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Efficacy and optimal dosing interval of the long-acting beta$_2$ agonist, vilanterol, in persistent asthma: A randomised trial

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KEYWORDS
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Summary
Background: Vilanterol (VI) is a novel once-daily long-acting beta$_2$ agonist with inherent 24-h activity. The aim of this study was to evaluate the efficacy of three once-daily doses and one twice-daily dose of VI used concurrently with ICS in adult patients (≥18 years) with persistent asthma. Safety was also assessed.
Methods: Multicentre, randomised, double-blind, placebo-controlled, five-period crossover study consisting of 7-day treatment periods separated by 7-day wash-out periods. Seventy-five patients, maintained on ICS, received VI 6.25, 12.5 and 25 mcg once-daily (evening), VI 6.25 mcg twice-daily (morning/evening), and placebo. The primary endpoint was trough forced expiratory volume in 1 s (FEV_1) (mean of 23 h and 24 h post evening dose) on Day 7; secondary endpoint was weighted mean 24-h serial FEV_1 on Day 7.
Results: All VI groups demonstrated statistically significant increases in trough FEV_1 versus placebo ($p < 0.001$). There was a statistically significant increase in weighted mean 24-h FEV_1 for each VI group versus placebo ($p < 0.001$). The effects of once-daily VI on trough FEV_1 and weighted mean 24-h FEV_1 were dose dependent. The incidence of adverse events (AEs) was low in each VI treatment group and was not dose dependent (5–9%; placebo = 18%); no drug-related AEs or serious AEs were reported.
Conclusion: Once-daily treatment with VI was well tolerated and associated with improvements in lung function. The VI 6.25 mcg twice-daily dose showed the greatest change in trough FEV_1, however, similar changes in weighted mean 24-h FEV_1 with VI 12.5 mcg once-daily were observed. Although our study was not powered to demonstrate non-inferiority of once- versus twice-daily dosing of VI, the data suggest no advantage over a 24-h period of twice-daily over once-daily dosing for the same total daily dose.
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Introduction

Inhaled corticosteroids (ICS) are recommended for patients with asthma who are symptomatic on as-needed short-acting beta$_2$ agonist (SABA) (Step up from Step 1 to Step 2).[1,2] Combination therapy consisting of an ICS and an inhaled long-acting beta$_2$ agonist (LABA) is recommended for patients with persistent asthma who remain symptomatic despite ICS therapy (Step up from Step 2 to Step 3).[1,2] Combination therapy in asthma is associated with increased lung function and decreases in symptoms, exacerbation frequency and need for rescue medication compared with ICS alone.[2–5] Current ICS/LABA combination therapies (comprising the LABA salmeterol or formoterol) are licensed for twice-daily use. Less complex dosing schedules such as once-daily dosing may help to improve adherence to asthma therapies as adherence to treatment can be problematic with long-term use.[6,7] Poor adherence to therapy is associated with poor asthma control.[8,9] Vilanterol (VI; GW642444M) is a once-daily LABA with inherent 24-h activity in development in combination with the novel ICS, fluticasone furoate (FF) for asthma and COPD. Once-daily dosing with FF/vilanterol (VI) in a fixed-dose combination inhaler may increase treatment adherence by providing greater convenience to the patient. The efficacy and safety of VI dosed once-daily in the evening has been demonstrated in patients with persistent asthma uncontrolled on ICS therapy.[10] In this dose-ranging study, regular once-daily treatment in the evening with VI was well tolerated and resulted in prolonged bronchodilation of at least 24 h at doses $\geq$12.5 mcg once-daily with the greatest benefit seen at the 25 mcg dose.

The primary aim of the present phase IIb study was to evaluate the efficacy of selected doses of VI (concurrently with ICS) compared with placebo. The secondary aim was to investigate the optimal dose interval (once-daily versus twice-daily) of VI. Safety and tolerability of VI were also assessed. The study was carried out in adult patients with persistent asthma. Preliminary results have been presented in the form of an abstract.[11]

Methods

Study subjects

At Visit 1 (screening) adult patients ($\geq$18 years of age) were eligible to enter the 7 ($+$7 day) run-in period if they had asthma according to the National Institutes of Health criteria, forced expiratory volume in 1 s (FEV_1) reversibility of $\geq$12% and $\geq$200 mL following salbutamol/albuterol, and had been taking ICS at a stable dose for $\geq$4 weeks prior to screening and could replace their current SABA with albuterol/salbutamol for rescue use during the study. Details of permitted and prohibited medications are provided in Online Appendix 1. At the end of run-in, to be eligible for randomisation, patients had to demonstrate *either* an evening pre-dose percent predicted FEV_1 between 40% and $<$80%, or a FEV_1 percent predicted of $\geq$80–85% and had reported symptoms and/or used rescue salbutamol/albuterol on at least three of the last seven days of run-in. Other criteria for randomisation included: normal laboratory test results (for haematological and clinical chemistry assessments) physical exams and ECG; no reported asthma exacerbations during run-in and no change in baseline asthma medication. Further information on eligibility criteria at run-in and randomisation are provided in Online Appendix 2.

All study participants gave written informed consent and the study was approved by local ethics review committees and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study design and treatments

This was a randomised, multicentre, double-blind, placebo-controlled, five-period crossover study (HZA113310; www.clinicaltrials.gov registration number NCT00980200) conducted at nine centres in the USA between 15 September 2009 and 5 January 2010. Patients were randomly allocated to one of five treatment sequences with each 7 ($+$3) day treatment period separated by a 7 ($-$3/$+$7) day wash-out period; all patients received VI 6.25 mcg twice-daily, VI 6.25 mcg once-daily, VI 12.5 mcg once-daily, VI 25 mcg once-daily and placebo. Patients were followed for 7 ($\pm$3) days at the end of the fifth treatment sequence or early withdrawal. Treatments were administered via a new dry powder inhaler. All patients and investigators were blinded to treatment assignment, and the placebo and VI formulations were indistinguishable. The central randomisation schedule was generated by the sponsor using a validated computerised system (RandAll). Patients were randomised using Registration and Medication Ordering System (RAMOS), an automated, interactive telephone based system that was used by the investigator or designee to register the patient, randomise the patient and receive medication assignment information. Compliance was assessed at the end of each 7-day treatment period by reviewing the dose counter on the new dry powder inhaler. Drug treatments and the inhaler device were manufactured by GlaxoSmithKline, United Kingdom.

Outcome measurements

The primary efficacy endpoint was trough (pre-bronchodilator and pre-dose) FEV_1 at the end of the 7-day treatment period (mean of 23-h and 24-h assessments post evening dose). The secondary endpoint was the weighted mean for 24-h serial FEV_1 (average area under the curve) on Day 7. Serial 24-h FEV_1 was measured on Day 7 of each of the five treatment periods at: pre-dose, 30 and 60 min and 3, 5, 11, 12, 12.5, 13, 15, 17, 23 and 24 h post dose. Other endpoints included the proportion of patients obtaining $\geq$200 mL and $\geq$12% increase from baseline in FEV_1 (0–24 h) on Day 7.

Safety evaluation

Safety assessments included physical examination, laboratory assessments (haematological, biochemical and urinalysis), ECG, vital signs and adverse events (AEs). Physical examinations and laboratory assessments were made at screening/run-in, at the end of the final (fifth) treatment sequence and if the patient was withdrawn early from the

study. ECGs were performed at screening/run-in. AEs and vital signs were assessed at screening/run-in, during all five treatment periods and if the patient was withdrawn early from the study. AEs were also assessed at follow up. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Patients were withdrawn from the study due to lack of efficacy if they experienced an asthma exacerbation (defined as worsening asthma requiring treatment with oral/systemic steroids or emergency department visit or in-patient hospitalisation for the treatment of asthma).

Statistical analysis

To determine an appropriate sample size, the study was powered to demonstrate superiority of each VI treatment versus placebo for the primary endpoint. It was estimated that approximately 75 patients were required to be randomised to obtain 65 evaluable patients. This sample size provided approximately 90% power to detect a 125 mL treatment difference, assuming a within-patient standard deviation of 210 mL, with a two-sided significance level of 5%. Additionally, a sample size of 65 ensured that the half-width of the 95% confidence interval for the treatment differences between any dose of VI and placebo was no larger than approximately 75 mL.

The primary treatment comparisons were of each dose regimen of VI versus placebo for trough FEV_1 on Day 7. Although comparisons of the once-daily and twice-daily dosing regimens were of interest, the study was not powered to demonstrate non-inferiority of the once-daily regimens relative to the twice-daily regimen. The primary and secondary statistical analyses were performed using a mixed effects analysis of covariance (ANCOVA) models with fixed effects for treatment, period, sex and age. Subject was fitted as a random effect and the period baseline measurement (pre-dose FEV_1 on Day 1) was included as part of a bivariate response.

The intent-to-treat (ITT) population comprised all randomised patients who received at least one dose of study drug; all analyses of efficacy and safety measures were performed in this population. The per-protocol (PP) population comprised all patients in the ITT population not identified as major protocol violators; this population was used for confirmatory analyses of the primary efficacy endpoint only. Further details of the analysis populations in this study are provided in Online Appendix 3.

An exploratory efficacy analysis consisting of a repeated measures analysis of change from period baseline in serial FEV_1 on Day 7 was performed; the model allowed for effects due to the mean of the period baselines, period, period baseline, treatment, sex, age, time (nominal) and contained time-by-treatment and time-by-baseline interaction terms.

Results

Study population

Of 136 patients screened, 75 underwent randomisation (ITT population) and 72 completed the study (Fig. 1). There were 74 patients in the PP population. Table 1 shows baseline patient characteristics including ICS use and screening lung function of the ITT population. Mean exposure to study medication was 9.5—9.8 days and mean overall compliance was >99%.

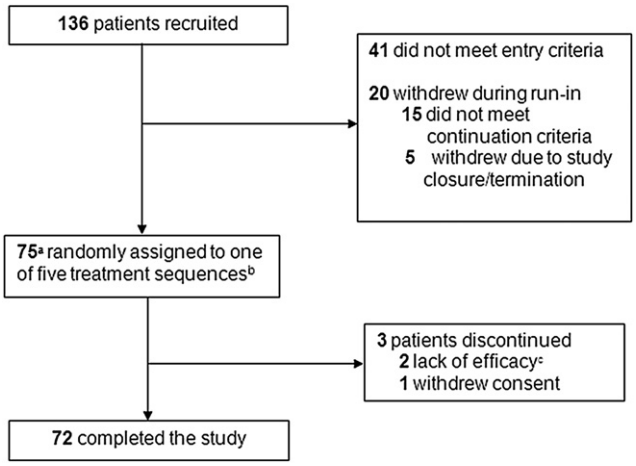

Figure 1 Patient disposition and reasons for discontinuation. [a]Intent-to-treat population. [b]VI (6.25 mcg OD, 6.25 mcg BD, 12.5 mcg OD and 25 mcg OD) and placebo treatment. [c]One patient had PEF reading below stability limit and one patient had FEV_1 reading below stability limit. BD, twice-daily; FEV_1, forced expiratory volume in 1 s; OD, once-daily; PEF, peak expiratory flow; and VI, vilanterol.

Efficacy

All doses of VI were associated with statistically significant increases in trough FEV_1 on Day 7 versus placebo and the differences from placebo with VI OD were dose-related (VI 6.25 mcg OD, 94 mL [95% CI: 49, 140 mL]; VI 12.5 mcg OD, 102 mL [95% CI: 57, 147 mL]; VI 25 mcg OD 125 mL [95% CI: 80, 170 mL]; VI 6.25 mcg BD 140 mL [95% CI: 95, 185 mL]; $p < 0.001$, all groups) (Fig. 2). Results in the per-protocol population were consistent with those in the ITT population (data not shown).

All doses of VI were associated with statistically significant increases in weighted mean 24-h serial FEV_1 versus placebo ($p < 0.001$) (Fig. 3). The effects with once-daily VI were dose dependent (6.25 mcg, 153 mL; 12.5 mcg, 168 mL; 25 mcg, 185 mL); the response to VI 6.25 mcg twice-daily was 166 mL.

A repeated measures analysis (difference from placebo in change from period baseline in FEV_1 with VI over 0—24 h on Day 7) showed greater changes with VI 12.5 mcg once-daily than 6.25 mcg twice-daily during the first 12 h but the overall 24-h profiles were similar for the two dosing regimens (Fig. 4a). There were also greater changes in lung function with VI 25 mcg once-daily than with 6.25 mcg twice-daily at 0—13 h and the changes were similar during the 13—23-h period (Fig. 4b).

The proportion of patients who obtained a ≥200 mL and ≥12% increase from baseline FEV_1 on Day 7 at any individual timepoint was 19—38% across the VI groups and 12—22% for placebo.

Table 1 Patient baseline demographics and screening lung function (intent-to-treat population).

	$n = 75$
Age, years	38.9 (14.37)
Female, *n* (%)	47 (63)
Race, *n* (%)	
White	51 (68)
African American/African heritage	23 (31)
Asian	1 (1)
Duration of asthma, *n* (%)	
<6 months	0
≥6 months to <1 year	1 (1)
≥1 year to <5 years	3 (4)
≥5 years to <10 years	9 (12)
≥10 years	62 (83)
Screening lung function	
Pre-bronchodilator FEV_1 (L)	2.233 (0.7043)
Percent predicted FEV_1 (%)	66.4 (10.37)
Percent reversibility in FEV_1 (%)	27.9 (15.24)
ICS[a] use, *n* (%)	
Fluticasone propionate	27 (36)
Budesonide	23 (31)
Mometasone furoate	15 (20)
Beclometasone dipropionate	8 (11)
Ciclesonide	2 (3)

Values are mean (SD) unless otherwise stated.
FEV_1, forced expiratory volume in 1 s.
[a] Maximum allowable daily dose: fluticasone propionate metered dose inhaler (MDI) ≤880 mcg[b]/≤1000 mcg[c]; fluticasone propionate dry powder inhaler (DPI) ≤1000 mcg; budesonide DPI/MDI ≤2000 mcg; mometasone furoate ≤880 mcg; beclomethasone dipropionate ≤1680 mcg[b]/≤2000 mcg[c]; ciclesonide ≤320 mcg[b]/≤400 mcg.[c]
[b] =ex-actuator dose.
[c] =ex-valve dose.

Safety

VI was well tolerated at all doses and both dosing schedules. The incidence of AEs was low in each VI treatment group and not dose dependent (5–9%; placebo = 18%) (Table 2). The most common AE was nasopharyngitis, which was reported by one patient each with 6.25 mcg once-daily and 6.25 mcg twice-daily, by two patients with VI 12.5 mcg once-daily, by one patient with 25 mcg once-daily and by no patients with placebo. No AEs led to permanent discontinuation of study drug or withdrawal from the study and no AEs were considered to be related to study treatment. No pharmacologically predictable AEs were reported (e.g. hypertension, extrasystoles or tremor). No serious AEs or deaths were reported during the study.

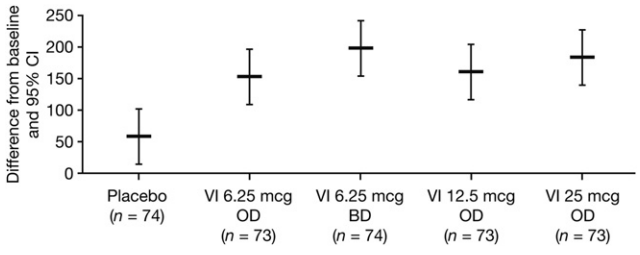

Figure 2 Least squares mean change from baseline in trough FEV_1 (mL) on Day 7 (intent-to-treat population). BD, twice-daily; OD, once-daily; and VI, vilanterol.

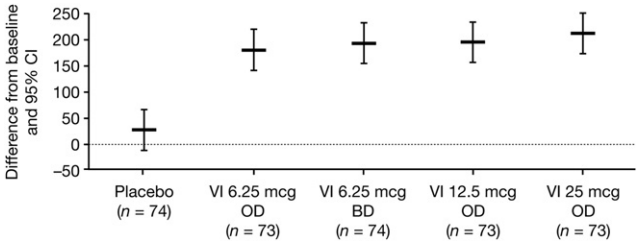

Figure 3 Weighted mean 24-h serial FEV_1 (mL) on Day 7 (intent-to-treat population). BD, twice-daily; OD, once-daily; and VI, vilanterol.

The majority of patients did not have any reported clinically relevant changes from pre-study baseline in vital signs. Less than 20% of patients across the treatment groups had an increase in pulse rate of >10 beats/min, and was generally no greater with active treatment than with placebo. The majority of patients (>80% across treatment groups) showed a change from baseline of −15 to 15 mmHg in diastolic and systolic blood pressure at pre-dose on Day 7.

Two patients reported an asthma exacerbation (one with placebo and one with VI 12.5 mcg once-daily), both took systemic/oral corticosteroids for their exacerbation but neither patient withdrew from the study.

Discussion

The main objective of this study was to test the efficacy of three once-daily doses (6.25, 12.5 and 25 mcg) and one

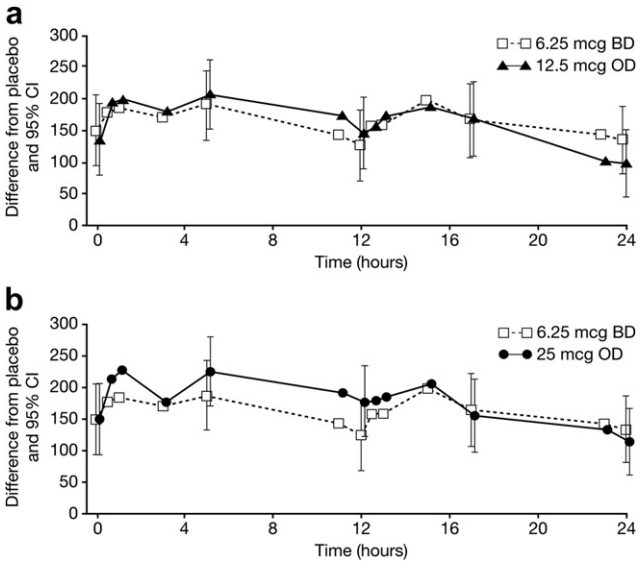

Figure 4 Repeated measures analysis of serial FEV_1 (0–24-h) comparing (a) 6.25 mcg BD with 12.5 mcg OD and (b) 6.25 mcg BD with 25 mcg OD on Day 7 (intent-to-treat population). Values are treatment differences (mL) from placebo. BD, twice-daily; OD, once-daily; and VI, vilanterol.

Table 2 Summary of most common[a] on-treatment adverse events (intent-to-treat population).

	Placebo (n = 74)	VI 6.25 mcg OD (n = 73)	VI 6.25 mcg BD (n = 74)	VI 12.5 mcg OD (n = 73)	VI 25 mcg OD (n = 73)
Any event, n (%)	13 (18)	5 (7)	7 (9)	4 (5)	6 (8)
Number of patients with most common event (%)	4 (5)	5 (7)	4 (5)	2 (3)	4 (5)
Nasopharyngitis	0	1 (1)	1 (1)	2 (3)	1 (1)
Upper respiratory tract infection	1 (1)	0	3 (4)	0	0
Road traffic accident	0	0	0	0	3 (4)
Back pain	2 (3)	0	0	0	0
Headache	1 (1)	2 (3)	1 (1)	0	0
Rhinitis perennial	0	2 (3)	0	0	0

BD, twice-daily; OD, once-daily; and VI, vilanterol.
[a] Most common is defined as ≥3% in any treatment group.

twice-daily dose (6.25 mcg) of VI for 7 days in adult patients with persistent asthma receiving maintenance ICS. Safety and tolerability of VI were also assessed. VI dosed once-daily or twice-daily was associated with significant increases from baseline trough FEV_1 versus placebo (primary endpoint), with the greatest numerical improvement reported with VI 6.25 mcg twice-daily. Significant improvements in weighted mean 24-h serial FEV_1 (versus placebo) were also observed with both once-daily and twice-daily VI. The effects of once-daily VI on lung function were dose-related with the greatest numerical increases at 25 mcg for both trough FEV_1 and weighted mean serial 24-h FEV_1 relative to baseline.

Our study was a confirmatory study to the larger B2C109575 study (n = 614 patients randomised).[10] B2C109575 was a 28-day, placebo-controlled, dose-ranging study that investigated the efficacy and safety of five VI doses (3, 6.25, 12.5, 25 and 50 mcg) administered once-daily in the evening in patients with persistent asthma and receiving maintenance ICS. Preliminary results showed that although VI 12.5 mcg had a favourable therapeutic ratio, the greatest benefit was seen with VI 25 mcg once-daily.[10] The information provided from the B2C109575 study formed the basis of the VI doses and treatment periods selected in the present study. Although our study was not a definitive dose-ranging study, the significant improvements with once-daily VI at 12.5 and 25 mcg provide additional support to the previously observed efficacy and tolerability of VI at these doses.[10] Although results cannot be directly compared between our study and the B2C109575 study due to differences in trial design, duration and study population, the magnitude of improvements reported for once-daily VI at 6.25, 12.5 and 25 mcg on trough FEV_1 and weighted mean 24-h serial FEV_1 were similar.

A further objective of our study was to compare the efficacy of VI dosed once-daily versus twice-daily. Although our study was not powered to directly compare once-daily with twice-daily dosing, results for weighted mean serial 24-h FEV_1 support once-daily dosing of VI. The VI 12.5 mcg once-daily dose was associated with a similar magnitude of bronchodilation at Day 7 as VI 6.25 mcg twice-daily, indicating similar improvements regardless of whether the same total daily dose was given once-daily or twice-daily (Fig. 3). Weighted mean serial 24-h FEV_1 may be a more relevant endpoint than trough FEV_1 to demonstrate the 24-h activity of a therapy, but the results seen with once-daily VI on both these endpoints support the 24-h duration of effect of VI.

Currently licensed ICS/LABA combination therapies (such as fluticasone propionate/salmeterol and budesonide/formoterol) for asthma are dosed twice-daily due to their duration of action. In a study that compared (versus placebo) the duration of bronchodilation following a single dose of fluticasone propionate/salmeterol or budesonide/formoterol, sustained bronchodilation over 24 h was observed for both drug combinations, however, the authors hypothesised that this may not be clinically significant as lung function values had approached baseline values by 24 h.[12] In contrast, in our study, sustained clinically relevant bronchodilation was observed over 24 h versus placebo with both VI dose regimens and all VI doses. Furthermore, a greater proportion of patients obtained a ≥200 mL and ≥12% improvement in baseline FEV_1 across the VI treatment groups compared with placebo.

VI was well tolerated at all doses and both dose regimens. The incidence of AEs was low and similar across the active treatment groups with the highest incidence of AEs reported in the placebo group. No AEs commonly associated with LABA use were reported (eg. tremor, hypertension, extrasystoles). Nasopharyngitis was the AE most commonly reported with VI but was not dose-related. Three road traffic accidents were reported as AEs by three patients in the VI 25 mcg dose group but none were considered treatment related. The investigators confirmed that the circumstances of the accidents were not suggestive of there being any association of a drug-related effect. Two patients reported an asthma exacerbation on the last day of their final (fifth) treatment sequence and received corticosteroids for their exacerbation but were not withdrawn from the study. No serious AEs, hospitalisations or deaths were reported in our study. The overall favourable safety profile of VI in this short-term study supports that reported for the same once-daily doses of VI investigated in the 28-day B2C109575 study.[10] The long-term safety and tolerability of VI clearly needs to be assessed in future trials.

Our study has important strengths, including the cross-over design which meant patients acted as their own 'controls' and the high overall rate of compliance across the treatment groups (>99%). A limitation of the study was that the primary endpoint was change in trough FEV_1 relative to placebo. Although this endpoint is sufficiently sensitive to show the dose responsiveness of a treatment,

weighted mean 24-h serial FEV_1 represents a measure more suited to assessing the relative effects of once-daily and twice-daily dosing. Furthermore, weighted mean FEV_1 considers changes (above baseline) in bronchodilation over a 24-h period and can therefore provide a better assessment (versus trough FEV_1) on whether there is an efficacy advantage when VI is dosed twice-daily versus once-daily. A further limitation of our study was that it was not formally powered for non-inferiority of once-daily versus twice-daily dosing of VI. Rather, the relative effects of the different dose intervals were compared by assessing the overlap in point estimates and 95% CI for placebo-adjusted improvements from baseline. In addition, the study was of a short duration but was designed to substantiate the findings of B2C109575 and to provide information on once-daily versus twice-daily dosing.

In summary, once-daily administration of VI (6.25—25 mcg) over 7 days in patients with asthma maintained on ICS was associated with significant improvements in lung function relative to placebo, with maximal improvements in lung function over 24 h observed with VI 25 mcg once-daily. The similar improvements in weighted mean 24-h serial FEV_1 with 12.5 mcg once-daily and 6.25 mcg twice-daily suggests no advantage over a 24-h period of twice-daily versus once-daily dosing for the same total daily dose. Once-daily treatment with VI was well tolerated with no safety signals. The findings support the further development of VI as part of a once-daily fixed combination therapy with an ICS for the treatment of asthma.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rmed.2012.03.007.

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Author contribution

All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors. All authors developed the design and concept of the study, had full access to and interpreted the data, and wrote the manuscript. **R.S.** was one of the study principal investigators. **J.L., L.F., N.G.S.,** and **L.J.** approved the statistical plan. **N.G.S.** was the clinical study investigation lead. **J.L.** and **L.F.** were both involved in the study design; **J.L** led the statistical analysis and **L.F** provided the final statistical quality checks. All authors vouch for the accuracy and completeness of the data and the data analysis.

Conflict of interest

R.S. was a principle investigator in this clinical trial, which was sponsored by GlaxoSmithKline and administered by his employer Carolina Research. **J.L., L.F., N.G.S., L.J.** and **B.H.** are employees of and hold stock/shares in GlaxoSmithKline.

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