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Fluticasone furoate/vilanterol 200/25 mcg in Asian asthma patients: A randomized trial

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Efficacy;
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Summary
Background: This study investigated the efficacy and safety of the inhaled corticosteroid (ICS)/long-acting beta$_2$-agonist (LABA) combination fluticasone furoate (FF)/vilanterol (VI) in Asian asthma patients.
Methods: A 12-week, double-blind, double-dummy, active-comparator, parallel-group, multicenter study. 309 Asian asthma patients (≥12 years, uncontrolled with high-strength ICS or mid-dose ICS/LABA) were randomized (1:1) and included in the intent-to-treat population; 155 received once-daily FF/VI 200/25 mcg and 154 received twice-daily fluticasone propionate (FP) 500 mcg. The primary endpoint was change from baseline in daily evening peak expiratory flow (PEF) averaged over 12 weeks. Secondary endpoints were mean change from baseline in % rescue-free 24-h periods, daily morning PEF, % symptom-free 24-h periods, and overall Asthma Quality of Life Questionnaire score. Safety assessments were performed.
Results: For change from baseline in daily evening PEF, the adjusted mean treatment difference for FF/VI versus FP of 28.5 L/min (95% confidence interval [CI]: 20.1, 36.9) was clinically and statistically significant ($p < 0.001$). For change from baseline in % rescue-free 24-h periods, the adjusted mean treatment difference (1.0%; 95% CI: −7.3, 9.2) was not statistically

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significant ($p = 0.821$). Statistical significance could not be inferred for the remaining endpoints due to the statistical hierarchy employed. Incidence of on-treatment adverse events was similar with FF/VI (26%; 3% treatment-related; $n = 1$ serious) and FP (27%; 3% treatment-related; $n = 2$ serious); none were fatal. No further safety concerns were identified.

Conclusions: FF/VI improved evening PEF over 12 weeks versus FP in Asian patients, with a similar safety profile. The results are generally consistent with a global study comparing the same treatments.

Introduction

Background

Asthma is a chronic condition affecting over 300 million people worldwide, and, although the prevalence of asthma in Asia is generally low [1], it is increasing [2]. Inhaled corticosteroids (ICSs) are considered the most effective anti-inflammatory treatments for all severities of asthma and their use is recommended by global [2], Chinese [3], Filipino [4], and Korean guidelines [5]. For patients with asthma uncontrolled with low-strength ICS alone, an ICS/long-acting beta$_2$-agonist (LABA) combination is recommended in preference to increasing ICS strength [2—5]. Another factor contributing to poor asthma control is sub-optimal adherence [6] and it has been demonstrated that once-daily therapy may help to improve treatment adherence in asthma patients [7—9]. As asthma control across Asian countries is sub-optimal [10,11], a once-daily ICS/LABA combination may be a useful treatment option for Asian asthma patients.

Fluticasone furoate (FF)/vilanterol (VI) is a once-daily ICS/LABA combination that has 24-h efficacy in asthma patients [12—15]. In a global study, FF/VI 200/25 mcg once daily has demonstrated statistically significant improvements in lung function compared with fluticasone propionate (FP) 500 mcg twice daily [12], which is an established ICS maintenance therapy for asthma [2].

It is known that responses to treatment can vary across ethnic groups [16,17], including in Asians [17]. The aim of this study was to evaluate the efficacy and safety of FF/VI 200/25 mcg once daily, administered via the ELLIPTA®[1] dry powder inhaler, in adult asthma patients of Asian ancestry whose asthma was uncontrolled with high-strength ICS or mid-strength ICS/LABA. FP 500 mcg twice daily was included as an active control because it was considered an appropriate treatment for this patient population. Additionally, the comparison of FF/VI 200/25 mcg once daily versus FP 500 mcg twice daily has previously been investigated in a global study, allowing indirect comparison of the findings of this study conducted in Asia with those from the global study, which was conducted in Germany, Japan, Poland, Romania, Russia, and the United States [12].

Methods

Study design and patients

This was a randomized, double-blind, double-dummy, active-comparator, parallel-group, multicenter study (GSK study number: HZA113714; clinicaltrials.gov registration number: NCT01498653) conducted at 24 centers in 3 countries (12 China, 10 South Korea, 2 the Philippines) between January 17, 2012 and February 1, 2013. After a 2-week run-in period, eligible patients were randomized (1:1) to FF/VI 200/25 mcg once daily, delivered in the evening via the ELLIPTA dry powder inhaler (equivalent to a delivered dose of FF/VI 184/22 mcg), or FP 500 mcg twice daily delivered via the DISKUS inhaler, for 12 weeks. The randomization schedule was created using a validated computer system (RandAll [GSK, London, UK]). Randomization was conducted following a telephone call to the Registration and Medication Ordering System (RAMOS [GSK, London, UK]), in accordance with the randomization schedule. Follow-up contact was performed 1 week after the last dose of study medication was taken.

To be eligible at screening, male or female outpatients, aged 12 years or over (18 years or over if required by local regulations) with a diagnosis of asthma at least 12 weeks prior to screening had to demonstrate a forced expiratory volume in one second (FEV_1) of 40—90% predicted normal and reversibility of $\geq$12% and $\geq$200 mL 10—40 min after 2—4 inhalations of albuterol (salbutamol). Predicted FEV_1 values were based upon National Health and Nutrition Examination Survey III, using the Asian adjustment [18]. Patients should have been using ICS or ICS/LABA for at least 12 weeks prior to screening, and at a stable strength for at least 4 weeks prior (equivalent to FP 500 mcg twice daily without a LABA, or FP/salmeterol 250/50mcg twice daily). Patients were not eligible if they were current smokers or had a smoking pack history $\geq$10 pack-years, had experienced life-threatening asthma within the last 10 years, had respiratory conditions that had not been resolved within 4 weeks of screening, had an exacerbation requiring treatment with oral corticosteroids within 12 weeks, if they had a concurrent respiratory disease or any other uncontrolled condition, or if they had evidence of oral candidiasis.

[1] ELLIPTA is a registered trademark of the GlaxoSmithKline group of companies.

During the 2-week run-in period, all patients continued on their current ICS therapy and were required to cease LABA therapy the day before screening. A change was made to the protocol allowing some patients who were receiving ICS/LABA to switch to an equivalent dose of another ICS, if the same ICS was not available as a standalone formulation due to hospital prescribing lists. Additionally, patients' current short-acting beta$_2$-agonist reliever medication was replaced with albuterol for use as-needed.

After run-in, patients were randomized to treatment if they demonstrated a morning FEV_1 of 40–90% predicted normal and had recorded either a score $\geq$3 on the combined daytime and night-time asthma symptom scale or albuterol use on at least 4 of the last 7 days of run-in on a daily-diary card. Patients were excluded if they had clinically significant abnormal laboratory tests or electrocardiogram (ECG) data at screening, changes in asthma medication, or a respiratory tract, sinus or middle-ear infection during run-in that changed asthma management or their ability to participate in the study. Treatment compliance was assessed throughout the study by reviewing the dose-counter on the patients' inhaler. Concomitant medication use is summarized in e-Appendix 1.

Written, informed consent was obtained from each patient prior to the performance of any study procedures, and the study was approved by local ethics committees and conducted in accordance with the Declaration of Helsinki [19] and Good Clinical Practice guidelines [20].

Outcome measurements

The primary efficacy endpoint was mean change from baseline in daily evening peak expiratory flow (PEF) averaged over the 12-week treatment period, which was measured by patients using an electronic diary with integrated peak flow meter (the AM3 device [eResearchTechnology, Hoechberg, Germany]).

The secondary efficacy endpoints were mean change from baseline in % rescue-free 24-h periods during the 12-week treatment period, recorded using the electronic diary; mean change from baseline in daily morning PEF averaged over the 12-week treatment period; mean change from baseline in % symptom-free 24-h periods during the 12-week treatment period, recorded using the electronic diary; and change from baseline in overall Asthma Quality of Life Questionnaire (AQLQ [+12]) score at Week 12.

Other selected endpoints included change from baseline in Asthma Control Test™ (ACT) score at Week 12, number of withdrawals due to lack of efficacy during the treatment period, and change from baseline in morning FEV_1 at Endpoint (patient's last on-treatment FEV_1 measurement). Morning FEV_1 was measured by spirometry during clinic visits on Days 1, 28, 56, and 84.

Safety evaluations

Safety endpoints included the incidence of adverse events (AEs; coded using the Medical Dictionary for Regulatory Activities dictionary) and serious AEs (SAEs). AEs related to the pharmacology of steroids (including pneumonia, candidiasis) or LABA (including cardiovascular events, effects on glucose and potassium) were of special interest. Clinical laboratory assessments (hematology, clinical chemistry, and liver function) were performed at screening and Week 12, vital signs (pulse rate, blood pressure) at every visit from screening to Week 12, and 12-lead ECG data, including QT interval using Fridericia's correction (QTc[F]), was assessed at screening and Week 12.

Statistical analysis

It was planned to screen a total of 600 patients to randomize sufficient patients to provide 151 evaluable patients per treatment group; this number would provide 90% power to detect a treatment difference for FF/VI compared with FP of 15 L/min in daily evening PEF. Evaluable patients were defined as those providing evening PEF data for at least 4 of the 7 days prior to randomization, and at least 4 days after randomization. All patients who were randomized and received at least one dose of study treatment were included in the intent-to-treat (ITT) population; the per-protocol (PP) population comprised all patients in the ITT population who did not have any full protocol deviations. Patients with partial protocol deviations were included in the PP population but their data was excluded from the date of their deviation onwards.

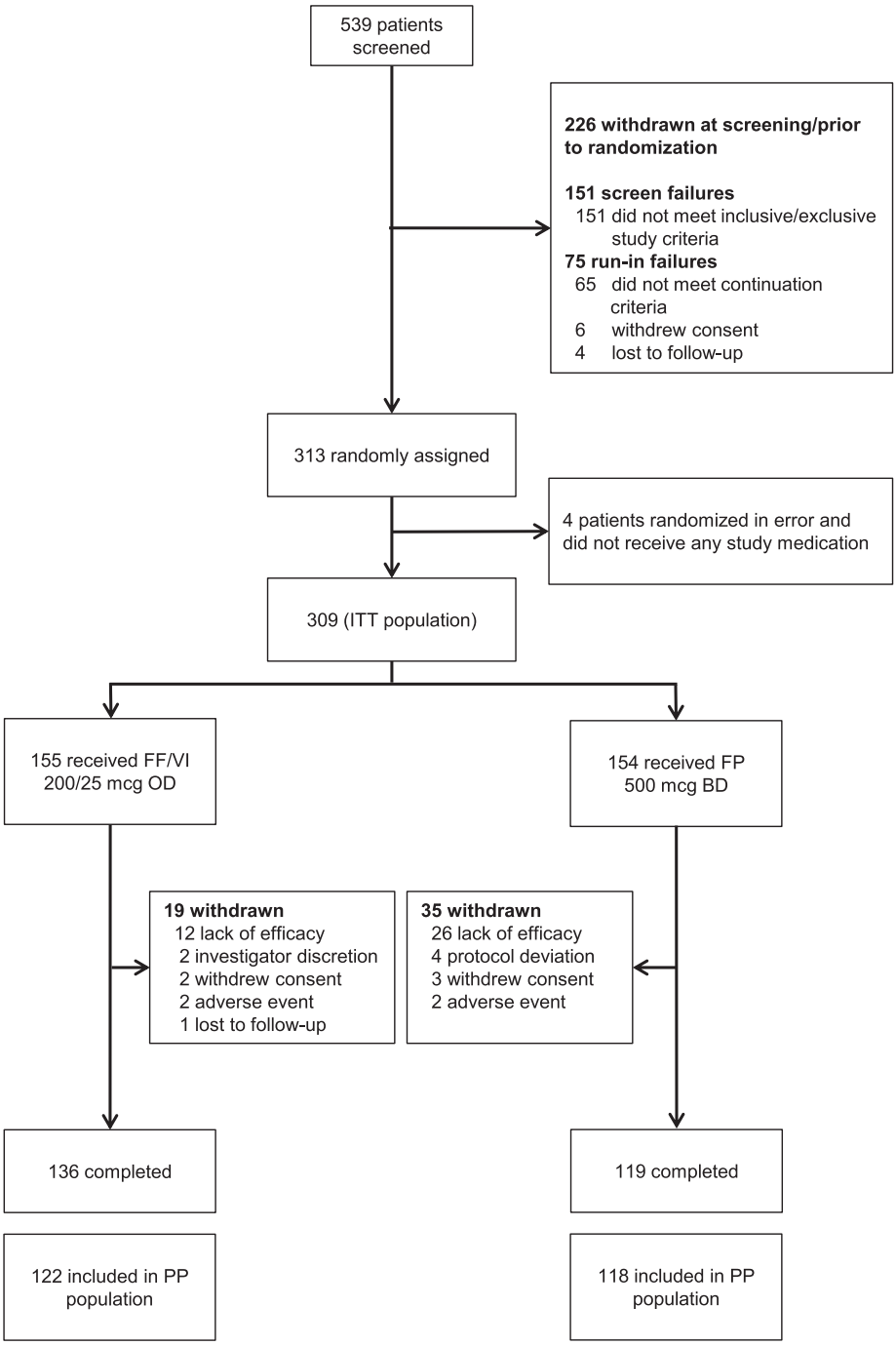
All efficacy endpoints were analyzed for the ITT population using an analysis of covariance (ANCOVA) model with treatment effects due to baseline, region, sex, age, and treatment group. For the primary endpoint, only evaluable patients were included and the analysis was repeated on the PP population. Additionally, the primary endpoint was analyzed using a repeated-measures model on the ITT population using weekly evening PEF means from Weeks 1–12, with interaction terms for week-by-treatment and week-by-baseline.

Data were analyzed using a step-down closed multiplicity testing procedure and a statistical hierarchy was applied to the efficacy endpoints, whereby failure to achieve significance ($p < 0.05$) for the previous treatment comparison of FF/VI 200/25 mcg once daily versus FP 500 mcg twice daily in the hierarchy meant that significance could not be inferred for any of the remaining endpoints. The hierarchy was applied to the efficacy endpoints in the following order: 1) evening PEF, 2) % rescue-free 24-h periods, 3) morning PEF, 4) % symptom-free 24-h periods, 5) AQLQ (+12) score.

Results

Study population

Of the 313 patients randomized, four were randomized in error, and 309 were included in the ITT population; 255 patients (83%) completed the study (Fig. 1) and the most common reason for withdrawal was lack of efficacy (n = 38, 12%). The PP population included 240 patients (77%), which was lower than expected due to an error at the sites in the Philippines, whereby the majority of patients received an incorrect ICS strength during the run-in period (patients on FP/salmeterol 250/50 mcg twice daily were switched to FP 500 mcg twice daily during run-in,



BD = twice daily; FF = fluticasone furoate; FP = fluticasone propionate; ITT = intent-to-treat; OD = once daily; PP = per-protocol; VI = vilanterol

Figure 1 CONSORT diagram.

instead of FP 250 mcg twice daily), and an additional three patients were enrolled despite prior treatment with ICS/LABA at a dose greater than that stipulated in the protocol.

Patient demographics and screening/baseline characteristics are presented in Table 1. The majority of patients (89%) were between 18 and 64 years of age and 59% were female. The mean % predicted FEV_1 improved during the run-in period, from 63.45% at screening to 67.53% at baseline. Mean (standard deviation) treatment compliance was high for patients receiving active treatment, at 95.7% (9.72) for FF/VI only via ELLIPTA and 95.4% (8.68) for FP only via DISKUS; however, it should be noted that compliance was assessed using the dose counter on the inhalers, and that it

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

Demographic	FF/VI 200/25 mcg OD $N = 155$	FP 500 mcg BD $N = 154$	Total $N = 309$
Age	46.9 (12.93)	48.8 (13.41)	47.9 (13.19)
Range	13–71	15–79	13–79
Female, *n* (%)	96 (62)	86 (56)	182 (59)
Duration of asthma, years	12.39 (12.857)	13.44 (13.551)	12.91 (13.196)
Range	0.0–55.7	0.3–55.0	0.0–55.7
Screening characteristics			
Pre-bronchodilator FEV_1 (L)	1.669 (0.4237)	1.646 (0.5108)	1.658 (0.4685)
Range	0.72–3.10	0.75–3.68	0.72–3.68
Percent predicted FEV_1	63.84 (12.936)	63.07 (12.467)	63.45 (12.690)
Range	40.0–90.0	40.0–89.4	40.0–90.0
Post-bronchodilator FEV_1 (L)	2.111 (0.5330)	2.072 (0.6282)	2.092 (0.5818)
Range	0.95–3.48	1.05–4.20	0.95–4.20
Percent reversibility FEV_1	27.31 (14.570)	26.98 (14.262)	27.14 (14.395)
Range	12.1–102.6	12.1–89.1	12.1–102.6
Baseline characteristics			
Pre-bronchodilator FEV_1 (L)	1.777 (0.4933)	1.767 (0.5519)	1.772 (0.5225)
Range	0.77–3.22	0.75–3.41	0.75–3.41
Percent predicted FEV_1	67.51 (13.249)	67.55 (13.432)	67.53 (13.319)
Range	40.5–90.0	40.2–89.7	40.2–90.0

All data are presented as mean (SD) unless otherwise stated. BD = twice daily; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; FP = fluticasone propionate; ITT = intent-to-treat; OD = once daily; SD = standard deviation; VI = vilanterol.

is possible to advance the dose counter without actually inhaling a dose of the study medication.

Efficacy

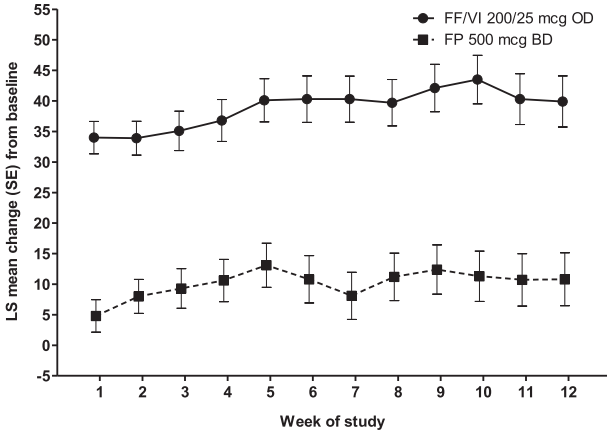
There were improvements from baseline in evening PEF with both FF/VI (39.1 L/min; standard error [SE]: 3.01) and FP (10.5 L/min; SE: 3.03) (Table 2, Fig. 2). The adjusted treatment difference for FF/VI compared with FP (28.5 L/min; 95% CI: 20.1, 36.9) was statistically significant ($p < 0.001$) (Table 2, Fig. 3). The adjusted treatment difference in the PP population for FF/VI versus FP was 28.7 L/min (95% CI: 19.3, 38.2) (Fig. 3) and was also statistically significant ($p < 0.001$).

Change from baseline and adjusted treatment differences for the secondary endpoints are presented in Table 3 and Fig. 3. The comparison of % rescue-free 24-h periods for FF/VI compared with FP (adjusted treatment difference: 1.0%; 95% CI: −7.3, 9.2) was not statistically significant ($p = 0.821$), but there were numerical improvements from baseline with both treatments (mean change from baseline: 32.4% with FF/VI; 31.5% with FP). Due to the failure to achieve statistical significance for this endpoint, and because of the statistical hierarchy, no inference of

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

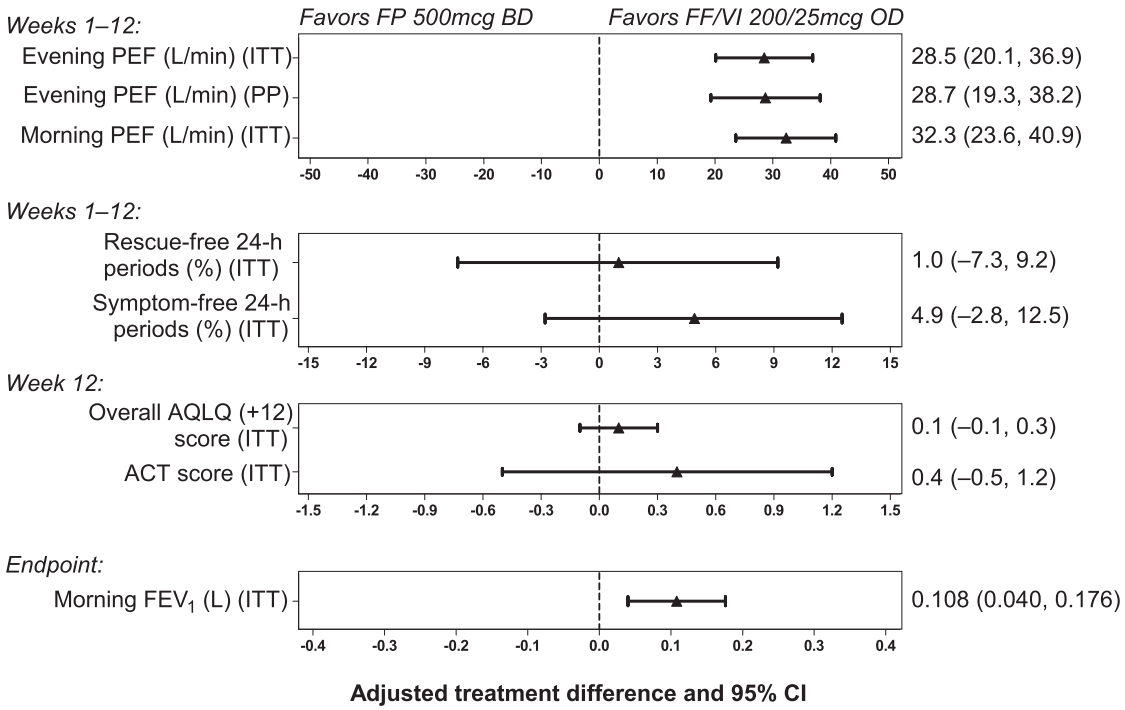
	FF/VI 200/25 mcg OD $N = 155$	FP 500 mcg BD $N = 154$
n	154	152
LS mean	302.5	274.0
LS mean change (SE)	39.1 (3.01)	10.5 (3.03)
FF/VI 200/25 OD versus FP 500 BD		
Difference (95% CI)	28.5 (20.1, 36.9)	
p value	<0.001	

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



BD = twice daily; FF = fluticasone furoate; FP = fluticasone propionate; ITT = intent-to-treat; LS = least-squares; OD = once daily; PEF = peak expiratory flow; SE = standard error; VI = vilanterol

Figure 2 Repeated measures analysis of change from baseline in evening PEF (L/min) (ITT population).



ACT = Asthma Control Test™; AQLQ = Asthma Quality of Life Questionnaire; BD = twice daily; CI = confidence interval; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; FP = fluticasone propionate; ITT = intent-to-treat; OD = once daily; PEF = peak expiratory flow; PP = per-protocol; VI = vilanterol

Figure 3 Adjusted treatment differences for all efficacy endpoints (ITT population).

significance could be made for the remaining endpoints and the following results should be interpreted as descriptive only. For all of the remaining secondary endpoints, there were numerical improvements from baseline with both FF/VI and FP and the adjusted treatment differences favored FF/VI (morning PEF: 32.3 L/min [95% CI; 23.6, 40.9], % symptom-free 24h periods: 4.9% [−2.8, 12.5], and overall AQLQ [+12] score: 0.12 [−0.08, 0.32]).

At Week 12, there were improvements from baseline in ACT score with both treatments (mean change (SE): 4.7 (0.29) with FF/VI; 4.3 (0.31) for FP) (Fig. 3); 91 (65%) patients with FF/VI had an ACT score ≥20, compared with 73 (59%) patients with FP. There was also a lower percentage of withdrawals due to lack of efficacy in the FF/VI group (8%) than in the FP group (17%) (Fig. 4). There were numerical improvements from baseline in 12-h post-dose morning FEV_1 at Endpoint with both FF/VI and FP; the adjusted treatment difference was 0.108L (95% CI: 0.040, 0.176) (Fig. 3).

Safety results

A summary of on-treatment AEs, most frequently reported AEs, and AEs of special interest known to be associated with either ICS or LABA treatment are presented in Table 4. A similar proportion of patients reported on-treatment AEs with FF/VI (26%) and with FP (27%). The most frequently reported on-treatment AE was upper respiratory tract infection, which was reported by a lower proportion of patients with FF/VI (n = 13, 8%) compared with FP (n = 18, 12%). The incidence of treatment-related AEs was low for both FF/VI (n = 5, 3%: n = 1 oropharyngeal pain and headache, n = 2 oropharyngeal pain, n = 1 oral paresthesia, n = 1 allergic dermatitis) and FP (n = 5, 3%: n = 1 oropharyngeal pain, n = 1 oropharyngeal discomfort, n = 1 asthma exacerbation, n = 2 upper respiratory tract infection). A total of 4 patients (FF/VI: n = 1 asthma exacerbation, n = 1 thyroid cancer; FP: n = 1 asthma exacerbation, cardiac failure, and respiratory failure, n = 1 drug eruption) withdrew from the study due to AEs. There were three on-treatment SAEs (FF/VI: n = 1, acute bronchial asthma; FP: n = 1 drug rash, n = 1 asthma exacerbation, cardiac failure, and respiratory failure); all led to withdrawal from the study but only the asthma exacerbation with FP was considered to be treatment-related. There were no deaths during the study.

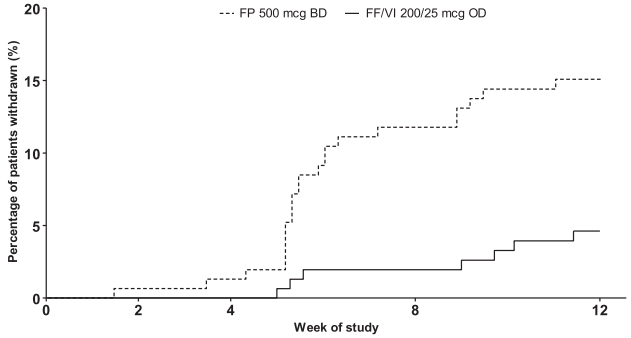
Four patients (FF/VI: n = 1, FP: n = 3) experienced severe asthma exacerbations while on treatment and all were withdrawn from the study as a result. Severe exacerbations were only reported as an AE if they met SAE criteria: three of these exacerbations were not considered to meet the SAE criteria and were not reported as AEs. More patients in the FF/VI group (n = 15, 10%) reported AEs of

Table 3 Statistical analysis of change from baseline for secondary endpoints (ITT population).

	FF/VI 200/25 mcg OD $N = 155$	FP 500 mcg BD $N = 154$
Percentage of rescue-free 24h periods, Weeks 1−12		
n	155	152
LS mean change (SE)	32.4 (2.95)	31.5 (2.98)
FF/VI 200/25 OD versus FP 500 BD		
Difference (95% CI)	1.0 (−7.3, 9.2)	
p value	0.821	
Equivalent number of additional rescue-free days per week		
LS mean change from baseline	2.3	2.2
LS mean difference from FP 500 BD	0.1	
Morning PEF (L/min), Weeks 1−12		
n	154	152
LS mean	307.8	275.5
LS mean change (SE)	46.2 (3.07)	14.0 (3.10)
FF/VI 200/25 OD versus FP 500 BD		
Difference (95% CI)	32.3 (23.6, 40.9)	
Percentage of symptom-free 24h periods, Weeks 1−12		
n	155	152
LS mean change (SE)	25.4 (2.74)	20.6 (2.77)
FF/VI 200/25 OD versus FP 500 BD		
Difference (95% CI)	4.9 (−2.8, 12.5)	
Equivalent number of additional rescue-free days per week		
LS mean change from baseline	1.8	1.4
LS mean difference from FP 500 BD	0.3	
Overall AQLQ (+12) score, Week 12		
n	140	123
LS mean	5.34	5.23
LS mean change (SE)	0.80 (0.069)	0.69 (0.074)
FF/VI 200/25 OD versus FP 500 BD		
Difference (95% CI)	0.12 (−0.08, 0.32)	

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

special interest than in the FP group ($n = 8$, 5%); four of these AEs were considered to be treatment-related by the investigator (FF/VI: $n = 2$ oropharyngeal pain, $n = 1$ allergic dermatitis; FP: $n = 1$ oropharyngeal pain) and two were SAEs (cardiac failure, drug eruption, both with FP). Additionally, pneumonia was reported by two patients in the FF/VI group; both events were non-serious (1 mild in intensity; 1 moderate in intensity) and unrelated to study treatment, and they resolved within 13 days.



ITT = intent-to-treat; FP = fluticasone propionate; BD = twice daily; FF = fluticasone furoate; VI = vilanterol; OD = once daily

Figure 4 Withdrawals due to lack of efficacy over the treatment period (ITT population).

There was no evidence of any trend for patients to have abnormal results for clinical chemistry, liver function, or hematology assessments. No statistically significant differences were observed between the two treatment groups post-baseline for any of the vital signs assessments or for ECG parameters (including QTc[F]) at Week 12; no patients were reported as having abnormal clinically-significant ECG results at screening or at Week 12.

Discussion

The aim of this study was to evaluate the efficacy and safety of FF/VI 200/25 mcg once daily in adult asthma patients of Asian ancestry. FF/VI 200/25 mcg once daily in the evening produced a statistically significant and clinically relevant improvement in evening PEF compared with FP 500 mcg twice daily. Numerical improvements from baseline in the percentage of rescue-free 24-h periods were observed for the treatment comparison of FF/VI versus FP, however, the adjusted treatment difference was not

Table 4 Overview of AEs, most-frequent AEs (≥3% in either treatment arm), and AEs of special interest (ITT population).

	FF/VI 200/25 mcg OD *N* = 155	FP 500 mcg BD *N* = 154
On-treatment AEs		
Any AE	40 (26)	41 (27)
Treatment-related AEs	5 (3)	5 (3)
AEs leading to permanent discontinuation of the study drug	2 (1)	2 (1)
Serious AEs	1 (<1)	2 (1)
Treatment-related, serious AEs	0	1 (<1)
Fatal AEs	0	0
Most-frequent on-treatment AEs (≥3% in either treatment arm)		
Upper respiratory tract infection	13 (8)	18 (12)
Nasopharyngitis	6 (4)	6 (4)
Rhinitis allergic	5 (3)	2 (1)
Oropharyngeal pain	4 (3)	1 (<1)
AEs of special interest		
Patients with any AE of special interest	15 (10)	8 (5)
Hypersensitivity	3 (2)	4 (3)
Local steroid effects	4 (3)	1 (<1)
Cardiovascular effects	3 (2)	1 (<1)
Effects on glucose	1 (<1)	2 (1)
Lower respiratory tract infection, excluding pneumonia	2 (1)	0
Pneumonia	2 (1)	0

Data are *n* (%). AE = adverse event; BD = twice daily; FF = fluticasone furoate; FP = fluticasone propionate; ITT = intent-to-treat; OD = once daily; VI = vilanterol.

statistically significant. There were also numerical improvements from baseline with FF/VI compared with FP for the remaining secondary and other endpoints. The safety profiles of FF/VI and FP were generally similar, the overall incidence of SAEs was low (≤1% in either treatment group), and there were no deaths.

In this study, improvements from baseline in lung function were observed with both FF/VI and FP. The statistically significant improvement in evening PEF for FF/VI versus FP in this 12-week study (28.5 L/min [95% CI: 20.1, 36.9]) was greater than the minimal patient perceivable improvement of 18.79 L/min [21], and is similar to the improvement observed at 12 weeks in the previous 24-week global study [12] of 24.0 L/min (95% CI: 16.3, 31.7) [22]. The use of evening PEF as a primary endpoint in the present study provides evidence that in Asian patients, treatment with FF/VI 200/25 mcg over 12 weeks can significantly improve lung function 24-h after dosing. The observed numerical improvements in the adjusted mean treatment difference for FF/VI 200/25 mcg versus FP 500 mcg in morning PEF were similar between the present study (32.3 L/min; 95% CI: 23.6, 40.9]) and the global study (31.0 L/min; 95% CI: 23.3, 38.8) [22], although statistical significance could not be inferred for this observation in either study. Lung function is at its lowest in the early morning due to diurnal variation [23] and, although the endpoints discussed above measure improvements in trough values (i.e., 24 h post-dose), the numerical improvements of 108 mL (95% CI: 40, 176) observed in morning FEV_1 are also encouraging.

Despite the improvements in lung function for the comparison for FF/VI 200/25 mcg versus FP 500 mcg, no statistically significant treatment difference was observed for rescue-free 24-h periods, which was the first secondary endpoint in the statistical hierarchy. As a result, statistical significance for the comparison of FF/VI versus FP for the remaining endpoints could not be inferred although there were numerical improvements with FF/VI compared with FP for all remaining endpoints. The numerical improvement in the % of rescue-free 24-h periods was slightly less than that observed over Weeks 1–24 in the global study, and the difference in % symptom-free 24-h periods was similar to the improvements over Weeks 1–24 in the global study; these endpoints were only analyzed as change from baseline over the 24 week treatment period in the global study [12]. The numerical improvements from baseline in overall AQLQ (+12) score were greater than the minimally important difference of 0.5 [24] in both treatment groups (FF/VI: 0.80; FP: 0.69), which was also true at Week 12 in the global study (FF/VI: 0.74; FP: 0.74) [22]. Patients in both groups also showed improvements in ACT score by more than the minimally important difference of 3 [25] (LS mean change 4.7 for FF/VI and 4.3 for FP), which is also consistent with the global study [12] (LS mean change 4.8 for FF/VI and 3.9 for FP) [22]. Overall, these results indicate that both FF/VI and FP are effective in establishing control of asthma symptoms, and although there were numerical improvements with FF/VI compared with FP for symptomatic endpoints, there was no statistically significant difference.

The rates of AEs were similar with both FF/VI (26%) and FP (27%), the incidence of SAEs was low, and no patients died during the study. Additionally, the incidence of local steroid effects was low (only oropharyngeal pain was reported) and the incidence of any LABA-related effects, including cardiovascular events and glucose effects (no potassium effects were reported), was low, with events occurring in ≤2% of patients in either treatment group. The incidence of severe asthma exacerbations was low in this population that was treated with high-strength ICS or mid-strength ICS/LABA at the time of screening; however, the interpretation of exacerbation rate is limited by the fact this 12-week study was not of sufficient length to assess exacerbation rates over time. Additionally, the strict withdrawal criteria meant that patients were withdrawn from the study before they experienced an exacerbation, which is highlighted by the findings that only four patients experienced severe asthma exacerbations while on-treatment, whereas 38 patients were withdrawn due to lack of efficacy. There were no safety concerns related to clinical laboratory assessments, vital signs, or ECG parameters in this study and the safety results are consistent with previous observations of the 200/25 mcg strength of FF/VI [12,26].

The patients recruited to this study were treated with high-strength ICS or mid-strength ICS/LABA at screening, and represented a suitable patient population in terms of disease severity for evaluation of the 200/25 mcg strength of FF/VI. The loss of patients from the PP population in the Philippines due to the run-in error could be seen as a weakness; however, the similar results observed for the primary endpoint between the PP population, which excluded these patients, and the ITT population, supports the robustness of the results. This study was limited by the lack of a placebo arm to which the treatment effects of FF/VI and FP could be compared, but it is considered unethical for asthma patients who require high-strength ICS or mid-strength ICS/LABA maintenance therapy to receive placebo; moreover FP 500 mcg twice daily was used as a comparator in this study, and is a high-dose ICS treatment known to be effective in asthma [2]. The treatment duration of 12 weeks was considered sufficient to demonstrate efficacy and tolerability in this study population.

In conclusion, FF/VI 200/25 mcg once daily demonstrated clinically and statistically significant improvements in evening PEF compared with FP 500 mcg twice daily in this study of patients of Asian ancestry aged 12 years and older with persistent asthma uncontrolled on high-strength ICS or mid-dose ICS/LABA combination products. Overall, FF/VI 200/25 mcg once daily had an AE profile generally similar to that of FP 500 mcg twice daily. The results are generally consistent to the comparison of FF/VI 200/25 mcg once daily with FP 500 mcg twice daily in the previous global Phase III study [12].

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Author contribution and role of funding source

JC, LJ, and SS were involved in the conception and design of the study; JL, JK, SHL, CW, and XZ were involved in the acquisition of data; JC was involved in data analysis and JL, SHL, CW, JC, LJ, and SS were involved in interpreting the data.

Employees of the sponsor were involved in the conception, design, and conduct of the study, and in data collection and analysis. All authors, including 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.

Statement of interest

J. Lin has received speaker's honoraria from GSK, AstraZeneca, and Merck Sharpe & Dohme; has been a member of global advisory boards for Boehringer Ingelheim. S.H. Lee has declared no conflict of interest. J. Crawford, L. Jacques, and S. Stone are employees of and hold stock in GSK. J. Kang and Z. Xiangdong have declared no conflicts of interest. C. Wang has received speaking and consulting fees from AstraZeneca, GSK, and Novartis.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2014.10.012.

References

[1] Global Initiative for Asthma (GINA). Global burden of asthma. http://ginasthma.org/local/uploads/files/GINABurdenReport_1.pdf [accessed 17.11.14].
[2] Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention 2014. http://www.ginasthma.org/local/uploads/files/GINA_Report_2014.pdf. Date last updated: May 2014. [accessed 17.11.14].
[3] National asthma study group: Chinese guideline 2008 for the prevention and management of asthma. Chin Tubc Res Dis 2008;31:177—85.
[4] Philippine consensus report on the diagnosis and management of asthma 2008. http://philchest.org/publications/clinical-practice-guidelines/ [accessed: 17.11.14]
[5] Korean asthma management guideline for adults. The Korean academy of asthma, allergy and clinical immunology. 2011. http://www.allergy.or.kr/file/2011_new.pdf [accessed: 17.11.14].
[6] Emilsson M, Berndtsson I, Lötvall J, Millqvist E, Lundgren J, Johansson Å, Brink E. The influence of personality traits and beliefs about medicines on adherence to asthma treatment. Prim Care Respir J 2011;20:141—7.
[7] 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;14:88—98.
[8] 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.
[9] Cochrane GM. Compliance and outcomes in patients with asthma. Drugs 1996;52(Suppl. 6):12—9.
[10] Su N, Lin J, Chen P, Li J, Wu C, Yin K, et al. Evaluation of asthma control and patient's perception of asthma: findings and analysis of a nationwide questionnaire-based survey in China. J Asthma 2013;50:861—70.
[11] Lai CK, De Guia TS, Kim YY, Kuo SH, Mukhopadhyay A, Soriano JB, et al. Asthma control in the Asia-Pacific region:

the Asthma Insights and Reality in Asia-Pacific study. J Allergy Clin Immunol 2003;111:263—8.
[12] O'Byrne PM, Bleecker ER, Bateman ED, Busse WW, Woodcock A, Forth R, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. Eur Respir J 2014;43:773—82.
[13] Woodcock A, Bleecker ER, Lötvall J, O'Byrne PM, Bateman ED, Medley H, 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 2013;144:1222—9.
[14] Bateman ED, O'Byrne PM, Busse WW, Lötvall J, Bleecker ER, Andersen L, et al. Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. Thorax 2013;69:312—9.
[15] Bleecker ER, Lötvall J, O'Byrne PM, Woodcock A, Busse WW, Kerwin EM, et al. Fluticasone furoate-vilanterol 100—25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. J Allergy Clin Immunol Pract 2014;2:553—61.
[16] Bjornsson TD, Wagner JA, Donahue SR, Harper D, Karin A, Khouri MS, et al. A review and assessment of potential sources of ethnic differences in drug responsiveness. J Clin Pharmacol 2003;43:943—67.
[17] Huang SM, 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 2008;84:287—94.
[18] Hankinson JL, Kawut SM, Shahar E, Smith LJ, Stukovsky KH, Barr RG. Performance of American Thoracic Society-recommended spirometry reference values in a multiethnic sample of adults: the multi-ethnic study of atherosclerosis (MESA) lung study. Chest 2010;137:138—45.
[19] 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 64th WMA General Assembly, Fortaleza, Brazil; October 2013. http://www.wma.net/en/30publications/10policies/b3/index.html. Date last updated: October 2008. [accessed: 17.11.14].
[20] International Conference on Harmonisation tripartite guideline: guidance for good clinical practice E6 (R1); 10 June 1996. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf [accessed: 17.11.14].
[21] Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? Eur Respir J 1999;14:23—7.
[22] GSK data on file: 2011N128470_00 Allen A, Barendse S, Forth R, Nunn C, Shafiq A, Toler WT. Clinical study report. HZA106829: a randomised, double-blind, parallel group, multicentre study of fluticasone furoate/GW642444 inhalation powder, fluticasone furoate inhalation powder alone, and fluticasone propionate alone in the treatment of persistent asthma in adults and adolescents. 21 February 2012 [Unpublished data].
[23] Medarov BI, Pavlov VA, Rossoff L. Diurnal variations in human pulmonary function. Int J Clin Exp Med 2008;1:267—73.
[24] 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;47:81—7.
[25] Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. J Asthma Allergy Immunol 2009;124.719—723.e1.
[26] Busse WW, O'Byrne PM, Bleecker ER, Lötvall J, Woodcock A, Andersen L, et al. Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the β2 agonist vilanterol administered once daily for 52 weeks in patients >=12 years old with asthma: a randomised trial. Thorax 2013;68:513—20.