ACCP
American College of Clinical Pharmacology
Advancing Clinical Care through Pharmacology®

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Vilanterol, a Novel Inhaled Long-Acting β-Agonist, in Children Aged 5–11 Years With Persistent Asthma: A Randomized Trial

Clinical Pharmacology in Drug Development
3(3) 215–221

DOI: 10.1002/cpdd.92

Amanda Oliver[1], Sandi VanBuren[2], Ann Allen[3], Melanie Hamilton[4], Lee Tombs[5], Rodger Kempsford[3], and Paul Qaqundah[6]

Abstract

This multi-center, randomized, double-blind, placebo-controlled, two-way crossover study was designed to characterize the safety, tolerability, pharmacokinetic, and pharmacodynamic profile of single and once-daily repeat doses of vilanterol 25 μg in children aged 5–11 years. Twenty-eight children with persistent asthma received a single inhaled dose of vilanterol 25 μg or placebo via the ELLIPTA™ dry powder inhaler (DPI) on Day 1, followed 7 days later by once-daily treatment for 7 days. Nine (33%) subjects reported adverse events (AEs) with vilanterol 25 μg and 6 (23%) with placebo. No serious or drug-related AEs were reported; 3 subjects experienced upper respiratory tract infection (URTI) with vilanterol 25 μg versus none with placebo. Similar pharmacokinetic profiles of vilanterol 25 μg were observed irrespective of age or gender. No clinically relevant changes in heart rate, Fridericia's correction (QTcF), maximum glucose or minimum potassium parameters were observed during treatment with vilanterol 25 μg compared with placebo treatment. Vilanterol was well-tolerated and no long-acting $ß_2$-agonist (LABA)-mediated AEs were observed. The pharmacokinetic profile of vilanterol 25 μg suggests exposure is similar regardless of age or gender in a pediatric population aged 5–11 years.

Keywords

pharmacokinetics and pharmacodynamics, tolerability, vilanterol, children, asthma

Preferred step-up therapy for uncontrolled asthma in children aged 5 years or older takes the form of addition of a long-acting $ß_2$-agonist (LABA) to a low-dose inhaled corticosteroid (ICS); ICS dose increase or addition of a leukotriene-receptor antagonist (LTRA) or theophylline may also be considered.[1,2] Recent data suggest that on a population level the addition of a LABA to ICS provides the best response in terms of improving control, compared to increase of ICS dose or addition of LTRA. However, on an individual level increased ICS dose or addition of an LTRA did provide the best response in some cases.[3]

Uncontrolled pediatric asthma has been reported at a prevalence of 46% in a sample of 2,429 pediatric subjects with asthma.[4] The reasons for this are unclear, but likely include factors such as poor adherence[5] and lack of responsiveness to treatment.[6–8] There is a need for novel therapies that have the potential to increase asthma control in children.

Vilanterol is a novel once-daily LABA with established efficacy and tolerability in adult asthma.[9] It is being developed with the once-daily ICS fluticasone furoate, which has also demonstrated efficacy and tolerability in adult asthma[10–12] for planned simaltaneous delivery via the ELLIPTA™ dry powder inhaler

[1]GlaxoSmithKline, Uxbridge, UK
[2]GlaxoSmithKline, King of Prussia, PA, USA
[3]GlaxoSmithKline, Stevenage, UK
[4]GlaxoSmithKline, Ware, UK
[5]Synergy, Slough, UK
[6]Pediatric Care Medical Group, Huntington Beach, CA, USA

Submitted for publication 18 December 2012; accepted 8 November 2013

Corresponding Author: Dr. Amanda Oliver, GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT, UK
(e-mail: amanda.j.oliver@gsk.com)
Clinical trial registration (www.clinicaltrials.gov): NCT01453296.

(DPI) (ELLIPTA™ is a trademark of the GlaxoSmithKline group of companies). Both agents have the potential to improve asthma control in the pediatric population and are being assessed in a pediatric development program.

This paper describes the results of the first placebo-controlled crossover study, assessing the safety, tolerability, pharmacodyamics and pharmacokinetics of repeat dosing of vilanterol 25 μg in pediatric subjects with persistent asthma aged between 5 and 11 years and receiving stable concomitant ICS. The 25 μg dose of vilanterol represents the sole dose progressed to phase III studies in adults.

Methods

Study Population

Male and female (pre-menarchal) subjects aged 5–11 years with a diagnosis of asthma at least 6 months prior to screening and body weight ≥15 kg were enrolled. Inclusion criteria included the presence of controlled asthma (Childhood Asthma Control Test score of >19[13] and peak expiratory flow [PEF] ≥75% predicted) and the absence of any other significant medical condition, except eczema and rhinitis. A stable, as-needed short-acting $ß_2$-agonist and low-to-medium-dose ICS (≤400 μg daily fluticasone propionate or equivalent) regimen for at least 4 weeks prior to screening was also required for entry into the study. Exclusion criteria included receipt of theophyllines, LABAs, or oral $ß_2$-agonists within 4 weeks of screening; asthma exacerbation requiring emergency room attendance within 3 months, or hospitalization within 6 months of screening; and visual evidence of oral candidiasis. The study (GlaxoSmithKline protocol: HZA112776; ClinicalTrials.gov identifier: NCT01453296) was conducted in accordance with Good Clinical Practice and the guiding principles of the 2008 Declaration of Helsinki. The study was reviewed and approved by Quorum Review Institutional Review Board of Seattle, WA, USA. Informed consent was provided by the parent or legal guardian of each study participant. In addition, subjects 7–11 years of age provided written assent.

Study Design

This was a multi-center, randomized, double-blind, placebo-controlled, two-way crossover study. Within 28 days prior to dosing subjects and their parent or guardian attended a screening visit during which they were familiarized with the ELLIPTA DPI, and the study entry criteria were verified. Subjects were separated into two cohorts: cohort I included ages 8–11 years, and cohort II included ages 5–7 years. As per the study protocol, dosing of cohort II only occurred after analysis of blinded safety and pharmacokinetic data from at least six subjects in cohort I. To maintain the study blind during the interim safety review, the pharmacokinetic data from cohort I used scrambled subject identifications, and parameters were derived for each subject using nominal times.

Randomization was stratified by age, and each subject was randomized to 1 of 2 treatment sequences, consisting of two 14-day study periods made up of a single dose, 7-day washout, and 7 days repeat dosing. The treatment sequences were as follows; vilanterol 25 μg followed by matching placebo, or matching placebo followed by vilanterol 25 μg. Both treatments were administered in the morning via the DPI. Subjects were dosed in the clinic under the supervision of study staff on study Days 1, 8 (the first day of repeat dosing), and 14; home dosing under the supervision of the parent/guardian was required on study Days 9–13 within 3 hours of the nominal time of morning dosing on Day 1. Prior to the first study dose subjects and their parent/guardian were trained on use of the DPI. Subjects were generally, but not exclusively dosed on different days. Subjects remained in the study unit for pharmacokinetic, pharmacodynamic, and safety assessments following dosing on Day 1 (approximately 2 hours); Day 8 (approximately 1 hour) and Day 14 (approximately 8 hours). Subjects fasted from at least 3 hours pre-dose until at least 2 hours post-dose on Days 1 and 14. PEF was measured each day prior to dosing and the results recorded on the study diary card. Site staff contacted the parent/guardian on Days 10 and 12 to ensure compliance with dosing, to query for any adverse events (AEs), and to answer any questions. Morning dosing was employed due to the impracticality of collecting post-dose samples during night-time. A follow-up visit took place 7–14 days after the final dose of study medication.

Safety Assessments

AEs and serious AEs were recorded throughout the study. AEs representing possible LABA systemic pharmacodynamic effects were pre-defined as AEs of special interest. These included; cardiovascular effects, including effects on heart rate; effects on potassium and glucose; hypersensitivity; and tremor.

PEF measurements were performed as a safety assessment in triplicate at screening and pre-dose and 20 minutes post-dose on Days 1, 8, and 14, and pre-dose on Days 9–13 of each treatment period. Additional safety assessments included clinical laboratory assessments (hematology, chemistry and urinalysis), vital signs (systolic and diastolic blood pressure and heart rate) and 12-lead electrocardiogram using Fridericia's correction (QTcF). Heart rate and QTcF were statistically analyzed as a pharmacodynamic assessment.

Pharmacokinetic Assessments

Blood samples (2 mL into KEDTA tubes) were collected up to 8 hours post-dose via an indwelling catheter on Day 14 of each treatment period. Samples were collected pre-dose, and 10 minutes, 30 minutes and 1, 2, and 4 hours post-dose; in subjects weighing $\geq$20 kg samples were also collected at 6 and 8 hours post-dose.

Plasma obtained via centrifugation was stored in a polypropylene tube at $\leq -20^{\circ}$C until analysis. Plasma samples (200 μL aliquot) were analyzed for vilanterol by solid phase extraction using [$^{2}H_{12}$]–GW642444 as internal standard, followed by high performance liquid chromatography using tandem mass spectrometry detection using an Applied Biosystems API-5000 (Applied Biosystems/MDS Sciex, Foster City, CA). A gradient system using 10 mM ammonium formate containing 0.1% formic acid and acetonitrile containing 0.1% formic acid was run with column 50 mm × 2.1 mm i.d. Hypersil Gold, 3 μm, Thermo Scientific running at 50°C. The ion transition for vilanterol was m/z 486–159. The validation range of the assay was 10–10,000 pg/mL. The lower limit of quantification of vilanterol was 10 pg/mL and the within-run precision, between-run precision and bias were all $\leq$14.4%. Quality controls prepared at three different concentrations analysed with each batch of samples met the acceptance criteria.

Pharmacokinetic parameters were derived from the initial time-concentration data by standard non-compartmental analysis using WinNonLinPro Version 5.2 (Pharsight Corporation, St Louis, MO). The following parameters were derived: maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), time of last quantifiable plasma concentration (t) and area under the plasma concentration–time curve from time 0 to the last time of measurable concentration ($AUC_{(0-t)}$). For individual values that were below the LLQ a value of ½ the LLQ was imputed for C_{max} calculations and a value of ½ the lowest observed AUC was imputed for AUC calculations. For time profile assessment values below the LLQ were set to zero.

Pharmacodynamic Assessments

Blood samples (2 mL into KEDTA tubes) were taken on Day 14 via an indwelling cannula; samples for glucose and potassium analysis were collected pre-dose and 10 minutes, 30 minutes and 1, 2, 4, 6, and 8 hours post-dose.

The enzymatic method of analysis for glucose samples was based upon the catalytic action of hexokinase on glucose and adenosine triphosphate to yield glucose-6-phosphate.[14] The glucose-6-phosphate is then reacted on by glucose-6-phosphate dehydrogenase with simultaneous reduction of nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide hydride (NADH). The absorbance of the reduced NADH, which is produced in an amount equimolar to the concentration of glucose is read bichromatically at 340/380 nm. The absorbance value is then compared to the absorbance produced by a known calibrator. The result is then printed out directly in mg/dL.

Serum potassium was measured by using a flowcell with an ion-selective electrode.[15]

Exploratory Pharyngometry and Inhalation Profile Assessments

Pharyngometry and inhalation profiles were determined at screening and pre-dose on Day 1 and Day 14 of each treatment period. Mouth and throat geometry was measured using acoustic reflectance (Eccovision, Sleep Group Solutions, North Miami Beach, FL). Inhalation profiles were measured with an instrumented blinding box connected to an inhalation profile recorder (GlaxoSmithKline, Ware, UK). Attributes of vilanterol dose emission from the DPI were modeled through replication of selected inhalation profiles using an in vitro simulation method (Electronic Lung [eLung], GlaxoSmithKline, Ware, UK)[16] and an anatomical throat cast. Analysis of these endpoints comprised the modeling and prediction of total emitted dose, ex-throat dose and mass of ex-throat dose less than 2 microns of vilanterol for each subject.

Statistical Methods

Primary endpoints were; AEs, clinical laboratory assessment, PEF (Days 1, 8, and 14), systolic/diastolic blood pressure, heart rate (maximum and weighted mean [wm] 0–2 hours on Days 1 and 14, and maximum and wm 0–2 hours and 0–8 hours on Day 14) and QTcF (wm and peak response on Day 1 [0–2 hours], and wm and peak response on Day 14 [0–2 hours, and 0–8 hours]). Secondary endpoints comprised pharmacokinetic parameters, serum glucose (maximum and wm at 0–2 hours and 0–8 hours on Day 14), and blood potassium (minimum and wm at 0–2 hours and 0–8 hours on Day 14).

No formal sample size calculation was performed, however at least 20 subjects were required to complete the study, including at least 8 subjects under 8 years of age and at least two subjects of each of the following ages: 5, 6, 8, 9, and 10 years, in order to ensure adequate representation of each age.

On Day 1 and Day 14, each of the maximum and wm (0–2 hours) endpoints for heart rate and QTcF was statistically analyzed using a mixed effects repeated measures model. Treatment, period, day, and treatment-day interaction were fitted as fixed effects, and subject as a random effect. On Day 1 and Day 14, point estimates and their associated 95% confidence intervals (CIs) were constructed for each treatment and the difference between treatments.

On Day 14, each of the maximum and wm (0–8 hours) endpoints for heart rate and QTcF were statistically analyzed using a mixed effects model. Treatment, period, subject baseline and period baseline were fitted as fixed effects, and subject as a random effect. Point estimates and their associated 95% CIs were constructed for each treatment and the difference between treatments. In addition, each of the wm (0–2 hours) and (0–8 hours) glucose and potassium, as well as maximum glucose (0–2 hours) and (0–8 hours) and minimum potassium (0–2 hours) and (0–8 hours) endpoints was statistically analyzed using a mixed effects model. Treatment and period were fitted as fixed effects and subject as a random effect.

Results

Subject Disposition and Baseline Characteristics

Twenty-eight subjects (18 male, 10 female) were randomized and 24 completed the study. All ages from 5 to 11 years were represented; the median age was 8 years. The mean height and weight were 131.2 cm and 32.00 kg, respectively. Fluticasone propionate was the most commonly recorded concomitant medication, taken by 20 subjects throughout the trial period. Salbutamol use was reported by 14 subjects. Subjects received all doses as planned except for those withdrawn and one subject who received vilanterol 25 μg during both treatment periods in error.

Safety and Tolerability Results

AEs were reported by six subjects during the placebo treatment period and by nine subjects during the vilanterol 25 μg treatment period. Headache, upper respiratory tract infection (URTI), and pyrexia were reported by more than one subject while all other AEs were reported by single subjects only. Headache occurred in the same number of subjects during placebo and vilanterol 25 μg treatment (n = 2), however URTI (and one viral URTI) and pyrexia were reported solely during vilanterol 25 μg treatment (n = 3 and n = 2, respectively). No serious AEs were reported, nor were any AEs deemed to be potentially treatment related by the investigator. Two AEs of special interest were reported; one subject presented with sinus bradycardia during placebo treatment which resulted in withdrawal. One subject experienced chest pain 23.5 hours following vilanterol 25 μg treatment (Day 10). The event resolved without any treatment after 31 minutes and the subjects continued in the study.

Three subjects withdrew due to AEs. One subject experienced a severe asthma exacerbation after 3 days repeat dosing of vilanterol 25 μg. The event occurred 19 hours post-dose and resolved 4 hours later with oral prednisolone 40 mg. This event met the protocol defined stopping criteria. One subject experienced disorientation, headache, and conversion disorder 36 minutes following the final dose on Day 14 of placebo treatment. A pediatric neurologist ruled out seizure disorder. One subject experienced sinus bradycardia (49 bpm) during the single dose placebo period and was withdrawn after 6 days of repeat placebo dosing. This event met the protocol defined stopping criteria. The event was not recorded as having been resolved but a normal heart rate of 58 bpm was recorded on follow-up 6 days after the last dose of placebo. None of these events were considered related to study treatment.

Clinical laboratory parameters were similar following 7 days of treatment with placebo or vilanterol 25 μg, no clinically significant abnormalities were observed. Mean PEF values, L/min (95% CI), at baseline were 230.6 (201.3, 259.9) for placebo treatment and 233.0 (206.4, 259.6) for vilanterol 25 μg. No evidence of a decrease in PEF was observed up to 20 minutes post-dose on Day 14 when PEF values were 243.3 (211.5, 275.0) for placebo treatment and 248.1 (217.3, 278.9) for vilanterol 25 μg treatment. No difference was observed between the mean systolic and diastolic blood pressure values recorded during placebo and vilanterol 25 μg treatment.

Pharmacokinetic Results

Twenty-five subjects were included in the pharmacokinetic analysis. Vilanterol in plasma was quantifiable in 17 of the 25 subjects up to 6 hours following administration of the final dose, and in 9 subjects at 8 hours post-dose. Two subjects had no quantifiable vilanterol concentrations. A mean concentration–time profile is presented in Figure 1 and pharmacokinetic parameters are summarized in Table 1. Vilanterol C_{max} was observed at a median time of 12 minutes post-dose. Individual scatterplots of C_{max} and $AUC_{(0-t)}$ by age (data not shown)

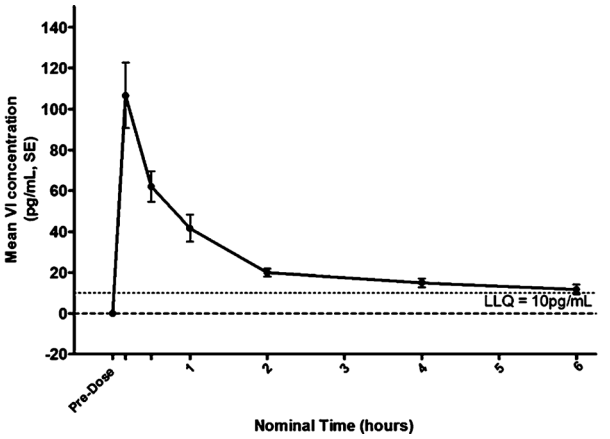

Figure 1. Mean (SE) vilanterol concentration-time profile following once-daily dosing for 7 days. LLQ, lower limit of quantification; VI, vilanterol.

Table 1. Summary of Pharmacokinetic Parameters

Parameter	Vilanterol 25 μg (N = 25)	
	Geometric mean (95% CI)	Arithmetic mean (SD)
$AUC_{(0-t)}$, pg h/mL	132.8 (96.0, 183.8)	166.2 (94.7)
$AUC_{(0-8)}$, pg h/mL	181.7 (145.0, 227.7)	199.6 (83.4)
C_{max}, pg/mL	97.4 (64.8, 146.5)	127.1 (69.4)
$t_{1/2}$ hours	2.98 (2.26, 3.93)	3.29 (1.49)
	Median (range)	
t_{max}, hours	0.20 (0.00, 1.00)	
t, hours	6.00 (1.00, 8.13)	

CI, confidence interval; SD, standard deviation; $AUC_{(0-8)}$ = area under the concentration-time curve from pre-dose to 8 hours; $AUC_{(0-t)}$ = area under the concentration-time curve from pre-dose to the last time of measurable concentration; C_{max}, maximum observed plasma concentration; t, time of last quantifiable plasma concentration; $t_{1/2}$, terminal phase half-life; t_{max}, time to C_{max}.

suggested no notable effect of age on the pharmacokinetic profile of vilanterol.

Pharmacodynamic Results

No clinically significant difference was observed between vilanterol and placebo treatment for all heart rate (Figure 2a) or QTcF (Figure 2b) parameters on Day 1 or Day 14. Serum glucose and blood potassium were not significantly clinically different between the vilanterol 25 μg and placebo treatment periods (Figure 2c/d). Treatment effects recorded for each of these parameters with vilanterol or placebo therapy are reported in the online supplement (Tables S1–S6).

Exploratory Pharyngometry and Inhalation Profile Assessments

Data of pharyngometry assessments were available for up to 15 subjects representative of the 5–11 year age range; it was not possible to accurately interpret data for the remaining subjects. Overall mean distance of assessment (lips to larynx), cross sectional area and oropharyngeal volume of the mouth and throat were 18.40 cm, 5.20 cm^2, and 93.40 cm^3 respectively, on Day 14 of active treatment. Inhalation profiles were available for up to 25 (also dependent on treatment period and study day) subjects due to unexpected equipment access issues during placebo treatment. Pressure drop versus time profiles recorded whilst inhaling across the resistance of the DPI resulted in an overall mean peak inspiratory flow rate (PIFR) of 61.80 L/min (standard deviation [SD] = 15.35 L/min) on Day 14 of active treatment. Individual

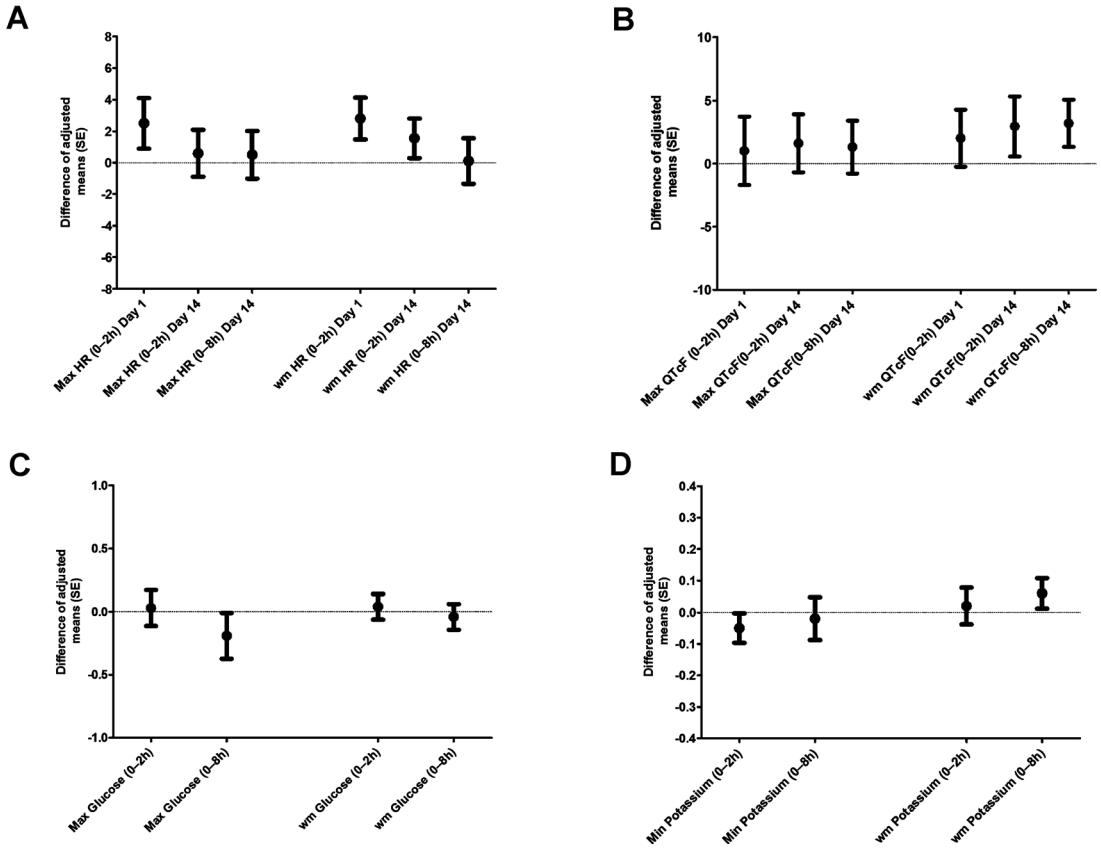

Figure 2. Treatment difference (arithmetic mean ± standard error) from placebo on Day 1 and Day 14 in (A) heart rate (bpm); (B) QTcF (msec); (C) serum glucose (mmol/L); (D) blood potassium (mmol/L). h, hours; HR, heart rate; QTcF, Fridericia's correction; wm, weighted mean; SE, standard error.

scatterplot analysis (not shown) indicated no relationship between age, height or body mass index and PIFR. Through use of the eLung in vitro simulation method, dose emission attributes of vilanterol delivered via the DPI were predicted for each subject. For Day 14 data the mean total emitted dose was predicted to be 20.3 μg (SD = 0.2), the mean nominal ex-throat dose to be 9.0 μg (SD = 0.7), and the mass of particles of less than 2 microns to be 4.2 μg (SD = 1.1).

Discussion

Pharmacologic therapy must be both safe and effective. The current study, employing a crossover placebo-controlled design, shows that vilanterol 25 μg is well tolerated in a population of pediatric subjects aged 5–11 years with mild-moderate asthma. No serious AEs were reported, none of the AEs reported were deemed potentially treatment related by the investigator prior to unblinding, and as monitored by PEF in the first 20 minutes post-dose, there was no indication of an adverse effect of VI on PEF. The reports of URTI occurring in three subjects and viral URTI in one subject during vilanterol therapy, as compared with no events during placebo could be a chance finding given the small study population and the scheduling of the study during the winter months; none of these events were assessed as being related to vilanterol by the investigator. Of the three AEs that lead to study withdrawal, one (sinus bradycardia) represented an AE of special interest, however this occurred during placebo treatment. The other AE of special interest (chest pain) did occur during vilanterol therapy but resolved without sequalae within 31 minutes of onset.

Known LABA adverse effects occur as a consequence of activity at systemic ß-receptors. Manifestations include increases in heart rate, QTcF, and serum glucose, and a decrease in serum potassium. Each of these parameters was assessed. No clinically significant changes in heart rate or QTcF were recorded for maximum or wm measures on Day 1 or Day 14 of vilanterol treatment relative to placebo. No change was observed in serum glucose or blood potassium with vilanterol 25 μg after 7 days repeat dosing compared to placebo.

Twenty-five of the 28 subjects provided pharmacokinetic data, and the concentration–time profile indicates vilanterol reached maximum plasma concentration shortly after dosing (t_{max} = 12 min), with a half-life of approximately 3 hours and an $AUC_{(0–t)}$ of 132.8 pg hours/mL. Quantifiable plasma concentrations in 9 of 25 subjects were present at 8 hours post-dose. Two subjects had no quantifiable vilanterol concentrations, and three subjects had vilanterol concentrations in the pre-dose samples. Although no documentation exists, it is highly likely the samples for these three subjects were drawn post-dose since vilanterol is absorbed very rapidly from the lung. Importantly, neither age nor gender appeared to be related to C_{max} or $AUC_{(0–t)}$, suggesting the pharmacokinetic profile of vilanterol is similar in all pediatric subjects. The pharmacokinetic profile of vilanterol in children appears similar to that in adults.[17,18]

A number of factors strengthen the findings of the present study. The crossover placebo-controlled design ensured that subjects acted as internal controls, as well as allowing the safety of vilanterol to be compared with that of placebo. The study population also represented the full range of ages set out in the study design, and the design ensured that vilanterol was established as safe and tolerable in a two-step manner. Firstly the safety of a single dose of vilanterol could be assessed in each child prior to starting 7 days of repeat dosing, and secondly pharmacokinetic and safety data from older children was reviewed prior to initiating the study in younger children. Despite the limited blood sampling volume permitted in pediatric trials, robust pharmacokinetic and pharmacodynamic data were obtained. Lastly the study assessed a novel exploratory endpoint directed at predicting the emitted dose from the DPI (see below). There were, however, some limitations. The treatment period only comprised a total of 8 days therapy with vilanterol, so long-term effects could not be assessed. Also the small (but representative) study population was not large enough to identify potential rare effects and only a single dose (25 μg) of vilanterol was assessed, though this does represent the maximum dose investigated in phase III adult trials of vilanterol.

Data collected from the eLung™ suggest that the PIFR when inhaling through the DPI was sufficient to predict consistent product performance.

Vilanterol 25 μg, when dosed once and as repeat doses for 7 days (eight total doses) was well tolerated in pediatric asthma subjects aged 5–11 years. No LABA-mediated effects of vilanterol were observed. There appears to be no relationship between vilanterol exposure and age or gender, suggesting that a single dose may be suitable for this population.

Acknowledgments

Sandra Hirschberg contributed to the design of the study and played a key role in setting up the study. Editorial support in the form of development of a first draft of this manuscript (under the guidance of the lead author), collation of comments on drafts of the manuscript, development of tables and figures, copyediting and referencing was provided by Geoff Weller, PhD, at Gardiner-Caldwell Communications. This support was funded by GlaxoSmithKline.

Declaration of Conflicting Interests

All authors except Paul Qaqundah and Lee Tombs are employees of GlaxoSmithKline, the sponsor of the study;

Paul Qaqundah has no conflict of interest to declare; Lee Tombs is a statistical consultant for Synergy. Editorial support was provided by Geoff Weller, PhD at Gardiner-Caldwell Communications.

Funding

Funding for this study and payment of the open-access fee for the manuscript was provided by GlaxoSmithKline.

References

1. Global strategy for asthma management and prevention. Global Initiative for Asthma. www.ginaasthma.org. Updated 2011. Accessed August 2012.
2. NHLBI Expert panel report 3. Guidelines for the diagnosis and management of asthma (EPR-3). NIH Publication No. 07-4051. Bethesda, MD, USA: U.S. Department of Health and Human Services, National Institutes of Health; National Heart, Lung and Blood Institute, National Asthma Education and Prevention Programme, August 2007, www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed August 2012.
3. Lemanske RF, Jr., Mauger DT, Sorkness CA, et al., Childhood Asthma Research and Education (CARE) Network of the National Heart, Lung, and Blood Institute. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med.* 2010;362:975–985.
4. Liu AH, Gilsenan AW, Stanford RH, Lincourt W, Ziemiecki R, Ortega H. Status of asthma control in pediatric primary care: results from the pediatric Asthma Control Characteristics and Prevalence Survey Study (ACCESS). *J Pediatr.* 2010;157:276–281. e3.
5. Krishnan JA, Bender BG, Wamboldt FS, et al., Adherence to inhaled corticosteroids: an ancillary study of the Childhood Asthma Management Program clinical trial. *J Allergy Clin Immunol.* 2012;129:112–118.
6. Gelfand EW. Pediatric asthma: a different disease. *Proc Am Thorac Soc.* 2009;6:278–282.
7. Nino G, Grunstein MM. Current concepts on the use of glucocorticosteroids and beta-2-adrenoreceptor agonists to treat childhood asthma. *Curr Opin Pediatr.* 2010;22:290–295.
8. Szefler SJ. Advances in pediatric asthma in 2010: addressing the major issues. *J Allergy Clin Immunol.* 2011;127:102–115.
9. Lötvall J, Bateman ED, Bleecker ER, et al. 24-h duration of the novel LABA vilanterol trifenatate in asthma patients treated with inhaled corticosteroids. *Eur Respir J.* 2012;40:570–579.
10. Bateman ED, Bleecker ER, Lötvall J, et al. Dose effect of once-daily fluticasone furoate in persistent asthma: a randomized trial. *Respir Med.* 2012;106:642–650.
11. Bleecker ER, Bateman ED, Busse W, et al. Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids. *Ann Allergy Asthma Immunol.* 2012;109:353–358.e4.
12. Busse WW, Bleecker ER, Bateman ED, et al. Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial. *Thorax.* 2012;67:35–41.
13. Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. *Eur Respir J.* 2010;36:1410–1416.
14. Stein MW. *Clinical Methods of Enzymatic Analysis*. Academic Press; 1965, 117.
15. Tietz NW. *Fundamentals of Clinical Chemistry*. 3rd ed. Philadelphia, USA: WB Saunders; 1987.
16. Burnell PKP, Malton A, Reavill K, Ball MHE. Validation and initial testing of the electronic lung^{TM} device. *J Aerosol Sci.* 1998;29:1011–1025.
17. Kempsford RD, Norris V, Siederer SK. The pharmacodynamics, pharmacokinetics and tolerability of repeat doses of the novel inhaled long-acting beta2 adrenoceptor agonist (LABA) GW642444 (25, 50 and 100 μg) in healthy subjects. *Am J Respir Crit Care Med.* 2010;181:A4461.
18. Kempsford RD, Norris V, Siederer SK. GW642444, a novel inhaled long-acting beta2 adrenoceptor agonist (LABA), at single doses of 25, 50 and 100 mcg, is well tolerated and demonstrates prolonged bronchodilation in asthmatic patients. *Am J Respir Crit Care Med.* 2010;181:A5413.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site.