of these companies to attend previous scientific meetings including the ERS and the AAAAI; has provided expert testimony for Barr Pharmaceuticals, and has participated in clinical research studies sponsored by AstraZeneca, GlaxoSmithKline, Merck Sharpe and Dohme, and Novartis. Dr O'Byrne has served as a consultant to AstraZeneca, Almirall, Boehringer Ingelheim, GlaxoSmithKline, and Merck; has served on advisory boards for AIM, Altair, Boehringer, GlaxoSmithKline, Medimmune and Merck; has received lecture fees from Chiesi; and has received research funding from Amgen, AstraZeneca, Asmacure, Genentech and Ono. Dr Bateman has served as a consultant to AlkAbello, Almirall, Cephalon, Hoffman la Roche, ICON and MS Consulting Group; been on advisory boards for Almirall, AstraZeneca, Boehringer Ingelheim, Elevation Pharma, Forest, GlaxoSmithKline, Merck, Napp, Novartis and Nycomed; and received lecture fees from AlkAbello, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer and Takeda; and his institution has received remuneration for participation in clinical trials sponsored by Actelion, Aeras, Almirall, AstraZeneca, Boehringer Ingelheim, Forest, GlaxoSmithKline, Hoffman La Roche, Merck, Novartis, Takeda and TEVA. Dr Busse has served as a consultant to Amgen, AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, MedImmune, Novartis and TEVA; served on advisory boards for Altair, Amgen, Centocor, GlaxoSmithKline, Johnson & Johnson, Merck Sharpe and Dohme and Pfizer; received lecture fees from Merck Sharpe and Dohme; and received research funding from AstraZeneca, Ception, GlaxoSmithKline, MedImmune and Novartis. Dr Medley, Ms Ellsworth and Dr Jacques are employees of and hold stock in GlaxoSmithKline.

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REFERENCES

1. National Institutes of Health. Guidelines for the diagnosis and management of asthma (EPR-3) 2007. NIH publication no. 08-4051. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/index.htm>. Accessed: 15 January 2013.
2. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Updated 2011. Available at: <http://www.ginasthma.org/guidelines-gina-report-global-strategy-for-asthma.html>. Accessed: 15 January 2013.
3. Greenstone IIG, Ni Chroinin M, Lasserson TJ, Ducharme F. Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. *Cochrane Database Syst Rev*. 2005;(4):CD005533.
4. Masoli M, Weatherall M, Holt S, Beasley R. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. *Thorax*. 2005;60(9):730–734.
5. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. *Cochrane Database Syst Rev*. 2010;(5):CD005535.
6. Price D, Robertson A, Bullen K, Rand C, Horne R, Staudinger H. Improved adherence with once-daily versus twice-daily dosing of mometasone furoate administered via a dry powder inhaler: a randomized open-label study. *BMC Pulm Med*. 2010;10:1.
7. Bateman ED, Bleecker ER, Lötvall J, et al. Dose effect of once-daily fluticasone furoate in persistent asthma: a randomized trial. *Respir Med*. 2012;106(5):642–650.
8. Bleecker ER, Bateman ED, Busse WW, et al. Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids. *Ann Allergy Asthma Immunol*. 2012;109(5):353–358.e4.

9. Busse W, Bleecker ER, Bateman ED, et al. Fluticasone furoate demonstrates efficacy in asthma patients symptomatic on medium doses of inhaled corticosteroid therapy: a randomised, placebo-controlled trial. *Thorax*. 2012;67(1):35–41.
10. Lötvall J, Bateman ED, Bleecker ER, et al. 24h duration of the novel LABA vilanterol trifenate in asthma patients treated with inhaled corticosteroids. *Eur Respir J*. 2012;40(3):570–579.
11. Hankinson JL, Kawut SM, Shahar E, Smith LJ, Stukovsky KH, Bar RG. Performance of American Thoracic Society-recommended spirometry reference values in a multiethnic sample of adults. *Chest*. 2010;137(1):138–145.
12. Advair™ Diskus prescribing information (FP/SAL). Available at:
http://us.gsk.com/products/assets/us_advair.pdf. Accessed: 15 January 2013.
13. Seretide™ Accuhaler/Seretide™ Evohaler prescribing information (FP/SAL). Available at:
<http://public.gsk.co.uk/products/seretide.html>. Accessed: 15 January 2013.
14. Navaratnam P, Friedman HS, Urdaneta E. Treatment with inhaled mometasone furoate reduces short-acting β_2 agonist claims and increases adherence compared to fluticasone propionate in asthma patients. *Value Health*. 2011;14(2):339–346.
15. Friedman HS, Navaratnam P, McLaughlin J. Adherence and asthma control with mometasone furoate versus fluticasone propionate in adolescents and young adults with mild asthma. *J Asthma*. 2010;47(9):994–1000.
16. Jentzsch NS, Camargos P, Sarinho ES, Bousquet J. Adherence rate to beclomethasone dipropionate and the level of asthma control. *Respir Med*. 2012;106(3):338–343.
17. Guest JF, Davie AM, Ruiz FJ, Greener MJ. Switching asthma patients to a once-daily inhaled steroid improves compliance and reduces healthcare costs. *Prim Care Respir J*. 2005;14(2):88–98.
18. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. *J Clin Epidemiol*. 1994;47(1):81–87.

19. Sterling R, Lim J, Frith L, Snowise NG, Jacques L, Haumann B. Efficacy and optimal dosing interval of the long-acting beta2 agonist, vilanterol, in persistent asthma: a randomised trial. *Respir Med*. 2012;106(8):1110–1115.
20. Fardon TC, Lee DK, Haggart K, McFarlane LC, Lipworth BJ. Adrenal suppression with dry powder formulations of fluticasone propionate and mometasone furoate. *Am J Respir Crit Care Med*. 2004;170(9):960–966.
21. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Arch Intern Med*. 1999;159(9):941–955.
22. Serevent (salmeterol) prescribing information. Available from:
http://us.gsk.com/products/assets/us_serevent_diskus.pdf. Accessed: 11 December 2012.
23. Saini SD, Schoenfeld P, Kaulback K, Dubinsky MC. Effect of medication dosing frequency on adherence in chronic diseases. *Am J Manag Care*. 2009;15(6):e22–33.
24. Salford Lung Study (SLS). Available at: <http://www.salfordlungstudy.co.uk/>. Accessed: 15 January 2013.

TABLES

Table 1 – Patient Demographics and Baseline Lung Function (Intent-to-Treat Population)

	FF/VI 100/25 µg OD PM	FP/SAL 250/50 µg BD
	N = 403	N = 403
Age (years)		
Mean (SD)	43.8 (15.9)	41.9 (16.9)
Range	12, 79	12, 80
Female, n (%)	244 (61)	245 (61)
Race		
White	242 (60)	232 (58)
Asian	124 (31)	125 (31)
African American/African Heritage	36 (9)	43 (11)
Other ^a	1 (<1)	3 (<1)
% reversibility of FEV ₁ ^b , l, mean (SD)	26.4 (14.4)	29.0 (18.0)
Pre-dose FEV ₁ (l), mean (SD)	2.011 (0.639)	2.048 (0.625)
% predicted FEV ₁ , mean (SD)	68.0 (11.7)	68.8 (11.0)
ICS use ^c at screening, n (%)	125 (31)	123 (31)
ICS/LABA use at screening, n (%)	279 (69)	279 (69)

^aNative Hawaiian or other Pacific islander; African American/African heritage and White. ^bScreening values.

^cPatients needed to have been maintained on a medium dose of ICS (eg, FP 250 µg twice daily) for ≥ 4 weeks prior to screening.

BD = twice daily; FEV₁ = forced expiratory volume in 1 second; FF = fluticasone furoate; FP = fluticasone propionate; ICS = inhaled corticosteroid; LABA = long-acting beta₂ agonist; OD = once daily; PM = afternoon; SAL = salmeterol; SD = standard deviation; VI = vilanterol.

Table 2 – Secondary Endpoints^a (Intent-to-Treat Population; N = 403 [FF/VI 100/25 µg OD PM]; N = 403 [FP/SAL 250 µg BD])

		Difference	
		FF/VI OD PM	
		vs FP/SAL	
	Treatment values	BD	95% CI
Time to onset of			
bronchodilator effect			
(median time (min) to	FF/VI: 59	HR: 0.948	0.797, 1.128
≥12% and ≥200 ml FEV ₁	FP/SAL: 61		
over baseline at			
randomization visit)			
0–4 h serial wmFEV ₁ (L)			
post-dose at			
randomization visit, LS	FF/VI: 0.316 (0.0149)	–0.030	–0.071, 0.012
mean (SE) change from	FP/SAL: 0.346 (0.0149)		
baseline			
0–4 h serial wmFEV ₁ post-	FF/VI: 0.360 (0.0184)	–0.034	–0.086; 0.017
dose at Week 24	FP/SAL: 0.394 (0.0186)		
% of patients obtaining ≥12%	12 h FF/VI: 56%;		12 h:0.96,
and ≥200 ml increase from	FP/SAL: 50%	12 h OR: 1.31	1.78
baseline in FEV ₁ at 12 h	24 h FF/VI: 51%;	24 h OR:1.09	24 h: 0.80,
and at 24 h at Week 24	FP/SAL: 50%		1.48
Change from baseline in	FF/VI: 0.281 (0.0191)	–0.019	–0.073, 0.034
clinic visit trough (pre-	FP/SAL: 0.300 (0.0193)		

bronchodilator and pre-

dose) FEV₁ at Week 24

^aResults are for all secondary endpoints other than the endpoint ‘individual serial FEV₁ assessments at Week 24’ (see Figure 3).

BD = twice daily; CI = confidence interval; FEV₁ = forced expiratory volume in 1 second; FF = fluticasone furoate; FP = fluticasone propionate; HR = hazard ratio; LS = least squares; OD = once daily; OR = odds ratio; PM = afternoon; SAL = salmeterol; SE = standard error; VI = vilanterol; wm = weighted mean.

Table 3 – Health Outcomes Assessments (Intent-to-Treat Population; $N = 403$ [FF/VI 100/25 μg OD PM]; $N = 403$ [FP/SAL 250 μg BD])

				Difference	
			LS mean	FF/VI OD	
	Mean score	Mean score	change (SE)	PM vs	
	at baseline	at Week 24	from baseline ^a	FP/SAL BD ^a	95% CI ^a
			FF/VI: 0.46		
AQLQ+12 (total score)	FF/VI: 5.35	FF/VI: 5.85	(0.043)	0.09	−0.03, 0.21
	FP/SAL: 5.37	FP/SAL: 5.79	FP/SAL: 0.37		
			(0.043)		
			FF/VI: 2.3		
ACT	FF/VI: 18.9	FF/VI: 21.2	(0.16)	0.2	−0.2, 0.7
	FP/SAL: 18.8	FP/SAL: 20.9	FP/SAL: 2.0		
			(0.16)		
EQ-5D – dimensions (% of patients reporting ‘no problems’)					
Mobility	FF/VI: 83%	FF/VI: 85%	N/A	OR: 1.37	0.86, 2.18
	FP/SAL: 83%	FP/SAL: 84%			
Self-care	FF/VI: 97%	FF/VI: 98%	N/A	OR: 1.14	0.38, 3.41
	FP/SAL: 98%	FP/SAL: 98%			
Usual activities	FF/VI: 75%	FF/VI: 84%	N/A	OR: 1.44	0.93, 2.24
	FP/SAL: 74%	FP/SAL: 82%			
Pain/discomfort	FF/VI: 67%	FF/VI: 69%	N/A	OR: 1.12	0.80, 1.58
	FP/SAL: 60%	FP/SAL: 66%			
Anxiety/depression	FF/VI: 78%	FF/VI: 77%	N/A	OR: 0.79	0.52, 1.19
	FP/SAL: 77%	FP/SAL: 81%			

EQ-5D – VAS score

			FF/VI: 5.5		
	FF/VI: 80.4	FF/VI: 85.6	(0.60)		
VAS score				1.4	–0.3, 3.0
	FP/SAL: 80.0	FP/SAL: 84.2	FP/SAL: 4.1		
			(0.60)		

^aAQLQ+12, ACT, EQ-5D VAS score: analysis performed using ANCOVA with covariates of baseline score, country, sex, age and treatment; EQ-5D dimensions: analysis performed using logistic regression with covariates of baseline, region, sex, age and treatment. ACT = Asthma Control Test; AQLQ+12 = Asthma Quality of Life +12 Questionnaire; BD = twice daily; CI = confidence interval; EQ-5D = European Quality of Life-5 Dimensions; FF = fluticasone furoate; FP = fluticasone propionate; LS = least squares; OD = once daily; OR = odds ratio; PM = afternoon; SAL = salmeterol; SE = standard error; VAS = visual analogue scale; VI = vilanterol.

Table 4 – On-Treatment AEs $\geq 3\%$ in Any Treatment Group, All Serious AEs and Treatment-Related AEs (Intent-to-Treat Population)

	FF/VI 100/25 µg	FP/SAL 250/50 µg
	OD PM	BD
N (%)	N = 403	N = 403
Any event	213 (53)	198 (49)
Nasopharyngitis	46 (11)	46 (11)
Headache	34 (8)	41 (10)
URTI	26 (6)	16 (4)
Cough	15 (4)	13 (3)
Back pain	11 (3)	11 (3)
Oropharyngeal pain	11 (3)	9 (2)
Sinusitis	12 (3)	7 (2)
Pyrexia	13 (3)	5 (1)
Productive cough	11 (3)	5 (1)
Treatment-related AEs (any)	19 (5)	15 (4)
SAEs		
Any event	4 (<1)	5 (1)
Pneumonia	0	1 (<1)
URTI	1 (<1)	0
Urinary tract infection	0	1 (<1)

Asthma	1 (<1)	2 (<1)
Myocardial ischemia	1 (<1)	0
Cholelithiasis	1 (<1)	0
CO poisoning	0	1 (<1)
Disorientation	0	1 (<1)
Treatment-related SAEs (any)	0	0

AE = adverse event; BD = twice daily; CO = carbon monoxide; FF = fluticasone furoate; FP = fluticasone propionate; OD = once daily; PM = afternoon; SAE = serious adverse event; SAL = salmeterol; URTI = upper respiratory tract infection; VI = vilanterol.

FIGURE 1. CONSORT/patient flow diagram.

^aMain reason was patients did not meet inclusion/exclusion criteria 613 (39%).

^bMain reason was patients did not meet continuation criteria 103 (7%).

AE = adverse event; BD = twice daily; FF = fluticasone furoate; FP = fluticasone propionate; ITT = intent-to-treat; OD = once daily; SAL = salmeterol; VI = vilanterol.

FIGURE 2. Adjusted means for 0–24 h serial wmFEV_1 at Week 24 (intent-to-treat population).

BD = twice daily; CI = confidence interval; FF = fluticasone furoate; FP = fluticasone propionate; LS = least squares; OD = once daily; SAL = salmeterol; VI = vilanterol.

FIGURE 3. Adjusted mean change from baseline in FEV_1 (l) over time at Week 24 for FF/VI dosed once daily and FP/SAL dosed twice daily (intent-to-treat population).

BD = twice daily; CI = confidence interval; FF = fluticasone furoate; FP = fluticasone propionate; LS = least squares; OD = once daily; SAL = salmeterol; VI = vilanterol.

FIGURE 4. Adjusted ratios to baseline for 24-h urinary cortisol excretion at Week 24 (urinary cortisol population).

BD = twice daily; CI = confidence interval; FF = fluticasone furoate; FP = fluticasone propionate; LS = least squares; OD = once daily; SAL = salmeterol; VI = vilanterol

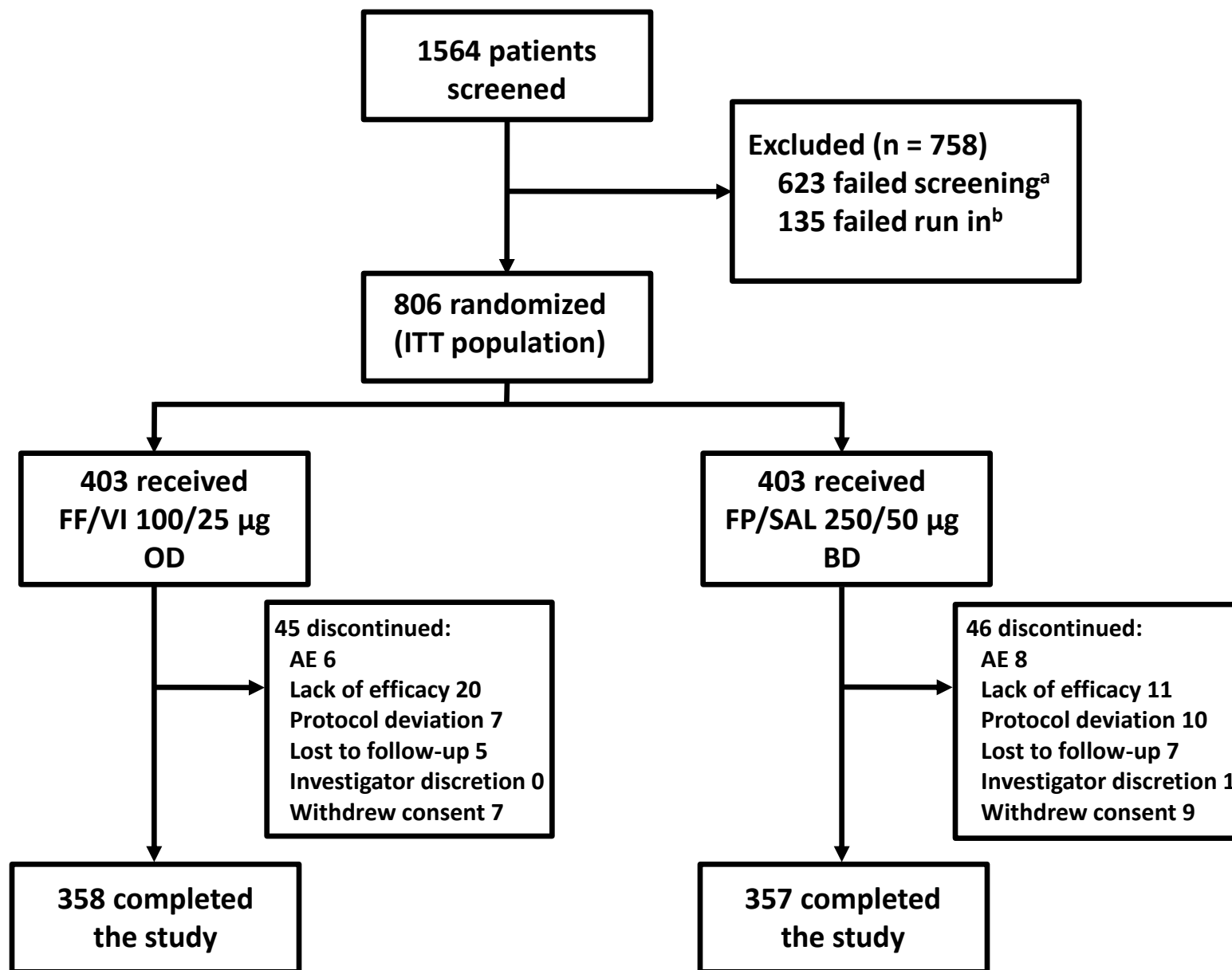


FIGURE 1. CONSORT/patient flow diagram.

^aMain reason was patients did not meet inclusion/exclusion criteria 613 (39%).^bMain reason was patients did not meet continuation criteria 103 (7%).

AE = adverse event; BD = twice daily; FF = fluticasone furoate; FP = fluticasone propionate; ITT =

intent-to-treat; OD = once daily; SAL = salmeterol; VI = vilanterol.

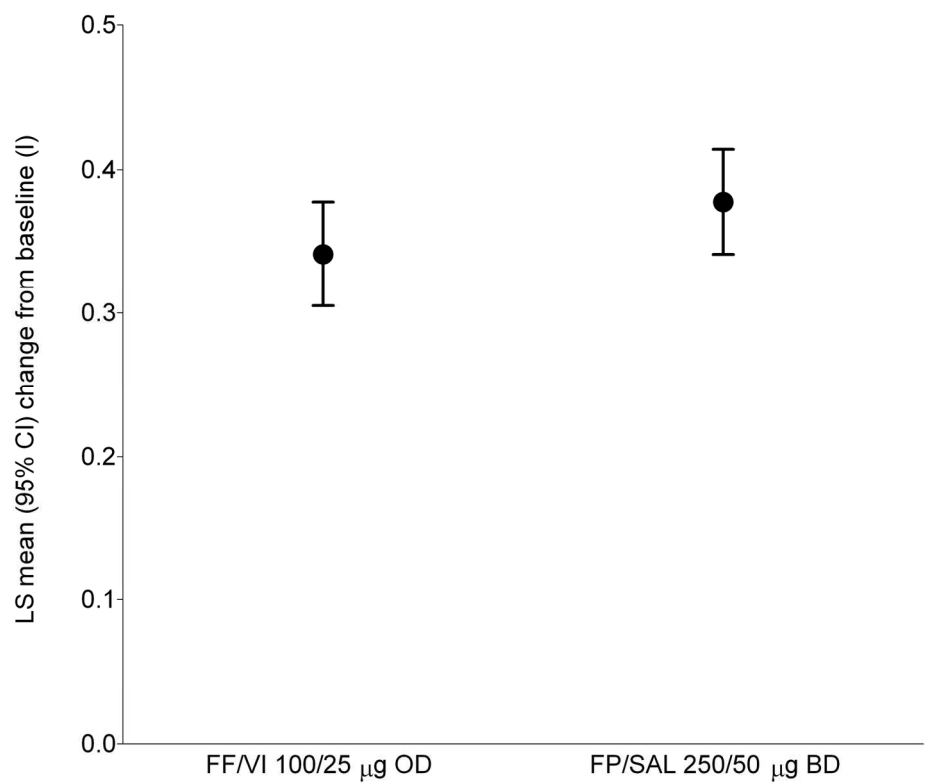


FIGURE 2. Adjusted means for 0–24 h serial $wmFEV_1$ at Week 24 (intent-to-treat population).
BD = twice daily; CI = confidence interval; FF = fluticasone furoate; FP = fluticasone propionate; LS = least squares; OD = once daily; SAL = salmeterol; VI = vilanterol.
160x128mm (300 x 300 DPI)

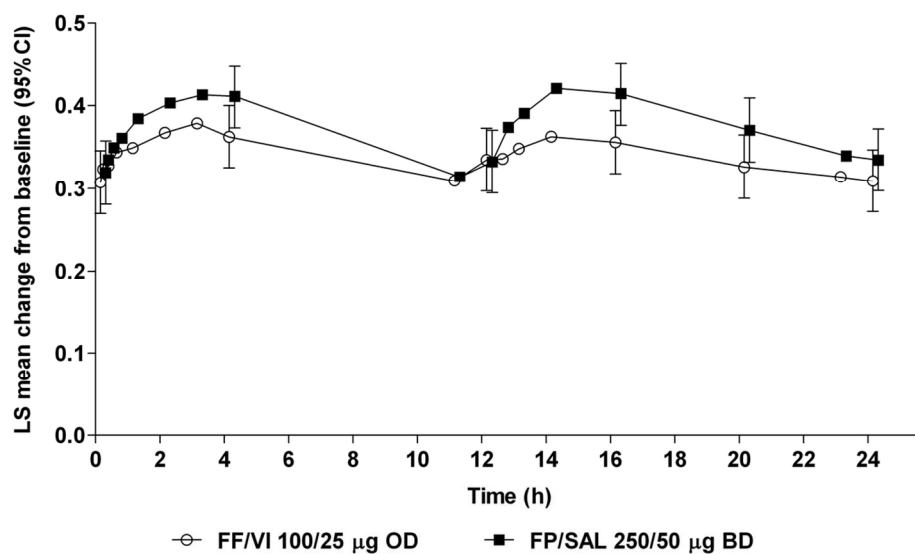


FIGURE 3. Adjusted mean change from baseline in FEV_1 (l) over time at Week 24 for FF/VI dosed once daily and FP/SAL dosed twice daily (intent-to-treat population).

BD = twice daily; CI = confidence interval; FF = fluticasone furoate; FP = fluticasone propionate; LS = least squares; OD = once daily; SAL = salmeterol; VI = vilanterol.

117x69mm (300 x 300 DPI)

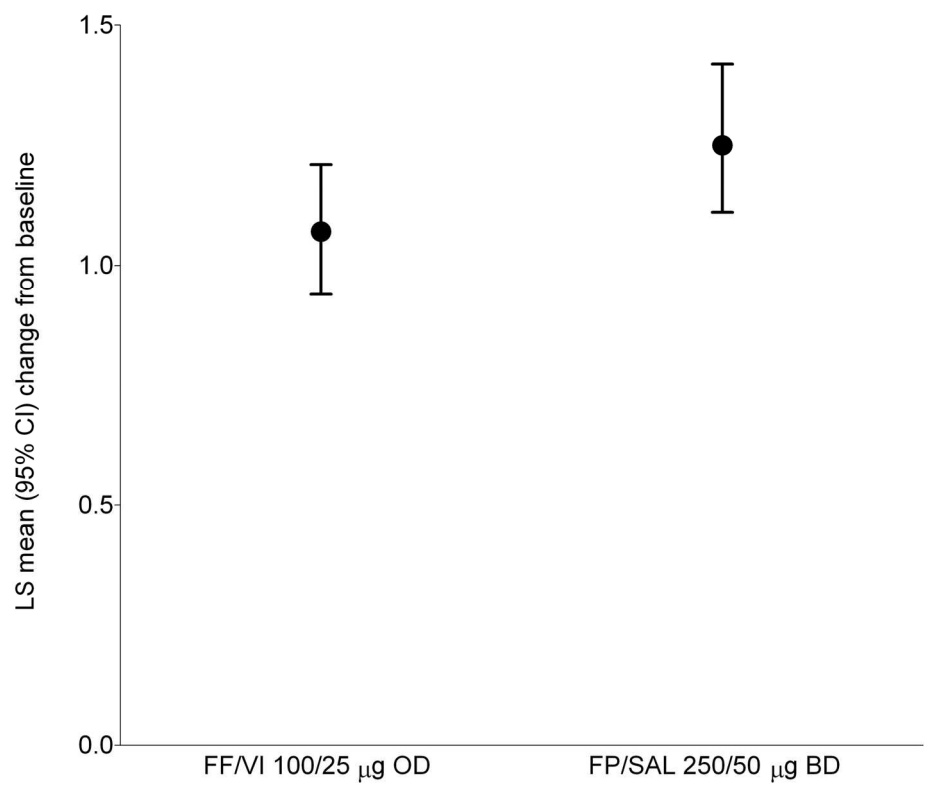


FIGURE 4. Adjusted ratios to baseline for 24-h urinary cortisol excretion at Week 24 (urinary cortisol population).
BD = twice daily; CI = confidence interval; FF = fluticasone furoate; FP = fluticasone propionate; LS = least squares; OD = once daily; SAL = salmeterol; VI = vilanterol.
160x128mm (300 x 300 DPI)

Efficacy and Safety of Fluticasone Furoate/Vilanterol Compared with Fluticasone Propionate/Salmeterol Combination in Adult and Adolescent Patients with Persistent Asthma: a Randomized Trial

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Supplemental Material

e-Appendix-1. Key Exclusion Criteria

Key exclusion criteria included a history of life-threatening asthma defined as an asthma episode that required intubation and/or was associated with hypercapnoea; respiratory arrest or hypoxic seizures within the last 5 years; respiratory infection; asthma exacerbation requiring oral corticosteroids or that resulted in overnight hospitalization within 12 weeks prior to Visit 1; concurrent respiratory disease and other concurrent diseases/abnormalities; visual evidence of candidiasis; drug or milk protein allergy, use of medication that would significantly affect the course of asthma or interact with study drug; use of immunosuppressive medications, and current smoker with a smoking history of at least 10 pack-years (eg, 20 cigarettes per day for 10 years).

e-Appendix-2. Details of the International Review Board Committee Names and Approval Numbers

List of Investigators and Independent Ethics Committees (IECs)/International Review Boards (IRBs) for HZA113091

Investigator	Description of Research Facility, Hospital/ Institution, and Address	Name of IEC/IRB Committee, Address, Committee Chair
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Chile		Approval Numbers Not applicable
Bisbal Malig, Carlos. MD	Hospital Regional de Rancagua, Avenida Libertador Bernardo O'Higgins No 611, Rancagua, Reg Del Libert Bern Ohiggins, Chile, 2841959.	Comité de Ética Hospital Regional de Rancagua, Avenida Libertador Bernardo O'Higgins No 611, Rancagua, Reg Del Libert Bern Ohiggins, Chile, 2841959. Chairperson: Herrera Soto, Carlos
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Korea		
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Kim, Mi-Kyeong	Chungbuk National University Hospital, 410 Gaesin-dong, Heungdeok-gu, Cheongju, Chungcheongbuk-do, Korea, 361-711.	Institutional Review Board, Chungbuk National University Hospital, 410 Gaesin-dong, Heungdeok-gu, Cheongju, Chungcheongbuk-do, Korea, 361-711. Approval Number 2010-06-036 Chairperson: Min, Kyung-Soo
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Kim, Cheol-Woo	Inha University Hospital, No 7-206, 3-Ga Shinheung-Dong Jung-Gu, Incheon, Korea, 400-711.	Inha University Hospital, No 7-206, 3-Ga Shinheung-Dong Jung-Gu, Incheon, Korea, 400-711. Approval Number 10-55 Chairperson: Shin, Seok-Hwan
Kim, Sang Ha	Wonju Christian Hospital, #162 Ilsan-dong Wonju-si, Kangwon-do, Korea, 220-701.	Wonju Christian Hospital, 162 Ilsan-dong, Wonju, Kangwon-do, Korea, 220-701. Approval Number CR110023 Chairperson: Kim, Hwang-Min
Park, Hae-Sim	Ajou University Hospital, San 5, Wonchon-dong, Yeongtong-gu, Suwon, Kyonggi-do, Korea, 443-721.	Ajou University Hospital, san 5 won chun-dong, Suwon-si, Korea, 443-721. AJIRB-GEN-CT3-10-155 Chairperson: Choi, Jin-Hyuk

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de Guia, Teresita S. MD	Philippine Heart Center, Division of Pulmonary and Critical Care, East Avenue, Diliman, Quezon City, Philippines, 1100.	Institutional Review Board, Philippine Heart Center, East Avenue, Diliman, Quezon City, Philippines, 1100. Chairperson: Durante, Marcelito L
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*No patients randomized.

All centres participated in the study under the US IND.

e-Appendix-3. Permitted Non-Asthma Medications and Prohibited Asthma and Non-Asthma Medications

Permitted non-asthma medications included: decongestants, intranasal corticosteroids (for relief of allergic symptoms), immunotherapy (provided patients were on a maintenance treatment for at least 4 weeks prior to screening and they remained in the maintenance phase for the duration of the study), topical corticosteroids and non-corticosteroid containing creams and antihistamines were also permitted. All medications for other disorders could be continued throughout the study provided their use would not be expected to affect the patient's lung function. However, no systemic corticosteroids for other conditions were permitted.

The following asthma medications were prohibited during the study: within 12 weeks of screening and during the study, systemic, oral, parenteral or depot corticosteroids and anti-IgE (eg, Xolair) medications. Within 1 day of screening visit and during the study, patients had to discontinue the following medications at screening with no doses taken on the day of screening until the end of the double-blind treatment period: anti-leukotrienes (including suppressors of leukotriene production and antagonists), inhaled LABAs as monotherapy or ICS/LABA combination, oral (eg, bambuterol) LABAs, theophyllines, anticholinergics, ketotifen, nedocromil sodium, sodium cromoglycate.

The following non-asthma medications were prohibited during the study: concurrent use of any other prescription or over-the-counter medication which could affect the course of asthma, or interact with sympathomimetic amines throughout the study (potent CYP3A4 inhibitors, eg, ritonavir, ketoconazole, etc.) within 4 weeks prior to screening. Medications not permitted during the study, Visit 1 to Visit 6 inclusive, included: anticonvulsants

(barbiturates, hydantoins, and carbamazepine), polycyclic antidepressants, beta-adrenergic blocking agents, phenothiazines, monoamine oxidase (MAO) inhibitors.

e-Appendix-4: Results for the Post-Hoc Analyses

Post-hoc analyses of change from baseline in the Asthma Quality of Life +12 Questionnaire (AQLQ+12) domains of Activity Limitation, Symptoms and Emotional Function did not show a difference for fluticasone furoate/vilanterol (FF/VI) vs fluticasone propionate/salmeterol (FP/SAL). For the AQLQ+12 domain of Environmental Stimuli, adjusted mean changes of 0.58 and 0.31 were reported for the fluticasone furoate (FF)/vilanterol (VI) and fluticasone propionate (FP)/salmeterol (SAL) groups, respectively. Further post-hoc analyses showed that the minimally important difference (MID) of ≥ 0.5 -point improvement in AQLQ+12 score was achieved by a greater number of patients receiving FF/VI vs FP/SAL at Week 24 (46% vs 38%; odds ratio: 1.50; 95% confidence interval [CI] 1.06, 2.13).

e-Appendix-5: Analyses Populations and Further Details Regarding the Power Calculations

Data for the intent-to-treat population (defined as all patients who were randomized to treatment and who received at least one dose of study drug) are reported for all efficacy and safety endpoints (excluding urinary cortisol [UC] assessments). Data for the UC population (defined as all patients targeted to provide 24 h urine samples and whose urine samples did not have confounding factors that affected the interpretation of results) are reported for results from UC assessments.

Up to 15% of patients were expected to withdraw from the study meaning that 820 patients should be randomized (410 patients per treatment group). A subset of ~296 patients (~148 per group) from the 820 patients randomized were targeted to provide a 24-h UC excretion assessment at baseline and at the end of the 24-week treatment period. This provided approximately 100 evaluable patients per treatment group. No sample size re-estimation was planned for this study.

e-Appendix-6: Results for Vital Signs

Systolic and Diastolic Blood Pressure

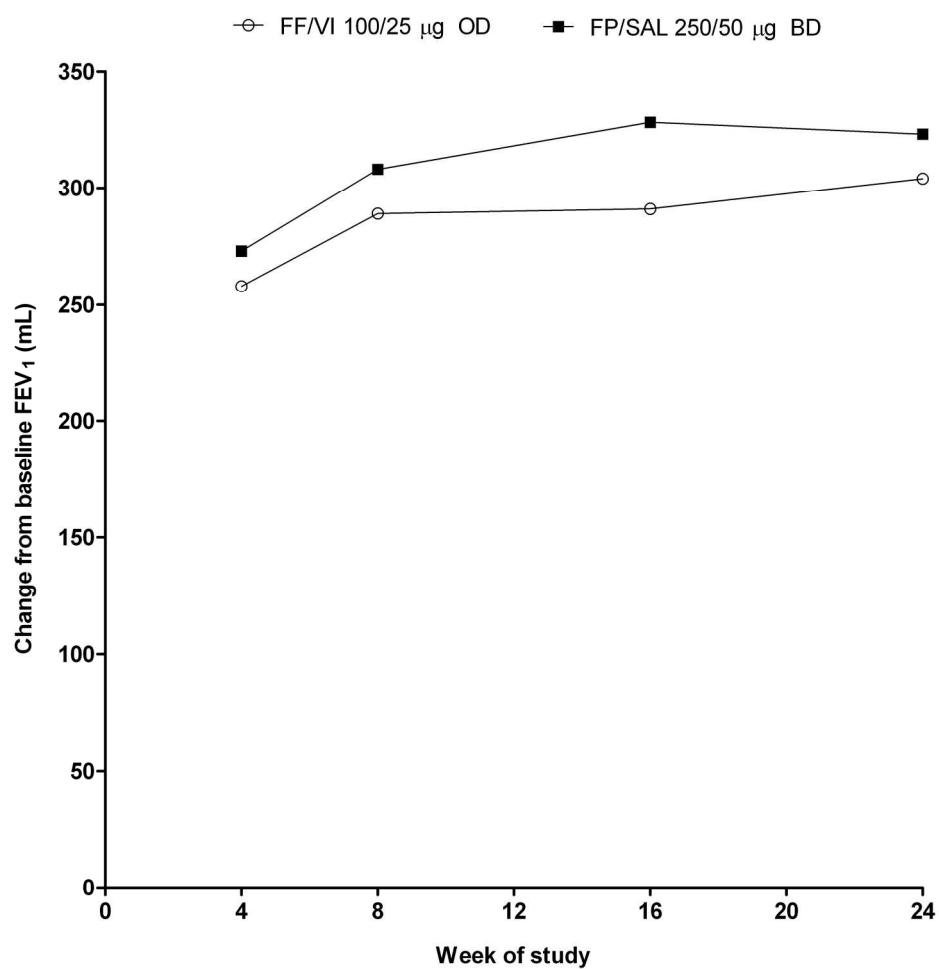
Mean changes from baseline in maximum systolic and minimum diastolic blood pressure were similar between the treatment groups. The mean change from baseline in maximum (post-baseline) systolic blood pressure was 7.2 mmHg with FF/VI and 7.0 mmHg with FP/SAL. For diastolic blood pressure, the mean change from baseline in minimum (post-baseline) blood pressure was -6.2 mmHg with FF/VI and -6.3 mmHg with FP/SAL group.

When analyzed per visit, the adjusted mean differences in pre-dose systolic blood pressure between FF/VI and FP/SAL were not statistically significant at any visit: Week 4 (-0.2 mmHg, $p = 0.757$), Week 8 (0.1 mmHg, $p = 0.934$), Week 16 (-0.8 mmHg, $p = 0.298$), and end of treatment (0.2 mmHg, $p = 0.787$). A similar trend was observed for pre-dose diastolic blood pressure. The adjusted mean differences in pre-dose diastolic blood pressure between the groups were not statistically significant at Week 4 (0.1 mmHg, $p = 0.875$), Week 8 (0.8 mmHg, $p = 0.168$), Week 16 (-0.1 mmHg, $p = 0.811$), and end of treatment (0.3 mmHg, $p = 0.618$).

Pulse Rate

As was observed for blood pressure, mean changes from baseline in pulse rate were similar between the treatment groups (FF/VI: 6.8 beats per minute [bpm]; FP/SAL: 7.3 bpm). Analysis of change from baseline in pulse rate by category by visit showed that up to 45% of patients in both the FF/VI and FP/SAL treatment groups recorded no or minimal change from baseline (change in the range of ± 5 bpm) for all visits: 45% and 42% patients, respectively, at Week 4; 39% patients in both groups at Week 8; 44% and 37% patients, respectively, at Week 16; and 38% and 37% patients, respectively, at end of treatment.

When analyzed per visit, the adjusted mean differences in pre-dose pulse rate between FF/VI and FP/SAL were not statistically significant at any visit: Week 4 (−1.0 bpm, $p = 0.097$), Week 8 (−0.6 bpm, $p = 0.275$), Week 16 (−1.0 bpm, $p = 0.095$), and end of treatment (−0.8 bpm, $p = 0.222$).



E-FIGURE 1. Change from baseline in pre-dose FEV₁ (mL) over Weeks 0–24 (intent-to-treat population).
199x198mm (300 x 300 DPI)