Tolerability of Fluticasone Furoate/Vilanterol Combination Therapy in Children Aged 5 to 11 Years With Persistent Asthma

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ABSTRACT

Background: Asthma is a chronic disease afflicting millions of children worldwide. Short-acting β_2-agonist reliever medications and inhaled corticosteroid (ICS) maintenance therapies are effective treatments; however, many children remain uncontrolled with short-acting β_2-agonist and ICS treatment, in which case guidelines recommend adding a long-acting β_2-agonist.

Objective: We sought to investigate the safety profile, tolerability, and pharmacokinetic (PK) and pharmacodynamic (PD) properties of the long-acting β_2-agonist vilanterol (VI) combined with the ICS fluticasone furoate (FF) administered via the ELLIPTA dry powder inhaler (GlaxoSmithKline, London, United Kingdom) in children aged 5 to 11 years with persistent asthma.

Methods: In this randomized, double-blind, repeated-dose, 2-way crossover study, data from 8- to 11-year-old children with asthma were reviewed before those from 5- to 7-year-old children with asthma. Patients received once-daily FF/VI, 100/25 μg, or FF, 100 μg, in the morning for 14 days, followed by a ≥7-day washout period before switching to the other treatment for 14 days; the study duration was ≤11 weeks. Primary end points were adverse events (AEs), clinical laboratory measurements, peak expiratory flow, maximum heart rate, blood pressure, and electrocardiographic parameters. Secondary end points comprised PK ($AUC_{0–4}$, C_{max}) and PD (serum potassium [0–4 hours], serum cortisol [0–12 hours], and glucose [0–4 hours]) parameters on day 14.

Results: Twenty-six children were randomized (58% boys; mean age, 8.1 years). No clinically significant changes in the primary end points were observed. Five patients reported 4 and 2 AEs with FF/VI and FF therapy, respectively. After FF/VI or FF treatment, the geometric mean ratios (90% CIs) for FF $AUC_{0–4}$ (1.02 [0.86–1.22]) and FF C_{max} (0.98 [0.65–1.48]) were similar. For serum glucose (0–4 hours) concentration, a difference of 0.50 mM (95% CI, 0.19–0.82 mM) was observed for FF/VI versus FF; no differences were observed for other PD parameters. No AEs were judged to be serious or treatment related. The PK profile of FF did not seem to be altered by VI and was not affected by age or sex. The significance of an increased serum glucose level is difficult to judge as measurements were taken from nonfasted patients. Results can be compared only with active treatment, and the ability to generalize is limited by the small number of patients in this single-center study.

Conclusions: Once-daily repeated dosing of FF/VI, 100/25 μg, using the ELLIPTA dry powder inhaler was as well tolerated as FF, 100 μg, in this small, selected population of 5- to 11-year-old, mostly white/caucasian children with persistent asthma. (*Clin Ther.* 2014;▮:▮▮▮–▮▮▮)

Key words: ICS, LABA, pediatric, pharmacodynamics, pharmacokinetics, tolerability.

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INTRODUCTION

Asthma continues to be a major chronic disease in children.[1,2] Initially, short-acting β_2-agonist (SABA) rescue medication can alleviate symptoms as needed and maintain asthma control. Loss of asthma control is associated with more frequent use of rescue medication, increased symptoms, increased exacerbation frequency or severity, and reduced lung function.[2–4] If control is not maintained with SABA use, maintenance therapy is initiated with a low-dose inhaled corticosteroid (ICS).[2] Many pediatric asthmatic patients remain uncontrolled despite the addition of ICS therapy.[5,6] In children aged ≥5 years with asthma uncontrolled by SABA and low-dose ICS treatment, the addition of a long-acting β_2-agonist (LABA) is recommended[2] and provides the best overall control compared with alternatives such as increasing the ICS dose and adding a leukotriene receptor antagonist.[7]

In children, ICSs and ICSs/LABAs are typically dosed twice daily. The ICS fluticasone furoate (FF) is in development as once-daily monotherapy and together with the LABA vilanterol (VI) is an ICS/LABA combination therapy for adults and adolescents with asthma. Once-daily dosing can improve adherence in asthmatic patients,[8–10] which would be beneficial in pediatric patients, where adherence is known to be low[11]; FF[12–14] and VI[15] have demonstrated efficacy and tolerability with once-daily dosing in asthmatic patients aged ≥12 years and are being investigated in a dedicated pediatric development program. The safety profiles and pharmacokinetic (PK) and pharmacodynamic (PD) properties of FF[16] and VI[17] monotherapy have been investigated in crossover placebo-controlled studies.

This study sought to assess the safety profile of FF/VI therapy versus that of FF monotherapy and to determine whether the administration of FF combined with VI via the ELLIPTA dry powder inhaler (DPI) (GlaxoSmithKline, London, United Kingdom) affected the PK or PD properties of FF.

METHODS

Study Population

Boys and girls (premenarchal) aged 5 to 11 years diagnosed as having asthma ≥6 months before screening and weighing ≥20 kg were enrolled. The inclusion criteria were controlled asthma (Childhood Asthma Control Test score of >19[18] and peak expiratory flow rate [PEFR] ≥75% of predicted); ≥4 weeks of stable asthma treatment with an ICS (fluticasone propionate, ≤400 μg daily, or an equivalent) and a SABA; and no significant medical conditions other than eczema or rhinitis. The exclusion criteria included the use of theophyllines, LABAs, or oral β_2-agonists; alteration of asthma therapy within 4 weeks; a history of life-threatening asthma; exacerbations requiring treatment with systemic corticosteroids or emergency department attendance (within 3 months); hospitalization (within 6 months); and visual evidence of oral candidiasis at screening. This study was approved by local ethics review committees (Quorum Review IRB, Seattle, Washington) and was conducted in compliance with Good Clinical Practice guidelines,[19] the Declaration of Helsinki,[20] and GlaxoSmithKline Standard Operating Procedures for all processes involved. Written informed consent was provided by a parent/guardian for each patient and was accompanied by informed assent from participants aged 7 to 11 years.

Study Design

This was a randomized, double-blind, repeated-dose, 2-period, crossover, Phase IIa study. Screening was within 28 days prior to dosing. Patients were separated into 2 cohorts: cohort I included those aged 8 to 11 years, and cohort II included those aged 5 to 7 years. Per the study protocol, dosing of cohort II occurred only after analysis of blinded tolerability and PK data from ≥6 patients in cohort I.

Patients were randomized and stratified by age (with ≥1 patient in each age group) to receive FF/VI, 100/25 μg, followed by FF, 100 μg, or FF, 100 μg, followed by FF/VI, 100/25 μg. The treatment periods were 14 days, separated by a washout period of ≥7 days, which was not formally capped. The planned total study length was ≤11 weeks, including screening and follow-up. Four patients exceeded the study duration (2 × 78 days, 1 × 84 days, and 1 × 98 days), but this was not judged to have affected the study outcome. Patients were dosed in the morning at the clinic on day 1, and tolerability assessments were performed up to 2 hours postdose. Patients self-dosed at home under parent/guardian supervision on days 2 to 13 within 1 hour of the original dose time. Parents/guardians were contacted on days 3, 7, and 10 to review dosing times, report adverse events (AEs), and deal with questions. Patients visited the clinic on day 14, were dosed within 1 hour of the original dose