ONLINE SUPPLEMENT

Exclusion criteria

Patients could not have a history of life-threatening asthma, evidence of concurrent respiratory disease, any asthma exacerbation requiring treatment with corticosteroids within 3 months of Visit 1, or other clinically significant medical conditions. Patients also had to have a negative oropharyngeal examination (no candidiasis), could not have participated in a previous phase III fluticasone/vilanterol study, could not have used tobacco products in the 3 months prior to screening or have historical use of ≥10 pack-years, milk protein allergy or specific drug allergies, or used prohibited medications within the specified time periods. Patients needed to be able to replace their current short-acting bronchodilator with salbutamol/albuterol from the morning of Visit 2 (baseline).

Prohibited medications

Asthma medications

The following asthma medications were prohibited during the time periods specified:

Within 12 weeks of Visit 1 and during the study:

- Anti-IgE (eg, XOLAIR)
- Oral, systemic or depot corticosteroids

From evening of Visit 2 and during the study:

- Anti-leukotrienes including suppressors of leukotriene production and antagonists
- Oral long-acting $beta_2$ agonists (eg, bambuterol)
- Inhaled long-acting $beta_2$ agonists (eg, salmeterol, formoterol)
- Transdermal beta agonists (eg, tulobuterol)
- Theophyllines
- Slow-release bronchodilators (eg, aminophylline)
- Anticholinergincs

- Ketotifen
- Nedocromil sodium
- Sodium cromoglycate
- Inhaled corticosteroids

Non-asthma medications

The following non-asthma medications were prohibited during the time periods specified:

Within 12 weeks of Visit 1 and during the study:

- Systemic corticosteroids for any condition

Within 4 weeks of Visit 1 and during the study:

- Potent cytochrome P450 3A4 inhibitors (eg, ketoconazole, ritonavir)

From Visit 1 and during the study:

Any other prescription or over-the-counter medication which could affect the course of asthma or interact with sympathomimetic amines, such as:

- Anticonvulsants (barbiturates, hydantoins, carbamazepine)
- Polycyclic antidepressants
- Beta-adrenergic blocking agents
- Phenothiazines
- Monoamine oxidate (MAO) inhibitors
- Ocular corticosteroids
- Chronic treatment with agents known to promote the development of cataracts (eg, potassium-sparing diuretics and allopurinol)
- Eyewash solutions (other than saline) should be withheld for 48 h prior to ocular assessments.

Urine cortisol (UC) population: factors leading to exclusion

The UC population consisted of patients in the ITT population with urine samples at baseline and at least one post-baseline assessment not having any of the following confounding factors:

- urine volumes <600mL (females) or <800mL (males)
- 24h creatinine excretion below lower limit of threshold range (mean ± 2.5 SD)
- collection time intervals outside 24 ± 2 hours
- end date of baseline urine collection after first dose of study medication
- start date of end of treatment urine collection more than 1 day after final dose of study medication
- use of corticosteroid in deviation from the protocol
- use of potent CYP3A4 inhibitor in deviation from the protocol.

Further information regarding statistical analysis used

An upper confidence limit for the probability of an event that does not occur in the finite population of patients studied could be provided using the "rule of 3" [1]. By enrolling 200 patients in each FF/VI treatment arm, if an event does not occur in 400 subjects on any strength of FF/VI, then this rules out with 95% confidence, a population event rate higher than 3/400 = 0.75%.

Treatment compliance with the dry powder inhaler (DPI) and the DISKUS

- Mean treatment compliance with the DPI was 99.4–99.9% in the FF/VI groups and 97.6% in the fluticasone propionate (FP) group, and with the DISKUS was 97.6–97.8% in the FF/VI groups and 96.3% in the FP group.

Details of summaries, analyses and statistical tests

- The proportion of patients reporting adverse events and serious adverse events was summarised for each treatment group using the MedDRA (Version 13.1) primary System Organ Class and preferred term.
- The proportion of patients who had severe asthma exacerbations (on-treatment and post-treatment) was summarised.
- Clinical chemistry and haematology values and change from baseline in laboratory values were summarised by treatment group and study visit using summary statistics. The number and proportion of patients with laboratory values outside the normal range were summarised by visit for each laboratory analyte.
- 24-h urinary cortisol (UC) excretion was log transformed and analysed using an analysis of covariance (ANCOVA) model (UC population) with effects due to log of baseline values, region, sex, age and treatment group.
- For oropharyngeal examinations, the number and proportion of patients with clinical evidence of oral candidiasis and with a positive swab were tabulated for each treatment group at screening, baseline and over the entire treatment period taking the worst case.
- Changes from baseline in ECG heart rate, QTc(F) and vital signs (diastolic and systolic blood pressure and pulse rate) at each visit were compared between treatment groups using a repeated measures model, with a repeated effect of visit within each subject and an associated unstructured covariance structure.
- Mean and maximum heart rate, and ventricular ectopics (including singles, couplets and runs) derived from Holter monitoring was summarised for all patients and a subset of patients who provided at least 16 hours of recorded Holter data, using summary statistics for continuous data. The number of patients with ventricular ectopics was presented and the number of ventricular ectopics was summarised using median, 25th and 75th percentiles, minimum and maximum.

- The number of events for posterior subcapsular opacity and intraocular pressure at each visit was summarised. LOCS III lens grade data (subcapsular opacity, cortical opacity, nuclear colour and nuclear opalescence), intraocular pressure, horizontal cup-to disc ratio, and visual acuity (LogMAR) values and the changes from baseline were summarised with descriptive statistics. Change from baseline in subcapsular opacity, cortical opacity and intraocular pressure were plotted using histograms and Cumulative Distribution Function graphs. The relative frequencies of changes in subcapsular opacity, cortical opacity and intraocular pressure for left and right eyes at Weeks 28 and 52 were tabulated by treatment group. The LOCS III lens grade data were also summarized by age subgroup (≥12 to <18 years, ≥18 to <40 years, ≥40 to <60 years, and ≥60 years) to assess any potential age-related change in the lens grades.

Outcomes of ophthalmic assessments

Posterior subcapsular opacity

Mean changes from baseline in posterior subcapsular opacity were small and similar across the three treatment groups at Weeks 28 and 52 (–0.01 to 0.01). Almost all patients in each treatment group had a change from baseline of <0.3 in posterior subcapsular opacity in each eye at Week 28 (97% to 100%) and at Week 52 (98% to 100%).

Intraocular pressure

Mean changes from baseline in intraocular pressure were small and similar across the treatment groups at Weeks 28 and 52 (–0.2 to 0.2 mmHg for FF/VI 100/25µg, –0.4 to 0.1 mmHg for FF/VI 200/25µg, and –0.3 to -0.1 mmHg for FP). Three patients had an increase in intraocular pressure ≥7 mmHg at any time post-baseline: 2 patients (<1%) in the FF/VI 100/25µg group and 1 patient (<1%) in the FF/VI 200/25µg group; no patient had an increase ≥11 mmHg. None of these increases in intraocular pressure were reported as adverse events.

Non-sustained ventricular tachycardia (case narratives)

Non-sustained ventricular tachycardia is a protocol-defined stopping (withdrawal) criterion.

- FF/V1 100/25 µg
    1. Event reported at Week 28. Patient had a history of hypertension. Two episodes of ventricular tachycardia were reported, one lasting for 3 beats and the other lasting for 4 beats. A normal Holter was recorded at screening and normal ECGs were recorded throughout the study. The patient was withdrawn from the study and the event was considered by the investigator not to be treatment related.
    2. Patient had no reported medical history associated with tachycardia. At the Visit 2 (Day 1) Holter, a 7-beat non-sustained ventricular tachycardia was reported and the patient was withdrawn from the study; the event was considered by the investigator not to be treatment related. A normal Holter was recorded for this patient at screening and normal ECGs were recorded at screening and at the early withdrawal visit with the interpretation of borderline PR interval.
- FF/VI 200/25 µg
    1. Event reported at Week 52. The patient had no reported medical history associated with tachycardia. This was a single episode lasting for 3 beats. The patient was withdrawn from the study and the event was considered by the investigator to be treatment related. For this patient a normal Holter was recorded at screening and normal ECGs were recorded throughout the study with interpretation of non-specific ST elevation at screening and bradycardia at Week 52.
    2. Event reported at Week 34 (unscheduled visit). The patient had no reported medical history associated with tachycardia. Event was a single episode lasting 5 beats and the patient was withdrawn from the study. The event resolved 20 days following the early withdrawal visit and was considered by the

investigator to be possibly related to study treatment. A normal Holter was recorded at Screening and normal ECGs were recorded throughout the study.

Sustained superventricular tachycardia (case narratives)

Sustained superventricular tachycardia is a protocol-defined stopping (withdrawal) criterion.

1. Event reported on Day 1. The patient had no reported medical history associated with tachycardia. Several runs of sustained supraventricular tachycardia were reported on Holter examination that led to the patient being withdrawn from the study. The event was resolved on the subsequent Holter recording 17 days later and was considered by the investigator to be possibly related to treatment.
2. Event reported on Day 1. The patient had no reported medical history associated with tachycardia. The event was resolved on the subsequent Holter recording 14 days later and was considered was considered by the investigator to be possibly related to treatment. The patient was withdrawn from the study due to the event.
3. Event reported at Week 28. The patient had no reported medical history associated with tachycardia.The event was reported as resolving at the time of study end and was not considered by the investigator to be related to study treatment. The patient was withdrawn from the study due to the event.

Online Supplement references

1. Hanley JA and Lippman-Hand A. If nothing goes wrong, is everything alright? Interpreting zero numerators. JAMA 1983;**259**:1743–1

Online Figure 1: Individual 24-h urinary cortisol excretion at Week 52 versus baseline (urinary cortisol population).