

# Efficacy and safety evaluation of once-daily fluticasone furoate/vilanterol in Asian patients with asthma uncontrolled on a low- to mid-strength inhaled corticosteroid or low-dose inhaled corticosteroid/long-acting beta2-agonist

Jiangtao Lin, M.D.,<sup>1</sup> Huaping Tang, M.D.,<sup>2</sup> Ping Chen, M.D.,<sup>3</sup> Haoyan Wang, M.D.,<sup>4</sup> Mi-Kyeong Kim, M.D., Ph.D.,<sup>5</sup> Jodie Crawford, M.Sc.,<sup>6</sup> Loretta Jacques, Ph.D.,<sup>7</sup> and Sally Stone, B.Sc.<sup>7</sup>

## ABSTRACT

**Background:** Response to inhaled corticosteroid (ICS)/long-acting beta2-agonist (LABA) combinations varies across ethnic groups.

**Objective:** To investigate the efficacy and safety of the ICS/LABA combination fluticasone furoate/vilanterol (FF/VI) 100/25 µg in Asian patients with asthma.

**Methods:** A randomized (1:1), 12-week, double-blind, placebo-controlled, parallel group, multicenter phase III study of once-daily FF/VI 100/25 µg versus placebo in patients of Asian ancestry ages ≥12 years with asthma, uncontrolled on a low- to mid-strength ICS or low-dose ICS/LABA. The primary end point was the mean change from baseline in the daily evening peak expiratory flow. Secondary end points were the mean change from baseline in percentage rescue-free 24-hour periods, daily morning peak expiratory flow, percentage symptom-free 24-hour periods, Asthma Quality of Life Questionnaire score, adverse events, and severe exacerbations.

**Results:** The intent-to-treat population was 307 patients. There were significant ( $p < 0.001$ ) improvements from baseline for FF/VI 100/25 µg versus placebo in evening peak expiratory flow (51.0 L/min [95% confidence interval {CI}, 42.2–59.7 L/min]) and all secondary end points (percentage rescue-free 24-hour periods 21.8% [95% CI, 14.6–29.1%]; morning peak expiratory flow 52.9 L/min [95% CI, 44.2–61.6 L/min]; percentage symptom-free 24-hour periods 15.8% [95% CI, 9.4–22.3%]; Asthma Quality of Life Questionnaire score 0.52 [95% CI, 0.28, 0.75]). On-treatment adverse events were 35% with FF/VI ( $n = 2$  [serious]), 31% with placebo; severe exacerbations were FF/VI ( $n = 1$ ), placebo ( $n = 7$ ).

**Conclusions:** In patients of Asian ancestry, once-daily FF/VI 100/25 µg produced statistically and clinically significant improvements in efficacy end points versus placebo, with a generally similar safety profile. Results were consistent with a global phase III study of FF/VI 100/25 µg. Clinicaltrials.gov NCT01498679.

(Allergy Asthma Proc 37:302–310, 2016; doi: 10.2500/aap.2016.37.3968)

The prevalence of asthma, a chronic lung condition, in Asia is >2%, and this is expected to rise over the next decade.<sup>1</sup> Asthma is believed to be responsible for ~1

in every 250 deaths worldwide, although many of these are preventable.<sup>1</sup> When stepping up maintenance therapy for patients whose asthma is uncontrolled on a low-dose inhaled corticosteroid (ICS), a combination of ICS and long-acting  $\beta_2$  agonist (LABA) is recommended in preference to increasing the ICS dose.<sup>2</sup>

Fluticasone furoate (FF)/vilanterol (VI) is an ICS/LABA combination administered once daily that has 24 hours of efficacy in asthma.<sup>3–6</sup> FF/VI is approved as maintenance therapy for asthma in a number of countries and regions, including Japan,<sup>7</sup> Hong Kong,<sup>8</sup> Australia,<sup>9</sup> and the European Union.<sup>10</sup> FF/VI is also approved for the treatment of asthma that is not adequately controlled on a long-term asthma control medication in the United States.<sup>11</sup> Once-daily adminis-

From the <sup>1</sup>Department of Respiratory Diseases, China-Japan Friendship Hospital, Beijing, China, <sup>2</sup>Department of Respiratory Diseases, Qingdao Municipal Hospital, Qingdao, Shandong, China, <sup>3</sup>Department of Respiratory Diseases, General Hospital of Shenyang Military Region, Shenyang, Liaoning, China, <sup>4</sup>Department of Respiratory Medicine, Beijing Friendship Hospital, Capital Medical University, Xichen District, Beijing, China, <sup>5</sup>Subdivision of Allergy, Department of Internal Medicine, Chungbuk National University Hospital, Cheongju, South Korea, <sup>6</sup>Quantitative Sciences Division, GlaxoSmithKline, Uxbridge, United Kingdom, and <sup>7</sup>Respiratory Medicines Discovery and Development, GlaxoSmithKline, Uxbridge, United Kingdom

This study was funded by GlaxoSmithKline  
J. Lin has received speaker's honoraria from AstraZeneca, GlaxoSmithKline, and Merck Sharpe & Dohme, and has been a member of global advisory boards for Boehringer Ingelheim. J. Lin, S. Stone, and J. Crawford are employees of and hold stock in GlaxoSmithKline. The remaining authors have no conflicts of interest pertaining to this article  
Supplemental data available at [www.IngentaConnect.com](http://www.IngentaConnect.com)

Address correspondence to Jiangtao Lin, M.D., Department of Respiratory Diseases, China-Japan Friendship Hospital, Beijing 100029, China

E-mail address: [jiangtao\\_l@263.net](mailto:jiangtao_l@263.net)

Copyright © 2016, OceanSide Publications, Inc., U.S.A.

tration may help improve treatment adherence<sup>12–14</sup> and, therefore, asthma control.<sup>15</sup> ICS/LABA combinations are recommended by Asian guidelines<sup>16–18</sup> as maintenance treatment in asthma, but responses to treatment can vary across ethnic groups,<sup>19,20</sup> including Asian patients.<sup>20</sup> Therefore, there is a need to assess the response to potential treatments across ethnic groups.

The aim of this study was to evaluate the efficacy and safety of FF/VI 100/25  $\mu\text{g}$  versus placebo administered once daily *via* the ELLIPTA dry powder inhaler (GlaxoSmithKline [GSK], London, U.K.), over 12 weeks in adult patients of Asian ancestry with asthma currently treated with low- to mid-strength ICS or low-strength ICS/LABA. The study was designed to allow indirect comparison with a global 12-week study of FF/VI 100/25  $\mu\text{g}$ ,<sup>6</sup> and the entry criteria for the two studies were almost identical. A similar study in Asian patients, designed to compare FF/VI 200/25  $\mu\text{g}$  versus fluticasone propionate 500  $\mu\text{g}$ , was conducted.<sup>21</sup>

## METHODS

### Study Design and Patients

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter phase III study (GSK study HZA113719; clinicaltrials.gov registration NCT01498679) conducted at 27 centers in three countries (16 in China, 2 in Philippines, 9 in South Korea; 1 center in South Korea did not randomize any patients) between January 18, 2012, and July 16, 2013.

Male or female outpatients of Asian ancestry, ages  $\geq 12$  years (or  $\geq 18$  years if required by local regulations), with a diagnosis of asthma at least 12 weeks before screening and a forced expiratory volume in 1 second ( $\text{FEV}_1$ ) of 40–90% predicted normal and reversibility of  $\geq 12\%$  and  $\geq 200$  mL 10–40 minutes after two to four inhalations of salbutamol were eligible to participate. The patients must also have used ICS or ICS/LABA for at least 12 weeks before screening, at a dose equivalent to low to mid strength (100–250  $\mu\text{g}$ ) twice-daily fluticasone propionate, or twice-daily fluticasone propionate/salmeterol (100/50  $\mu\text{g}$ ), with stable disease for at least 4 weeks. Patients were not eligible if they had experienced life-threatening asthma in the past 10 years, respiratory infections that were unresolved 4 weeks before the start of the study, or exacerbations that required treatment with oral corticosteroids within 12 weeks before screening. Patients with any concurrent respiratory disease or other uncontrolled conditions, or with evidence of oral candidiasis at screening were also excluded. Patients were not eligible if they were current smokers or former smokers with a smoking history of  $\geq 10$  pack-years.

Combination therapy was stopped the day before screening, and the patients were switched to the same dose of ICS for the 2-week run-in period, with current

short-acting  $\beta$ -agonist medication replaced with salbutamol for use as needed. After the run-in period, the patients were randomized to treatment if they demonstrated a morning  $\text{FEV}_1$  of 40–90% of predicted normal and had recorded on a daily diary card a score of  $>1$  on the combined daytime and night-time asthma symptom scale or salbutamol use on at least 4 of the last 7 days of the run-in period. Patients were excluded at randomization if they had clinically significantly abnormal laboratory test results or electrocardiogram (ECG) data at screening, evidence of a severe exacerbation during the run-in period, or visual evidence of oral candidiasis. Patients were also excluded if they had changed asthma medication or showed culture-documented or suspected respiratory tract, sinus, or middle-ear infections during the run-in period that changed asthma management, or an ability to participate in the study. Details of previous and concomitant medications are summarized in Supplemental Appendix 1.

Written informed consent was obtained from each patient before the performance of any study-specific procedures, and the study was approved by local ethics committees and conducted in accordance with the Declaration of Helsinki<sup>22</sup> and Good Clinical Practice guidelines.<sup>23</sup> Author contribution and the role of funding source are as follows: J. Lin, S. Stone, and J. Crawford were involved in the conception and design of the study; J. Lin, H. Tang, P. Chen, H. Wang, and M.-K. Kim were involved in the acquisition of data; J. Lin, H. Tang, P. Chen, M.-K. Kim, J. Lin, S. Stone, and J. Crawford were involved in data analysis and/or interpretation. Employees of the sponsor were involved in the conception, design, and conduct of the study, and in data collection and analysis. All the authors, including the authors employed by the sponsor, participated in the development of the manuscript and approved the final version. The decision to submit for publication was that of the authors alone.

### Treatments

After a 2-week run-in period, eligible patients were randomized (1:1) to receive FF/VI 100/25  $\mu\text{g}$  (equivalent to a delivered dose of FF/VI 92/22  $\mu\text{g}$ ) or placebo, with both treatments delivered once daily in the evening for 12 weeks *via* the ELLIPTA dry powder inhaler. Randomization was by the RandAll Web-based system (GSK) and an Interactive Voice Response System (GSK). Treatment compliance was assessed at weeks 4, 8, and 12 by reviewing the dose counter on the inhaler, and follow-up contact was 1 week after the last dose of study medication. Patients were withdrawn from the study if they experienced a severe asthma exacerbation or worsening asthma, if they needed additional treatment for worsening asthma with a drug other than the

study medication or study-supplied salbutamol, or at the investigator's discretion.

## Outcome Measurements

The primary efficacy end point was the mean change from baseline in daily evening peak expiratory flow (PEF) averaged over the 12-week treatment period, measured by the patients, who used an electronic diary, with an integrated peak flow meter (AM3; eResearch Technology, Hoechst, Germany). Secondary efficacy end points were the mean change from baseline in the percentage rescue-free 24-hour periods during the 12-week treatment period recorded by patients who used the supplied electronic diary; the mean change from baseline in daily morning PEF averaged over the 12-week treatment period; the mean change from baseline in percentage symptom-free 24-hour periods during the 12-week treatment period, recorded by patients who used the supplied electronic diary; and change from baseline in overall Asthma Quality of Life Questionnaire score at week 12 (AQLQ + 12).

## Safety Evaluations

Safety end points included the incidence of adverse events (AE) (coded by using the Medical Dictionary for Regulatory Activities)<sup>24</sup> and serious AEs (SAE), including severe exacerbations and oropharyngeal candidiasis. AEs of special interest were defined by using preselected Medical Dictionary for Regulatory Activities preferred terms and based on the known drug class AE profile or pharmacology of corticosteroids (*i.e.*, hypersensitivity, bone disorders, local steroid effects [*e.g.*, oral candidiasis, hoarseness], ocular effects, glucose effects, pneumonia, lower respiratory tract infections, and systemic effects [*e.g.*, hypothalamic-pituitary-adrenal axis]) and LABAs (*i.e.*, cardiovascular effects, effects on potassium, effects on glucose). Clinical laboratory assessments (hematology, clinical chemistry, and liver function) were performed at screening and at week 12, vital signs (pulse rate, blood pressure) at every visit from screening to week 12, and 12-lead ECG data at screening and week 12.

## Statistical Analysis

It was planned to screen 600 patients, to provide 302 evaluable patients for randomization into two treatment groups of 151, which provides 90% power to detect a treatment difference for FF/VI 100/25  $\mu\text{g}$  compared with placebo of 15 L/min in daily evening PEF averaged over the treatment period. Evaluable patients were defined as those who provided evening PEF data for at least 4 of the 7 days before randomization and at least 4 days after randomization. All randomized patients who received at least one dose of study treatment were included in the intent-to-treat (ITT) popu-

lation; the per-protocol population comprised all patients in the ITT population without any full protocol deviations.

Unless otherwise stated, all efficacy end points were analyzed for the ITT population by using an analysis of covariance model with treatment effects due to baseline, region, sex, age, and treatment group; the primary end point analysis included only evaluable patients. A supporting analysis by using a repeated measures model at each week on the ITT population and five additional sensitivity analyses were performed to assess the impact of missing evening PEF data (mainly due to early withdrawal) (see Supplemental Appendix 2). Pairwise comparisons with the per-protocol population were also performed for the primary efficacy end point. Withdrawals due to a lack of efficacy were analyzed by using Fisher's exact test.

Data were analyzed by using a step-down closed testing procedure applied to a predefined statistical hierarchy, whereby failure to achieve significance ( $p = <0.05$ ) for the previous treatment comparison of FF/VI 100/25  $\mu\text{g}$  versus placebo in the hierarchy meant that significance could not be inferred for any of the remaining end points. The hierarchy was applied to the efficacy end points in the following order: (1) evening PEF, (2) rescue-free 24-hour periods, (3) morning PEF, (4) symptom-free 24-hour periods, (5) AQLQ + 12.

## RESULTS

### Study Population

Of the 311 patients randomized, 307 were included in the ITT population and 196 (64%) completed the study (Fig. 1). Most patients in the FF/VI 100/25  $\mu\text{g}$  group completed the study ( $n = 131$  [86%]) compared with 65 patients (42%) in the placebo group; the most common reason for withdrawal in the placebo group was lack of efficacy ( $n = 72$  [47%]). Patient demographics and screening and baseline characteristics are presented in Table 1. Most patients (88%) were between 18 and 64 years old, and 56% were female patients. The mean percentage predicted FEV<sub>1</sub> improved during the run-in period, from 65.92% at screening to 68.99% at baseline in the ITT population. The mean treatment compliance was high (97.5% with FF/VI 100/25  $\mu\text{g}$ ; 104.7% with placebo).

### Efficacy

For the primary end point of daily evening PEF, there was an improvement from baseline with FF/VI 100/25  $\mu\text{g}$  (mean  $\pm$  standard error,  $39.2 \pm 3.14$  L/min) and a decrease with placebo (mean  $\pm$  standard error,  $-11.8 \pm 3.16$  L/min) (Table 2, Fig. 2). The adjusted treatment difference for FF/VI 100/25  $\mu\text{g}$  compared with placebo (51.0 L/min [95% confidence interval {CI}, 42.2–59.7 L/min]) was clinically and statistically

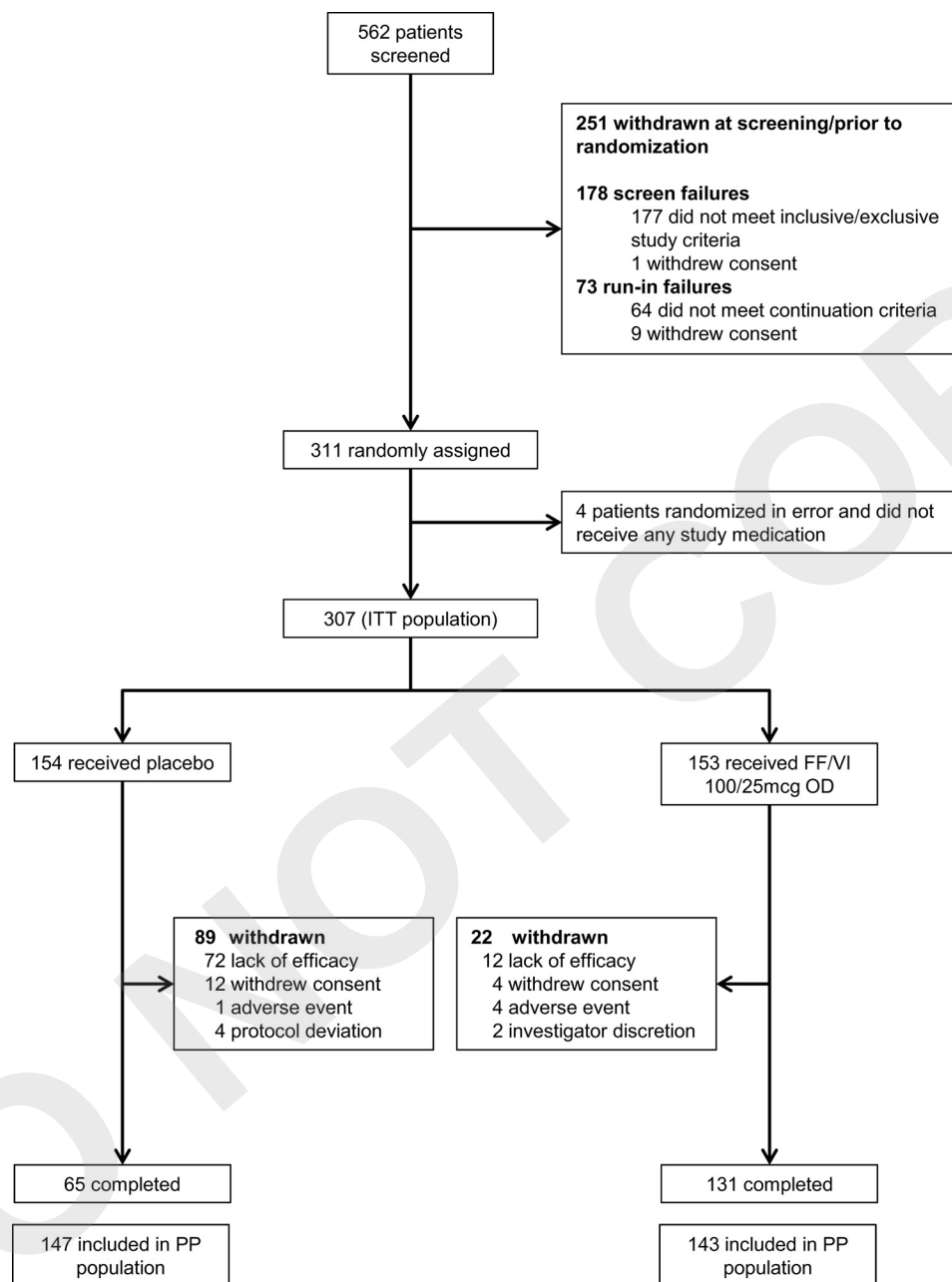


**Figure 1.** Patient flow. FF = Fluticasone furoate; ITT = intent to treat; OD = once daily; PP = per protocol; VI = vilanterol.

significant ( $p = <0.001$ ) (Table 2, Fig. 3). Similar results were seen in the PP population (data not shown). There was a higher proportion of missing data in the placebo group due to the higher early withdrawal rate compared with the FF/VI 100/25  $\mu\text{g}$  group (Supplemental Fig. 1). Supporting and sensitivity analyses supported the findings of the primary analysis of change from baseline in evening PEF (Supplemental Fig. 2).

The change from baseline and the adjusted treatment differences for the secondary end points are presented in Table 3 and Fig. 3. There were improvements from baseline with both FF/VI 100/25  $\mu\text{g}$  and placebo for

percentage rescue-free 24-hour periods, percentage symptom-free 24-hour periods, and overall AQLQ + 12 score. For daily morning PEF, there was an improvement from baseline with FF/VI 100/25  $\mu\text{g}$  and deterioration from baseline with placebo. The adjusted treatment differences for FF/VI 100/25  $\mu\text{g}$  versus placebo were statistically significant ( $p = <0.001$ ) for all secondary end points (percentage rescue-free 24-hour periods: 21.8% [95% CI, 14.6–29.1%], equivalent to 1.5 additional days per week without rescue use; morning PEF: 52.9 L/min [95% CI, 44.2–61.6 L/min]; percentage symptom-free 24-hour periods: 15.8% [95% CI, 9.4–22.3], equivalent to an additional 1.1. days per week

Table 1 Patient demographics, screening, and baseline characteristics (ITT population)

| Demographic                                        | Placebo (N = 154) | FF/VI 100/25 µg OD (N = 153) | Total (N = 307) |
|----------------------------------------------------|-------------------|------------------------------|-----------------|
| Age, mean (SD), y                                  | 47.4 ± 13.90      | 47.0 ± 14.01                 | 47.2 ± 13.94    |
| Female sex, no. (%)                                | 88 (57)           | 83 (54)                      | 171 (56)        |
| Duration of asthma, mean (SD), y                   | 11.72 ± 11.527    | 11.17 ± 11.934               | 11.45 ± 11.716  |
| Screening characteristics                          |                   |                              |                 |
| Prebronchodilator FEV <sub>1</sub> , mean (SD), L  | 1.789 ± 0.5921    | 1.769 ± 0.5384               | 1.779 ± 0.5651  |
| Predicted FEV <sub>1</sub> , mean (SD), %          | 66.45 ± 13.090    | 65.38 ± 13.120               | 65.92 ± 13.095  |
| Postbronchodilator FEV <sub>1</sub> , mean (SD), L | 2.241 ± 0.6852    | 2.236 ± 0.6755               | 2.238 ± 0.6793  |
| Reversibility FEV <sub>1</sub> , mean (SD), %      | 27.17 ± 13.237    | 27.19 ± 12.145               | 27.18 ± 12.683  |
| Baseline characteristics                           |                   |                              |                 |
| Prebronchodilator FEV <sub>1</sub> , mean (SD), L  | 1.862 ± 0.5694    | 1.852 ± 0.5536               | 1.857 ± 0.5607  |
| Predicted FEV <sub>1</sub> , mean (SD), %          | 69.57 ± 13.197    | 68.40 ± 12.972               | 68.99 ± 13.077  |
| Symptom-free 24-hr periods, mean (SD), %           | 7.9 ± 19.83       | 7.5 ± 18.38                  | 7.7 ± 19.09*    |
| Rescue-free 24-hr periods, mean (SD), %            | 26.5 ± 37.49      | 18.2 ± 32.19                 | 22.4 ± 35.14*   |

ITT = intent to treat; FF = fluticasone furoate; VI = vilanterol; OD = once daily; SD = standard deviation; FEV<sub>1</sub> = forced expiratory volume in 1 second.

\*From post hoc analysis.

Table 2 Statistical analysis of change from baseline in daily evening PEF (L/min), weeks 1–12 (ITT population)

|                               | Placebo (N = 154) | FF/VI 100/25 µg OD (N = 153) |
|-------------------------------|-------------------|------------------------------|
| No. patients                  | 151               | 153                          |
| LS mean                       | 270.2             | 321.2                        |
| LS change, mean ± SE          | −11.8 ± 3.16      | 39.2 ± 3.14                  |
| FF/VI 100/25 µg OD vs placebo |                   |                              |
| Difference (95% CI)           |                   | 51.0 (42.2–59.7)             |
| p Value                       |                   | <0.001                       |

PEF = peak expiratory flow; ITT = intent to treat; FF = fluticasone furoate; VI = vilanterol; OD = once daily; LS = least squares; SE = standard error; CI = confidence interval.

without symptoms; overall AQLQ + 12 score: 0.52 [95% CI, 0.28–0.75]).

### Safety Results

A summary of on-treatment AEs and the most-frequent on-treatment AEs is presented in Table 4. The incidence of on-treatment AEs was 35% with FF/VI 100/25 µg and 31% with placebo, with one additional posttreatment AE in the FF/VI 100/25 µg group. The most frequently reported on-treatment AE was upper respiratory tract infection reported by a similar proportion of patients with FF/VI 100/25 µg ( $n = 11$  [7%]) and placebo ( $n = 14$  [9%]).

The incidence of treatment-related (in the opinion of the investigator) AEs was 9% with FF/VI 100/25 µg and 2% with placebo. One on-treatment SAE with FF/VI 100/25 µg was atrial fibrillation ( $n = 1$ ) and was considered by the investigator to be treatment related and led to withdrawal of the patient from the study.

The patient was a 52-year-old woman with a medical history of atrial fibrillation. The event occurred on study day 62, was of moderate intensity, and of 24 days' duration. A further on-treatment SAE with FF/VI 100/25 µg was acute enteritis ( $n = 1$ ), this was not considered to be treatment related and did not lead to the withdrawal of the patient from the study. There were no on-treatment SAEs with placebo. No deaths occurred during the study.

Five patients (FF/VI 100/25 µg [ $n = 4$ ], placebo [ $n = 1$ ]) withdrew from the study due to AEs. More patients in the FF/VI 100/25 µg group (12 [8%]) reported AEs of special interest than in the placebo group (5 [3%]). Eight AEs of special interest reported by seven patients were considered treatment related (FF/VI 100/25 µg [one atrial fibrillation and hypertension, one each for arrhythmia, increased blood pressure, dysphonia, oropharyngeal pain, and bronchitis]; placebo [one rash pruritus]). There were no reports of pneumonia.

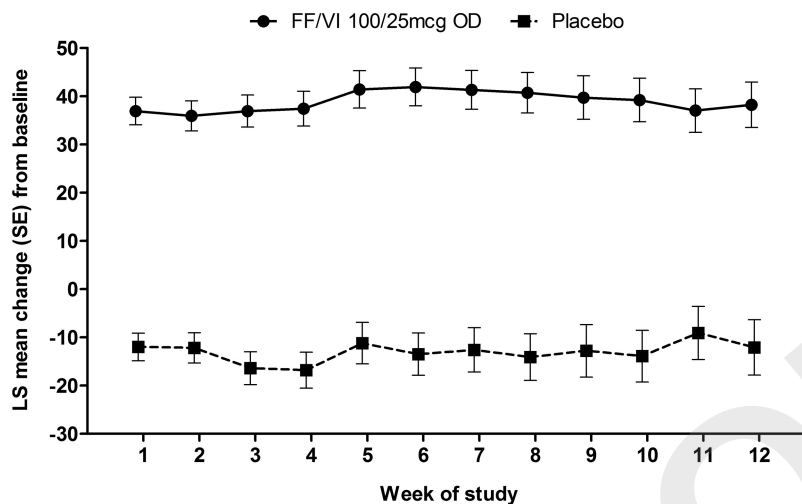


**Figure 2.** Repeated measures analysis of change from baseline in daily evening PEF (L/min) (ITT population). FF = Fluticasone furoate; ITT = intent to treat; LS = least squares; OD = once daily; PEF = peak expiratory force; SE = standard error; VI = vilanterol.

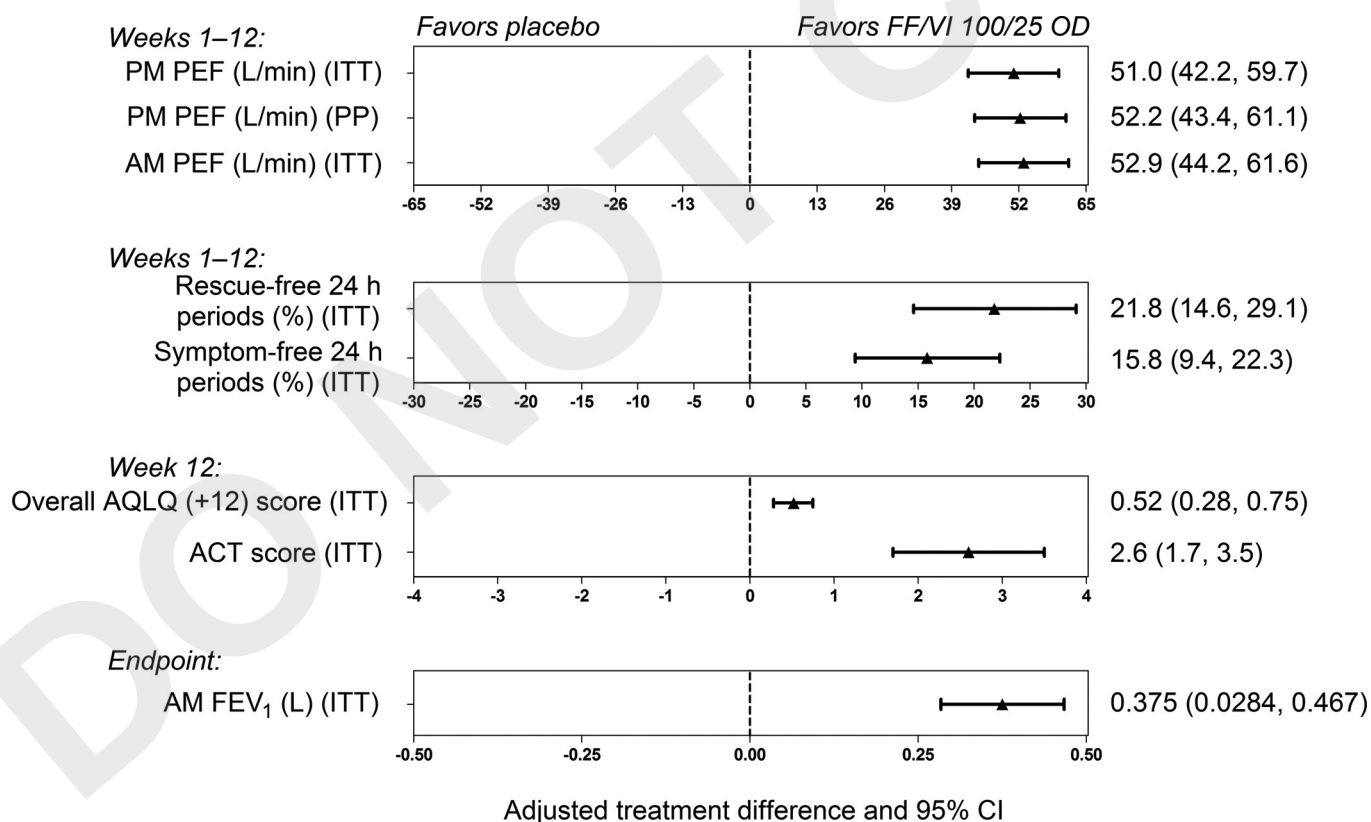


**Figure 3.** Adjusted treatment differences for all end points (ITT population). ACT = Asthma Control Test; AM = morning; AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; FEV<sub>1</sub> = forced expiratory volume in 1 second; FF = fluticasone furoate; ITT = intent-to-treat; OD = once daily; PEF = peak expiratory flow; PM = evening; PP = per-protocol; VI = vilanterol.

Severe asthma exacerbations were reported for eight patients (FF/VI,  $n = 1$ ; placebo,  $n = 7$ ); all severe asthma exacerbations were experienced while on treatment, and all the patients were withdrawn from the study. One patient in the placebo group also experienced an upper respiratory tract infection of mild intensity that started on day 4, which resolved after 7

days, and nasopharyngitis of mild intensity that started on day 41, which resolved after 3 days, before the severe asthma exacerbation on day 59. There was no evidence of any abnormal results for clinical chemistry, liver function, or hematology assessments, or abnormal vital signs, blood pressure, or ECG parameters.

Table 3 Statistical analysis of change from baseline for secondary end points (ITT population)

|                                                   | Placebo (N = 154) | FF/VI 100/25 µg OD (N = 153) |
|---------------------------------------------------|-------------------|------------------------------|
| Percentage of rescue-free 24-hr periods, wk 1–12  |                   |                              |
| No. patients                                      | 154               | 153                          |
| LS mean ± SE change                               | 8.3 ± 2.59        | 30.1 ± 2.60                  |
| FF/VI 100/25 µg OD vs placebo                     |                   |                              |
| Difference (95% CI)                               |                   | 21.8 (14.6–29.1)             |
| p Value                                           |                   | <0.001                       |
| Equivalent no. additional rescue-free days per wk |                   |                              |
| LS mean change from baseline                      | 0.6               | 2.1                          |
| LS mean difference to placebo                     |                   | 1.5                          |
| Morning PEF (L/min), wk 1–12                      |                   |                              |
| No. patients                                      | 153               | 153                          |
| LS mean                                           | 269.4             | 322.3                        |
| LS mean ± SE change                               | −9.3 ± 3.12       | 43.6 ± 3.12                  |
| FF/VI 100/25 µg OD vs placebo                     |                   |                              |
| Difference (95% CI)                               |                   | 52.9 (44.2, 61.6)            |
| p Value                                           |                   | <0.001                       |
| Percentage of symptom-free 24-hr periods, wk 1–12 |                   |                              |
| No. patients                                      | 154               | 153                          |
| LS mean ± SE change                               | 9.0 (2.30)        | 24.8 (2.31)                  |
| FF/VI 100/25 µg OD vs placebo                     |                   |                              |
| Difference (95% CI)                               |                   | 15.8 (9.4–22.3)              |
| p Value                                           |                   | <0.001                       |
| Equivalent no. additional rescue-free days per wk |                   |                              |
| LS mean change from baseline                      | 0.6               | 1.7                          |
| LS mean difference to placebo                     |                   | 1.1                          |
| Overall AQLQ score, wk 12                         |                   |                              |
| No. patients                                      | 71                | 135                          |
| LS mean                                           | 4.87              | 5.39                         |
| LS mean ± SE change                               | 0.33 ± 0.094      | 0.84 ± 0.068                 |
| FF/VI 100/25 µg OD vs placebo                     |                   |                              |
| Difference (95% CI)                               |                   | 0.52 (0.28–0.75)             |
| p Value                                           |                   | <0.001                       |

ITT = intent to treat; FF = fluticasone furoate; VI = vilanterol; OD = once daily; LS = least squares; SE = standard error; CI = confidence interval; PEF = peak expiratory flow; AQLQ = Asthma Quality of Life Questionnaire.

## DISCUSSION

In this study, we assessed the efficacy and safety of once-daily FF/VI 100/25 µg over 12 weeks in Asian patients ages ≥12 years, with asthma. Statistically significant and clinically relevant improvements in daily evening PEF were observed for the comparison of FF/VI 100/25 µg versus placebo. There also were statistically significant improvements for FF/VI 100/25 µg compared with placebo for all secondary end points (percentage rescue-free 24-hour periods, morning PEF, percentage symptom-free 24-hour periods, and overall AQLQ score). The safety profile of FF/VI 100/25 µg was similar to placebo, although there was a numerically higher incidence of AEs and drug-related AEs with FF/VI 100/25 µg than with placebo. The overall

incidence of SAEs was low in both treatment groups, and there were no deaths.

There was an improvement from baseline in daily evening PEF with FF/VI 100/25 µg, whereas a reduction in daily evening PEF was noted for patients who received placebo; despite the high number of early withdrawals in this study, sensitivity analyses of the impact of missing evening PEF data confirmed that the results with FF/VI 100/25 µg were robust. The statistically significant improvement in daily evening PEF for FF/VI 100/25 µg versus placebo is higher in this study (51.0 L/min) than in a previous global study that also compared FF/VI 100/25 µg with placebo,<sup>6</sup> in which the adjusted treatment difference at week 12 was 28.2 L/min (Supplemental Table 1). In the global

Table 4 Overview of AEs and most-frequent AEs ( $\geq 3\%$  in either treatment arm) (ITT population)

|                                                                         | Placebo, no.<br>(%) (N = 154) | FF/VI 100/25 $\mu\text{g}$ OD, no. (%)<br>(N = 153) |
|-------------------------------------------------------------------------|-------------------------------|-----------------------------------------------------|
| On-treatment AEs                                                        |                               |                                                     |
| Any AE                                                                  | 47 (31)                       | 53 (35)                                             |
| Treatment-related AEs*                                                  | 3 (2)                         | 14 (9)                                              |
| Any SAEs                                                                | 0                             | 2 (1)#                                              |
| Most-frequent on-treatment AEs ( $\geq 3\%$ in<br>either treatment arm) |                               |                                                     |
| Upper respiratory tract infection                                       | 14 (9)                        | 11 (7)                                              |
| Nasopharyngitis                                                         | 13 (8)                        | 7 (5)                                               |
| Headache                                                                | 3 (2)                         | 7 (5)                                               |
| Pyrexia                                                                 | 3 (2)                         | 4 (3)                                               |

AE = Adverse event; ITT = intent to treat; FF = fluticasone furoate; VI = vilanterol; OD = once daily; SAE = serious adverse event.

\*In the opinion of the investigator.

#On-treatment SAEs for FF/VI 100/25  $\mu\text{g}$ : cardiac disorders, 1 ( $<1\%$ ); gastrointestinal disorders, 1 ( $<1\%$ ).

study, statistical significance could not be inferred due to the use of a step-down statistical hierarchy. For a morning PEF, a greater improvement for FF/VI 100/25  $\mu\text{g}$  versus placebo was also seen in this study (52.9 L/min;  $p = <0.001$ ) compared with numerical improvements in the global study (33.3 L/min).<sup>6</sup> Although a 12-hour postdose morning FEV<sub>1</sub> is not a trough measurement, the statistically significant improvement with FF/VI 100/25  $\mu\text{g}$  versus placebo of 0.375 L (95% CI, 0.0284–0.467;  $p = <0.001$ ) supported the observed improvement in evening PEF; however, it should be noted that results for a 24-hour postdose lung function end points are more likely to reflect the 24-hour duration of action of FF/VI.

In the global study, statistical significance could not be inferred due to the use of a statistical hierarchy testing procedure for the improvement in the percentage of rescue-free 24-hours period (19.3% [95% CI, 13.0–25.6%])<sup>6</sup>; however, the similar improvement observed in the present study was found to be statistically significant (21.8%;  $p = <0.001$ ). The statistically significant improvements in the percentage symptom-free 24-hour periods for FF/VI 100/25  $\mu\text{g}$  versus placebo were of similar magnitude in the present study (15.8%;  $p = <0.001$ ) compared with the numerical improvements in the global study (18.0% [95% CI, 12.0–23.9%]).<sup>6</sup> Improvements in the overall AQLQ + 12 score were statistically significant and higher than the minimally important difference of 0.5<sup>25</sup> for the adjusted treatment comparison of FF/VI 100/25  $\mu\text{g}$  versus placebo (0.52), whereas the improvement versus placebo in the global study<sup>6</sup> was less than the minimally important difference (0.30).

A slightly greater proportion of patients reported AEs with FF/VI 100/25  $\mu\text{g}$  than with placebo, which

may be partially explained by the increased exposure to study medication in the FF/VI 100/25  $\mu\text{g}$  group, which was due to the high rate of withdrawal in the placebo group. The low incidences of SAEs, local steroid effects, LABA-related effects (including cardiovascular effects), and the absence of safety concerns related to clinical laboratory assessments, vital signs, and ECG parameters were generally consistent with the safety findings from other FF/VI studies,<sup>3,4,6</sup> including those that assessed FF/VI at the 100/25  $\mu\text{g}$  strength.<sup>4,6,26</sup>

The recruitment of patients currently treated with low- to mid-strength ICS or low-strength ICS/LABA represented a suitable patient population in terms of disease severity for evaluation of the 100/25  $\mu\text{g}$  strength of FF/VI. Compliance of patients in this study with study medication was very good. The treatment duration of 12 weeks was considered sufficient to demonstrate efficacy and short-term safety in this study population. However, the 12-week treatment duration was not sufficient to assess any long-term potential safety concerns, such as whether FF/VI 100/25  $\mu\text{g}$  has an effect on exacerbation frequency or severity. Although this is a limitation when studying a medicine for a chronic condition such as asthma, the effect of FF/VI was assessed in a previous study and was found to reduce the risk of severe asthma exacerbations when compared with FF alone.<sup>5</sup> The present study was placebo controlled, with strict withdrawal criteria at signs of worsening asthma to protect the patient, and the study design enabled comparison of results with the global study, with which the results were generally consistent.<sup>6</sup> However, the lack of an active control meant that the treatment effects of FF/VI 100/25  $\mu\text{g}$  could not be directly compared with other currently

available therapies, as has been investigated in previous FF/VI studies.<sup>4,26</sup>

## CONCLUSION

This study of patients of Asian ancestry, ages  $\geq 12$  years, with persistent asthma, uncontrolled on low- to mid-dose ICS or low-dose ICS/LABA, once-daily FF/VI 100/25  $\mu\text{g}$  produced a statistically and clinically significant improvement in daily evening PEF compared with placebo. This finding was supported by statistically significant improvements for FF/VI 100/25  $\mu\text{g}$  versus placebo for the remaining efficacy end points. FF/VI 100/25  $\mu\text{g}$  was generally well tolerated compared with placebo. Overall, these findings with FF/VI 100/25  $\mu\text{g}$  generally were consistent with those reported for the same strength of FF/VI in a previous phase III global study.<sup>6</sup>

## ACKNOWLEDGMENTS

The authors thank Pinal Patel (GSK) for his contributions to the analysis and interpretation of data and to the development of this manuscript, and thank the investigators who were involved in the recruitment of patients to this study.

## REFERENCES

1. Global Initiative for Asthma (GINA). Global Burden of Asthma. Available online at [http://ginasthma.org/local/uploads/files/GINABurdenReport\\_1.pdf](http://ginasthma.org/local/uploads/files/GINABurdenReport_1.pdf); accessed October 9, 2015.
2. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2014. Available online at <http://www.ginasthma.org/>; accessed October 9, 2015.
3. O'Byrne PM, Bleecker ER, Bateman ED, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. *Eur Respir J* 43:773–782, 2014.
4. Woodcock A, Bleecker ER, Lötval J, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: A randomized trial. *Chest* 144: 1222–1229, 2013.
5. Bateman ED, O'Byrne PM, Busse WW, et al. Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. *Thorax* 69:312–319, 2014.
6. Bleecker ER, Lötval J, O'Byrne PM, et al. Fluticasone furoate-vilanterol 100–25 mcg compared with fluticasone furoate 100 mcg in asthma: A randomized trial. *J Allergy Clin Immunol Pract* 2:553–561, 2014.
7. Relvar ELLIPTA [package insert], GlaxoSmithKline, Tokyo, Japan. Available online at <https://www.healthgsk.jp/content/dam/HCP%20Japan/ja/documents/products-basic-info/relvar/relvar.pdf>; accessed October 9, 2015.
8. Drug Office, Department of Health, the Government of the Hong Kong Special Administrative Region. Relvar ELLIPTA inhalation powder, pre-dispensed 200 mcg/25 mcg. Available online at <http://drugoffice.gov.hk/eps/productDetailActionNew.do?lang=en&section=consumer&id=120811>; accessed October 9, 2015.
9. Breo ELLIPTA product information, Australia. Available online at [http://www.gsk.com.au/products\\_prescription-medicines\\_detail.aspx?view=1610](http://www.gsk.com.au/products_prescription-medicines_detail.aspx?view=1610); accessed October 9, 2015.
10. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Summary of opinion (initial authorisation): Relvar Ellipta. September 19, 2013. Available online at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Summary\\_of\\_opinion\\_-\\_Initial\\_authorisation/human/002673/WC500150090.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002673/WC500150090.pdf); accessed October 9, 2015.
11. Breo ELLIPTA product information, United States. Available online at [www.gsksource.com/pharma/content/dam/Glaxo-SmithKline/US/en/Prescribing\\_Information/Breo\\_Ellipta/pdf/BREO-ELLIPTA-PI-MG.PDF](http://www.gsksource.com/pharma/content/dam/Glaxo-SmithKline/US/en/Prescribing_Information/Breo_Ellipta/pdf/BREO-ELLIPTA-PI-MG.PDF); accessed January 22, 2016.
12. Guest JF, Davie AM, Ruiz FJ, and Greener MJ. Switching asthma patients to a once-daily inhaled steroid improves compliance and reduces healthcare costs. *Prim Care Respir J* 14:88–98, 2005.
13. Price D, Robertson A, Bullen K, et al. 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.
14. Cochrane GM. Compliance and outcomes in patients with asthma. *Drugs* 52(suppl. 6):12–19, 1996.
15. Emilsson M, Berndtsson I, Lötval J, et al. The influence of personality traits and beliefs about medicines on adherence to asthma treatment. *Prim Care Respir J* 20:141–147, 2011.
16. The Chinese Medical Association. Chinese society of respiratory diseases asthma. Asthma prevention guide (definition, diagnosis, treatment and management of bronchial asthma). *Chinese Journal of tuberculosis and respiratory*. (Chinese guideline) 2008, 31:177–185.
17. Philippine Consensus Report on the Diagnosis and Management of Asthma, 2008. Available online at <http://philchest.org/publications/clinical-practice-guidelines/>; accessed October 9, 2015.
18. Korean Asthma Management Guideline for Adults. The Korean Academy of Asthma, Allergy and Clinical Immunology, 2011. Available online at [http://www.allergy.or.kr/file/2011\\_new.pdf](http://www.allergy.or.kr/file/2011_new.pdf); accessed October 9, 2015.
19. Bjornsson TD, Wagner JA, Donahue SR, et al. A review and assessment of potential sources of ethnic differences in drug responsiveness. *J Clin Pharmacol* 43:943–967, 2003.
20. Huang SM, and Temple R. Is this the drug or dose for you? Impact and consideration of ethnic factors in global drug development, regulatory review, and clinical practice. *Clin Pharmacol Ther* 84:287–294, 2008.
21. Lin J, Kang J, Lee SH, et al. Fluticasone furoate/vilanterol 200/25mcg in Asian asthma patients: A randomised trial. *Respir Med* 109:44–53, 2015.
22. WMA Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended (latest) by the 59th WMA General Assembly, Seoul, Korea, October 2008. Date last updated: October 2008. Available online at <http://www.wma.net/en/30publications/10policies/b3/index.html>; accessed October 9, 2015.
23. International Conference on Harmonisation Tripartite Guideline: Guidance for Good Clinical Practice E6 (R1). 1996. Available online at [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6/E6\\_R1\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf); accessed October 9, 2015.
24. Medical Dictionary for Regulatory Activities. Available online at <http://www.meddra.org/>; accessed May 16, 2016.
25. Juniper EF, Guyatt GH, Willan A, and Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. *J Clin Epidemiol* 47:81–87, 1994.
26. Busse WW, O'Byrne PM, Bleecker ER, et al. Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the  $\beta_2$  agonist vilanterol administered once daily for 52 weeks in patients  $\geq 12$  years old with asthma: A randomised trial. *Thorax* 68:513–520, 2013. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.