Efficacy and Safety of Fluticasone Furoate/Vilanterol Compared With Fluticasone Propionate/Salmeterol Combination in Adult and Adolescent Patients With Persistent Asthma

A Randomized Trial

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E-Appendix 1

Key Exclusion Criteria

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

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(Continued)
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(Continued)
Permitted Nonasthma Medications and Prohibited Asthma and Nonasthma Medications

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

Within 12 weeks of screening and during the study, systemic, oral, parenteral, or depot corticosteroids and anti-IgE (eg, omalizumab) asthma medications were prohibited. Within 1 day of the screening visit and during the study, patients had to discontinue the following medications at screening, with no doses taken on the day of screening until the end of the double-blind treatment period: antileukotrienes (including suppressors of leukotriene production and antagonists), inhaled long-acting β₂-agonists (LABAs) as monotherapy or inhaled corticosteroid/LABA combination, oral (eg, bambuterol) LABAs, theophyllines, anticholinergics, ketotifen, nedocromil sodium, and sodium cromoglycate.

Concurrent use of any other prescription or over-the-counter nonasthma medication that could affect the course of asthma or interact with sympathomimetic amines throughout the study (potent CYP3A4 inhibitors [eg, ritonavir, ketoconazole]) was prohibited within 4 weeks before screening. Medications not permitted during the study, including visits 1 to 6 were anticonvulsants (barbiturates, hydantoins, and carbamazepine), polycyclic antidepressants, β-adrenergic...
blocking agents, phenothiazines, and monoamine oxidase inhibitors.

E-APPENDIX 3

RESULTS FOR THE POST HOC ANALYSES

Post hoc analyses of change from baseline in the Asthma Quality of Life + 12 Questionnaire (AQLQ +12) domains of activity limitation, symptoms, and emotional function did not show a difference for fluticasone furoate/vilanterol (FF/VI) vs fluticasone propionate/salmeterol (FP/SAL). For the AQLQ +12 domain of environmental stimuli, adjusted mean changes of 0.58 and 0.31 were reported for the FF/VI and FP/SAL groups, respectively. Furthermore, post hoc analyses showed that the minimally important difference of a ≥0.5-point improvement in AQLQ +12 score was achieved by a greater number of patients receiving FF/VI vs FP/SAL at week 24 (46% vs 38%; OR, 1.50; 95% CI, 1.06-2.13).

E-APPENDIX 4

ANALYSES POPULATIONS AND FURTHER DETAILS ABOUT THE POWER CALCULATIONS

Data for the intention-to-treat population (defined as all patients who were randomized to treatment and who received at least one dose of study drug) are reported for all efficacy and safety end points (excluding urinary cortisol [UC] assessments). Data for the UC population (defined as all patients targeted to provide 24-h urine samples and whose urine samples did not have confounding factors that affected the interpretation of results) are reported. Up to 15% of patients were expected to withdraw from the study, meaning that 820 patients should be randomized (410 patients per treatment group). A subset of about 296 patients (about 148 per group) from the 820 patients randomized were targeted for a 24-h UC excretion assessment at baseline and at the end of the 24-week treatment period. This provided about 100 evaluable patients per treatment group. No sample size reestimation was planned for this study.

E-APPENDIX 5

RESULTS FOR VITAL SIGNS

Systolic and Diastolic BP

Mean changes from baseline in maximum systolic and minimum diastolic BP were similar between the treatment groups. The mean change from baseline in maximum (postbaseline) systolic BP was 7.2 mm Hg with fluticasone furoate/vilanterol (FF/VI) and 7.0 mm Hg with fluticasone propionate/salmeterol (FP/SAL). For diastolic BP, the mean change from baseline in minimum (postbaseline) BP was −6.2 mm Hg with FF/VI and −6.3 mm Hg with FP/SAL.

When analyzed per visit, the adjusted mean differences in predose systolic BP between FF/VI and FP/SAL were not statistically significant at any visit (week 4, −0.2 mm Hg [P = .757]; week 8, 0.1 mm Hg [P = .934]; week 16, −0.8 mm Hg [P = .298]; end of treatment, 0.2 mm Hg [P = .787]). A similar trend was observed for predose diastolic BP. The adjusted mean differences in predose diastolic BP between the groups were not statistically significant (week 4, 0.1 mm Hg [P = .875]; week 8, 0.8 mm Hg [P = .168]; week 16, −0.1 mm Hg [P = .811]; end of treatment, 0.3 mm Hg [P = .618]).

Pulse Rate

As was observed for BP, mean changes from baseline in pulse rate were similar between the treatment groups (FF/VI, 6.8 beats/min [bpm]; FP/SAL, 7.3 bpm). Analysis of change from baseline in pulse rate by category by visit showed that up to 45% of patients in both the FF/VI and the FP/SAL treatment groups recorded no or minimal change from baseline (±5 bpm) for all visits (week 4, 45% and 42% of patients, respectively; week 8, 39% of patients in both groups; week 16, 44% and 37% of patients, respectively; end of treatment, 38% and 37% of patients, respectively). When analyzed per visit, the adjusted mean differences in predose pulse rate between FF/VI and FP/SAL were not statistically significant at any visit (week 4, −1.0 bpm [P = .097]; week 8, −0.6 bpm [P = .275]; week 16, −1.0 bpm [P = .095]; end of treatment, −0.8 bpm [P = .222]).