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24h duration of the novel LABA vilanterol trifenatate in asthma patients treated with ICSs

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ABSTRACT: Current guidelines recommend adding LABA to ICS in patients with uncontrolled asthma. This study evaluated the novel, once-daily LABA vilanterol trifenatate (VI) in asthma patients who remained symptomatic despite existing ICS therapy.

Randomised, double-blind, placebo-controlled trial of VI (3, 6.25, 12.5, 25, and 50μg), administered once daily in the evening by dry powder inhaler for 28 days, in asthma patients aged ≥12 years symptomatic on current ICS therapy. Primary endpoint: trough (24h post-dose) FEV_1; secondary endpoints: weighted mean FEV_1, peak expiratory flow (PEF), symptom-/rescue-free 24-h periods, and safety.

A significant relationship was observed between VI dose and improvements in trough FEV_1 ($p=0.037$). Statistically significant increases in mean trough FEV_1, relative to placebo, were documented for VI 12.5–50μg (121–162mL; $p\leq0.016$). Dose-related effects of VI were observed on weighted mean (0–24h) FEV_1, morning/evening PEF, and symptom-/rescue-free 24-h periods. All doses of VI were well tolerated with low incidences of recognised LABA-related adverse events (tremor 0–2%; palpitations 0–2%; glucose effects 0–1%; potassium effects 0–<1%).

Once-daily VI 12.5–50μg resulted in prolonged bronchodilation of at least 24h with good tolerability in asthma patients receiving ICS. Based on the overall efficacy and adverse event profile from this study the optimum dose of VI appears to be 25μg.

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KEYWORDS: bronchodilator; asthma management; add-on therapy

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways involving several inflammatory cells and multiple mediators that can cause periodic airflow obstruction, which is characteristic of the disease [1, 2]. Asthma is associated with substantial burden to the patient and healthcare systems [3], particularly when control is poor [4]. With sustained controller treatment, patients may be maintained free of symptoms and other clinical features of asthma for prolonged periods [5]. However, evidence from cross-sectional surveys suggests that a high proportion of patients remain uncontrolled despite controller therapy [6-8].

Inhaled corticosteroids (ICS) are considered the cornerstone of controller asthma therapy and treatment guidelines recommend the addition of a long-acting inhaled $beta_2$ agonist (LABA) to ICS for those patients not adequately controlled on ICS [3]. This combination approach improves lung function and reduces asthma symptoms, rescue medication use and the number of exacerbations compared with ICS alone [9]. Thus, asthma control is achieved in a greater proportion of patients [5, 10, 11]. Currently available combination therapies, such as those that contain the LABAs salmeterol or formoterol, require twice-daily administration due to their duration of action, but treatment adherence remains a problem in chronic use [6]. This may be improved by the use of a single combination inhaler instead of two [12, 13], but further benefit might be provided by reducing the dosing frequency required for maintenance of control to once daily.

Vilanterol trifenatate (VI; GW642444M) is a LABA with inherent 24 hour activity that is being developed as a once-daily clinical treatment for asthma in combination with fluticasone furoate, a novel ICS also active for 24 hours [14]. Experimental models have shown that VI is potent and, compared with salmeterol, has a faster onset and longer duration

of action [15, 16]. VI is also highly selective for the $beta_2$ receptor with >1,000-fold greater selectivity for this receptor than for the $beta_1$ and $beta_3$ receptors [16].

The aim of the present study was to evaluate the efficacy, dose responsiveness, duration of effect, and safety of adding VI (dosed once-daily in the evening) to ICS therapy in patients with asthma who remained symptomatic on ICS alone. Some of the results of this study have been previously reported in abstract form [17, 18]

METHODS

Setting

A multinational, multicentre, randomised, double-blind, placebo-controlled, dose-ranging study (GSK: B2C109575; clinicaltrials.gov: NCT00600171) conducted between 12/2007 and 09/2008.

Patients

Patients were aged ≥12 years with asthma [19] first diagnosed ≥6 months prior to screening, with reversibility to salbutamol (400µg; increase in baseline forced expiratory volume in 1 second (FEV_1) of ≥12% and ≥200mL), pre-bronchodilator FEV_1 of ≥40% to ≤90% of predicted [20], and maintained on a stable dose of an ICS for ≥4 weeks prior to screening. Complete inclusion and exclusion criteria are provided in Appendix 1 (online data supplement).

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

Interventions

After a 14-day run-in, patients were randomised to receive VI (GlaxoSmithKline Clinical Trials Supplies, Ware, UK) 3µg, 6.25µg, 12.5µg, 25µg or 50µg, or placebo, administered once daily in the evening for 28 days via a single-step activation dry powder inhaler. VI was dosed in the evening as it is being developed as the LABA component of a new once-daily ICS/LABA combination. The ICS component of the combination, Fluticasone Furoate, exhibits non-inferior efficacy when dosed once-daily in the evening compared to twice-daily dosing [21], and as such VI was dosed in the evening to mimic the planned time of dosing of the ICS/LABA combination. The follow-up period was 7 days. Patients continued on their stable maintenance ICS throughout the study from screening through to follow-up. Short-acting $beta_2$ agonists (replaced by rescue salbutamol metered-dose inhalers at screening) were permitted, but not 6 hours prior to or during clinic visits.

Patients visited the clinic on Days 1, 7, 14, and 28 for FEV_1 measurements. On Days 1 and 28, serial measurements FEV_1 were made pre-dose and at various intervals up to 24 hours post-dose. Peak expiratory flow (PEF), symptom, and rescue medication data were recorded daily in an electronic eDiary.

Randomisation and masking

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. Prior to randomisation, patients were stratified by baseline % predicted FEV_1 ($\geq$40% to $\leq$65% and >65% to $\leq$90%) with a 1:1 (approximate) allocation using a randomly permuted block size of six.

Patients and investigators were blinded to treatment assignment, and the placebo and VI formulations were indistinguishable.

Outcome measurements

The primary efficacy endpoint was change from baseline in trough FEV_1 (defined as the mean of the evening pre-bronchodilator FEV_1 values obtained 23 and 24 hours after dosing) at Day 28.

Secondary endpoints were: change from baseline in weighted mean 24-hour serial FEV_1 on Days 1 and 28; change from baseline in daily morning and evening PEF averaged over Days 1–28; change from baseline in percentage of symptom-/rescue-free 24-hour periods during the 28-day treatment period; and difference in post-salbutamol FEV_1 between 24 hours after dosing on Days 1 and 28, between screening and 24 hours after dosing on Day 1, and between screening and 24 hours after dosing on Day 28.

The proportion of patients obtaining both ≥200mL and ≥12% increase from baseline in FEV_1 was calculated over 0–24 hours on Days 1 and 28. The change over 0–4 hours was an 'other' endpoint, while the change after 4 hours to 24 hours was a post-hoc analysis.

Safety evaluation

Safety was assessed by monitoring adverse events (AEs) and serious AEs (SAEs), worsening asthma/exacerbations, laboratory parameters, vital signs, 12-lead electrocardiogram, and potassium and glucose levels.

Statistical analysis

All efficacy analyses were prespecified in the intent-to-treat population. It was estimated that 594 patients (99 per group) would be needed provide 97% power (two-sided α=0.05) to

detect a dose-response effect of 200mL improvement in FEV_1 per 50 µg of VI, assuming a standard deviation of 430mL (GlaxoSmithKline, data on file).

The primary analyses were performed using SAS software (SAS Institute Inc., Cary, NC, USA) in a step-wise approach. Firstly, a dose-response test at Day 28 was performed. If statistically significant, pair-wise testing of each dose of VI *versus* placebo was performed using an ANCOVA model adjusted for baseline FEV_1, country amalgamation, age, sex, baseline % predicted FEV_1 stratum, and treatment group, using a last observation carried forward approach.

Serial FEV_1 on Days 1 and 28 was analysed using a repeated measures model adjusting for baseline and treatment factors. QTc interval was calculated by Fridericia formula (QTcF). Other statistical analyses are described in Appendix 2 (online data supplement).

Further information

Further methodological details can be found in Appendix 2 of the online data supplement.

RESULTS

Study population

Of 1,140 patients screened, 614 underwent randomisation and 539 completed the study (fig. 1). The main reasons for withdrawal were lack of efficacy (n=33) and meeting predefined discontinuation criteria (n=18).

The demographic and baseline clinical characteristics of patients in the six treatment groups are shown in table 1. Duration of asthma history was similar across treatment groups (≥10 years in 64–74% of patients) and most (67%) patients had a history of atopy. Percent predicted pre-bronchodilator FEV_1 (65–68%), absolute reversibility (518–563mL), and %

reversibility (24–27%) in FEV_1 were also comparable across the six groups. Mean exposure to study medication was 26–28 days and mean overall reported compliance to treatment was high (99–107%). During the study fluticasone propionate (32–44%) and budesonide (33–48%) were the most frequently used maintenance ICS therapies across the six study arms; mean (SD) beclomethasone-equivalent doses in each treatment group (mean (SD)) were as follows in each of the treatment groups.: placebo 814.4µg (537.5); VI 3µg 698.3µg (405.53); VI 6.25µg 747.6µg (467.68); VI 12.5µg 736.3µg (473.29); VI 25µg 736.4µg (411.78); and VI 50µg 709.8µg (517.24).

Efficacy

The mean change from baseline in trough (23–24 hours post dose) FEV_1 at Day 28 in the placebo group was 147mL. There was a significant relationship between the dose of VI and trough FEV_1 response (p=0.037 excluding placebo). Direct comparisons of each VI dose *versus* placebo showed statistically significant improvements in trough FEV_1 for 12.5µg, 25µg and 50µg VI, but not for the lower doses of 3µg and 6.25µg (table 2; fig. 2). Results in the per-protocol population were consistent with those in the intent-to-treat population (data not shown).

Serial FEV_1 data on Days 1 and 28 (fig. 3) show an onset of action at the first measurement time point (15 minutes) and a sustained duration of response over the 24 hours of observation, for all doses of VI. The ratio of peak post-dose FEV_1 (over the first 4 hours) vs. trough FEV_1 on Day 28 was approximately one in all VI groups and placebo (the ratio varied between 1.04 to 1.06, SD varied between 0.053 to 0.091). The change from baseline in weighted mean for 24-hour serial FEV_1 (average area under the curve minus baseline) was statistically significant for all doses of VI *versus* placebo on both Days 1 and 28 (except for the 6.25µg dose on Day 1). A dose-related effect of VI was observed on both Days 1 and 28,

with greatest improvements *versus* placebo seen for the 25µg (Day 1 and Day 28 data, respectively: 193mL and 165mL) and 50µg (215mL and 172mL) doses (fig. 3).

The study design also allowed for patients to be stratified according to baseline lung function (upper strata >65% to ≤90%; lower strata ≥40% to ≤65% FEV_1 % predicted). In the upper strata absolute mean reversibility ranged from 542.3mL to 616.7mL and from 22.4% to 26.4%. In comparison, mean absolute reversibility was slightly lower across the treatment groups (447.4mL to 542.8mL) in the lower strata, while mean % reversibility was slightly higher (26.4% to 31.1%). In the upper strata there was little evidence of a dose response at doses of 12.5 mcg or greater, there appeared to be a reasonable response to the 3µg dose which was not evident at the 6.25µg. In contrast, in the lower strata (table 2), there was some evidence of a dose-related effect ranging from no effect with 3µg (–49mL difference relative to placebo) to a 139mL increase with the 50µg dose.

All doses of VI increased morning and evening PEF in a dose-dependent fashion (fig. 4). Morning and evening PEF averaged over the 28-day treatment period were statistically significantly greater than placebo for all doses of VI (fig. 4), with the greatest increases recorded for 12.5µg, 25µg and 50µg VI, respectively, in morning PEF (32.3L/min, 36.2L/min, 42.1L/min) and evening PEF (28.5L/min, 33.6L/min, 38.0L/min (all $p< 0.001$)).

VI increased the percentage of symptom-free 24-hour periods *versus* placebo by 8–22% in a dose-dependent manner; the effect was statistically significant for all doses of VI, except 3µg (table 3). VI also dose-dependently increased the percentage of rescue-free 24-hour periods *versus* placebo by 11–28% ($p<0.05$ for all doses), with the greatest increases seen with the 25µg dose (table 3).

Comparable improvements in absolute FEV_1 post-salbutamol at screening and on day 1 were observed in all treatment arms and this effect was not attenuated by 28 days of therapy

with any dose of VI (fig. 5), There were no statistically significant differences between time points or active treatment and placebo ($p>0.05$; table 1, online data supplement).

The proportion of patients obtaining ≥200mL and ≥12% increase from baseline in FEV_1 (0–4 hours) on Days 1 and 28 increased with VI dose (fig. 1 , online data supplement). When measured over 0–24 hours, >50% of patients in the 25µg and 50µg VI groups maintained the ≥200mL and ≥12% improvement in FEV_1 for most time points.

Safety and tolerability

The incidence of AEs during treatment with VI was not dose related and was similar to placebo (table 4). Moreover, no SAEs were reported in any treatment group. No deaths or hospitalisations were reported. Cough was reported by only four patients (two 3µg VI, one 12.5µg VI, one 25µg VI; all considered unrelated to treatment by the study investigator). There was a low incidence of LABA class-related AEs. Tremor was reported by two patients (both received 6.25µg VI; one occurred on Day 1 and one on Day 6; one event was considered possibly treatment related). Palpitations considered possibly treatment related were reported by four patients (one placebo, two 3µg VI, one 6.25µg VI). One patient reported impaired glucose tolerance (12.5µg VI; considered possibly treatment related) and one patient had increased blood glucose levels (50µg VI; considered unrelated to treatment). No AEs of low potassium were reported. The incidence of asthma exacerbations was low and similar across treatment groups, with the greatest proportions reported for placebo (4%) and 3 µg VI (7%), compared with 0–3% in the other treatment groups.

No trends were observed for haematology, clinical chemistry, urinalysis values, or vital signs over time for any dose of VI, including glucose and potassium differences, and QTcF differences (Appendix 3, online data supplement). There was no evidence of a statistically significant difference in weighted mean change in pulse rate *versus* placebo 0–4

hours after dosing for any group at any time point (mean differences from placebo –1.8 to +1.8 beats per minute (bpm)), except for the 50µg VI group on Day 28 (+2.2 bpm, p=0.047; which was below the predefined level of clinically relevant concern defined as 6 bpm).

DISCUSSION

This report presents clinical data for inhaled VI, administered once-daily in the evening to asthma patients receiving maintenance ICS therapy. VI dose-dependently improved trough FEV_1 (the primary endpoint) showing a sustained duration of action of at least 24 hours at doses ≥12.5µg. Significant improvements were also observed on the endpoints of trough FEV_1 analysed by baseline FEV_1, weighted mean (0–24 hours) FEV_1, morning and evening PEF, and symptom-free and rescue-free 24-hour periods. All doses of VI were well tolerated.

The wide range of doses used in this study permit the dose-response profile of VI to be assessed. Doses were selected based on unpublished data from earlier trials, from which it was predicted that the 3µg dose would have no or little effect and the 50µg dose would likely cause maximal achievable bronchodilation. Indeed, a significant dose-related effect on lung function could be documented. This was further supported by the results showing that the 3µg dose of VI resulted in no significant effect, the 12.5µg dose caused intermediate effects, and the bronchodilator responses with 25µg and 50µg VI were more substantial. However, the two higher doses of VI caused similar improvement in lung function, suggesting that a maximal response to VI had been reached in this study population, representing the dose response curve plateau for FEV_1. Overall, slightly more pronounced effects were observed with VI 25µg *versus* 12.5µg, for example on endpoints of morning and evening PEF, as well as symptom-free and rescue-free 24-hour periods. The dose response was also assessed in the two strata; however caution should be applied when interpreting the results of the individual strata as the study was not powered to detect treatment differences within each stratum. What is evident is the overlap in response to individual doses in each stratum. There is no indication of a different dose being optimal in upper or lower strata.

The maintained significant effect of VI on the primary endpoint trough FEV_1, as measured 24 hours after the previous dose, confirms a 24-hour duration of effect of VI on lung function in asthma patients concomitantly being treated with maintenance ICS. The serial FEV_1 profiles also provide evidence of the 24-hour duration of VI at 12.5µg doses or higher, as the offset of effect from peak to trough are parallel to placebo treatment. This time course suggests that VI exerts a prolonged bronchodilatory effect and, as such, could be included in a once-daily treatment regimen in combination with an ICS for asthma. However, further studies are needed in order to determine how the duration of bronchodilation with VI compares with that of the older LABAs salmeterol and formoterol [22 - 24].

Statistically significant increases in FEV_1 were observed at the first time point measured (15 minutes after inhalation) and maximum effect was documented at 3–4 hours on Day 1, and within 1–2 hours on Day 28. Furthermore, the evidently sustained immediate bronchodilation of an inhaled short-acting $beta_2$ agonist during regular treatment with VI further argues against tolerance to the immediate bronchodilation of a $beta_2$ agonist used as rescue medication, as post-salbutamol FEV_1 values were similar between screening and Day 28 in all VI treatment groups despite the increase in pre-bronchodilator FEV_1observed as early as Day 1 with VI therapy. The current study was not designed to directly assess the detailed onset of action of VI or tolerance to the clinical effect at the level of the $beta_2$ receptor. However, the overall results argue that tolerance to the bronchodilator response of a short-acting $beta_2$ agonist is not apparent in this large asthma study, in which patients were concomitantly treated with ICS.

All doses of VI were well tolerated, with no SAEs reported in any treatment group, and AEs were not related to the dose of VI. Inhalation of $beta_2$ agonists is often associated with predictable effects such as tremor, hypokalemia, increased heart rate and increased QTcF intervals, which were observed to a minor extent with VI in this study. A minimal, not

clinically relevant effect on pulse rate was observed (increase of 2 bpm) with the highest dose of VI (50µg), which, however, would also be expected with other inhaled $beta_2$ agonists at such a high dose. Our data support the overall conclusion that doses of VI up to 50µg have limited side effects. Clearly, the influence on VI on rare events such as asthma-related worsening or mortality [25, 26] cannot be addressed in a study of this nature and therefore must be monitored in future long-term trials.

In selecting the optimal dose of a therapy, the aim is to attain maximal efficacy at the lowest possible dose, to avoid side effects, and to maintain highest possible therapeutic ratio. In the development of previous LABAs, increasing doses of salmeterol (50, 100, and 200µg) resulted in dose-related effects on lung function, but the highest dose produced significant effects on blood pressure, heart rate and tremor [27], making the two lower doses more suitable for further clinical development. In studies with formoterol, although 6µg, 12µg, and 24µg showed incremental dose-related efficacy on FEV_1 [28], the lowest dose, which was effective and devoid of side effects was selected for further development, again to attain highest possible therapeutic ratio. These efficacy data, together with the absence of dose-related AEs in this study, suggests that 12.5µg and/or 25µg may be suitable doses for further development as part of a fixed-dose combination therapy in adult asthma patients.

This study was powered to determine the dose-related effect of VI on trough FEV_1 and was sufficiently large to determine the frequency of recognised side effects. The placebo effect on FEV_1 was substantial, which is often seen in large parallel group studies in asthma. The reasons for the pronounced placebo effect are unclear, but may be related to the timing of the trough FEV_1 measurement, as evening lung function tends to be higher due to the circadian variation that is observed in asthma patients [22, 29, 30]. Another possible effect is the 'trial effect' of patients in the placebo arm increasing adherence to their maintenance ICS therapy and thus achieving greater than expected lung function. Unfortunately, as no data

were collected on adherence to maintenance therapy this can only be postulated. Importantly, significant dose-related effects of VI could be documented despite this placebo response.

In conclusion, regular once-daily treatment with VI was well tolerated and resulted in a prolonged duration of bronchodilation of at least 24 hours at doses of 12.5µg and greater, with a favourable therapeutic ratio at doses of 12.5µg and 25µg, with the greatest benefit seen at the 25µg dose. These findings in patients receiving maintenance ICS therapy suggest VI can be developed as a once-daily LABA in combination with a once-daily ICS for the treatment of asthma. Such once-daily combination therapies have the potential to improve adherence to therapy in patients taking long-term inhaled therapy.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

J. Lötvall has served as a consultant to and received lecture fees from AstraZeneca, GlaxoSmithKline, Merck Sharpe and Dohme, Novartis and UCB Pharma; has been partly covered by some of these companies to attend previous scientific meetings including the ERS and the AAAAI; and has participated in clinical research studies sponsored by AstraZeneca, GlaxoSmithKline, Merck Sharpe and Dohme, and Novartis. E.D.B. has served as a consultant to and received lecture fees from GlaxoSmithKline; and his institution has received remuneration for participation in clinical trials sponsored by GlaxoSmithKline. E.R.B. has served as a consultant to and received lecture fees from GlaxoSmithKline; and has performed clinical trials for GlaxoSmithKline, which have been administered by his employer Wake Forest University Health Sciences. W.W.B. has served as a consultant to AstraZeneca, Boehringer Ingelheim, Novartis and TEVA; served on advisory boards for Altair, Amgen, Centocor, GlaxoSmithKline, Johnson & Johnson, Merck Sharpe and Dohme, Pfizer and Wyeth; received lecture fees from Merck Sharpe and Dohme; and received research funding from AstraZeneca, Ception, GlaxoSmithKline, MedImmune and Novartis. A.W. has served as consultant to Almirall, AstraZeneca, Chiesi, GlaxoSmithKline, Merck Sharpe and Dohme, Novartis and Schering Plough; and has received research grants and travel expenses for attendance at ATS and ERS meetings from GlaxoSmithKline. R.F., J. Lim, S.S., L.J. and B.H. are employees of and hold stock in GlaxoSmithKline.

AUTHOR CONTRIBUTIONS

All authors developed the design and concept of the study, had full access to and interpreted the data, and wrote the manuscript. R.F., J.Lim, S.S., L.J. and B.H. approved the statistical plan. J.Lötvall wrote the first draft of the paper. R.F. and S.S. coordinated data gathering. J.Lim led the statistical analysis. All authors vouch for the veracity and completeness of the data and the data analysis.

ROLE OF THE FUNDING SOURCE

The independent steering committee (J.Lötvall, E.D.B., E.R.B., W.W.B., A.W.) together with authors employed by the sponsor (R.F., J.Lim, S.S., L.J, B.H.) had full access to the data and were responsible for the decision to publish the paper. Employees of the sponsor performed the statistical analysis, led by J.Lim. The sponsor did not place any restriction on authors about the statements made in the final paper.

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Tables

TABLE 1. Patient baseline demographics. Plus–minus values are mean ± standard deviation

Characteristic	Placebo n=102	3 µg VI n=101	6.25 µg VI n=101	12.5 µg VI n=100	25 µg VI n=101	50 µg VI n=102
Age at enrolment, years	39.9 ± 15.6	44.4 ± 13.5	42.4 ± 14.1	41.3 ± 15.3	42.2 ± 14.3	44.0 ± 15.2
Female sex, n (%)	61 (60)	52 (51)	51 (50)	56 (56)	61 (60)	57 (56)
Race, n (%)						
Caucasian	81 (79)	74 (73)	77 (76)	75 (75)	75 (74)	83 (81)
Asian	11 (11)	13 (13)	11 (11)	8 (8)	9 (9)	9 (9)
African-American/African	4 (4)	11 (11)	8 (8)	12 (12)	14 (14)	8 (8)
Other	6 (6)	3 (3)	5 (5)	5 (5)	3 (3)	2 (2)
Duration of asthma						
≥6 months to <1 year	0 (0)	2 (2)	1 (<1)	1 (1)	2 (2)	1 (<1)
≥1 year to <5 years	14 (14)	11 (11)	19 (19)	16 (16)	11 (11)	16 (16)
≥5 years to <10 years	20 (20)	13 (13)	11 (11)	12 (12)	14 (14)	20 (20)
≥10 years	68 (67)	75 (74)	70 (69)	71 (71)	74 (73)	65 (64)
Lung function[#]						
Prebronchodilator FEV_1, L	2.2 ± 0.7	2.3 ± 0.8	2.2 ± 0.6	2.3 ± 0.6	2.1 ± 0.6	2.2 ± 0.6
Prebronchodilator FEV_1, % of predicted	66.9 ± 12.0	65.8 ± 13.5	66.5 ± 10.8	67.6 ± 11.8	65.3 ± 12.1	65.9 ± 12.3
Reversibility – absolute, mL	556 ± 300	518 ± 271	563 ± 291	537 ± 280	540 ± 339	537 ± 254
Reversibility, % of predicted	26.6 ± 15.4	24.2 ± 13.5	26.3 ± 15.4	25.2 ± 16.2	27.4 ± 20.7	26.4 ± 15.5
Use of asthma medication, n (%)						
Fluticasone propionate	44 (43)	37 (37)	42 (42)	45 (45)	42 (42)	35 (34)
Budesonide	36 (35)	48 (48)	35 (35)	35 (35)	33 (33)	36 (35)
Other inhaled corticosteroids	21 (21)	16 (16)	24 (24)	20 (20)	24 (24)	31 (30)

FEV_1: forced expiratory volume in 1 second; VI: vilanterol trifenatate. [#]: Screening values.

TABLE 2. Mean trough FEV_1 and change from baseline at day 28 (intent-to-treat and FEV_1 strata populations). Plus–minus values are mean ± standard error

	Placebo n=102	3 µg VI n=101	6.25 µg VI n=101	12.5 µg VI n=100	25 µg VI n=101	50 µg VI n=102
ITT Population						
N	95	98	99	97	99	100
LS mean, mL	2,388	2,452	2,458	2,518	2,509	2,550
LS mean change, mL	147 ± 36	212 ± 36	217 ± 35	278 ± 36	269 ± 35	309 ± 35
Difference *versus*. placebo, mL		64	69	130	121	162
(95% CI)		(–36, 164)	(–29, 168)	(30, 230)	(23, 220)	(62, 261)
p-Value		0.208	0.169	0.011	0.016	0.001
Lower stratum (FEV1 % predicted ≥40–≤65%)						
n	43	44	41	40	46	45
LS mean, ml	2,450	2,402	2,487	2,559	2,522	2,590
LS mean change, ml	210 ± 57	161 ± 56	247 ± 57	319 ± 57	281 ± 54	349 ± 55
Difference vs. placebo, ml		–49	37	109	72	139
(95% CI)		(–198, 100)	(–113, 188)	(–44, 262)	(–75, 218)	(–9, 287)
Upper stratum (FEV1 % predicted >65–≤90%)						
n	52	54	58	57	53	55
LS mean, ml	2,338	2,495	2,435	2,488	2,499	2,517
LS mean change, ml	98 ± 49	254 ± 51	194 ± 48	247 ± 49	259 ± 49	276 ± 49
Difference vs. placebo, ml		156	97	149	161	178
(95% CI)		(22, 291)	(–35, 228)	(18, 281)	(27, 295)	(45, 312)

CI: confidence interval; FEV_1: forced expiratory volume in 1 second; LS: least square; VI: vilanterol trifenatate.

TABLE 3. Change from baseline in percentage of symptom-free and rescue-free 24-hour periods averaged over the 28-day treatment period (intent-to-treat population). Plus–minus values are mean ± standard error

	Placebo n=102	3 µg VI n=101	6.25 µg VI n=101	12.5 µg VI n=100	25 µg VI n=101	50 µg VI n=102
			Symptom-free 24-hour periods			
N	98	99	101	98	.g. 102	102
LS mean change, %	14.2 ± 3.27	22.6 ± 3.25	23.6 ± 3.21	26.8 ± 3.26	36.4 ± 3.21	32.3 ± 3.21
Difference vs. placebo						
LS mean difference, % (95% CI)		8.4 (–0.7, 17.5)	9.4 (0.4, 18.4)	12.7 (3.6, 21.8)	22.2 (13.3, 31.2)	18.1 (9.1, 27.2)
p-Value		0.069	0.040	0.006	<0.001	<0.001
			Rescue-free 24-hour periods			
n	99	99	101	98	101	102
LS mean change, %	15.0 ± 3.33	25.8 ± 3.33	27.3 ± 3.28	29.6 ± 3.34	43.4 ± 3.28	34.0 ± 3.28
Difference vs. placebo						
LS mean difference, % (95% CI)		10.8 (1.5, 20.1)	12.3 (3.1, 21.5)	14.7 (5.4, 24.0)	28.4 (19.3, 37.6)	19.0 (9.8, 28.3)
p-Value		0.023	0.009	0.002	<0.001	<0.001

CI: confidence interval; LS: least square; VI: vilanterol trifenatate.

TABLE 4. Summary of adverse event (AE) data (intent-to-treat population)

n (%)	Placebo n=102	3 µg VI n=101	6.25 µg VI n=101	12.5 µg VI n=100	25 µg VI n=101	50 µg VI n=102
Any on-treatment AE	37(36)	37 (37)	34 (34)	25 (25)	23 (23)	31 (30)
Any post-treatment AE[#]	6 (6)	4 (4)	5 (5)	0	5 (5)	2 (2)
Any drug-related AE	7 (7)	8 (8)	8 (8)	5 (5)	4 (4)	7 (7)
Any AE leading to permanent discontinuation of drug or withdrawal[¶]	1 (<1)	1 (<1)	2 (2)	1 (1)	1 (<1)	0
SAEs	0	0	0	0	0	0
Most frequent on-treatment AEs (≥3% in any treatment group)						
Headache	8 (8)	12 (12)	7 (7)	9 (9)	7 (7)	8 (8)
Upper respiratory tract infection	2 (2)	2 (2)	1 (<1)	3 (3)	2 (2)	2 (2)
Nasopharyngitis	4 (4)	2 (2)	2 (2)	0	0	2 (2)
Dizziness	2 (2)	1 (<1)	1 (<1)	1 (1)	0	3 (3)
Back pain	0	3 (3)	0	1 (1)	1 (<1)	0
Muscle spasms	0	0	2 (2)	0	0	3 (3)
Dyspnoea	3 (3)	0	0	0	0	0

AE: adverse event; SAE: serious adverse event; VI: vilanterol trifenatate. [#]: In the week following the 28-day dosing period; [¶]: Two patients were withdrawn due to AEs; four patients were withdrawn primarily due to protocol-defined stopping criteria, with AEs as a sub-reason

Figure legends

FIGURE 1. Patient enrolment and completion of the study.

[#]Data from this patient were not included in the efficacy and safety summary tables, but safety data were collected to ensure there were no safety issues.

[¶]Seven patients were randomised in error but did not receive study drug.

AE: adverse event; VI: vilanterol trifenatate.

FIGURE 2. Adjusted mean change from baseline in trough forced expiratory volume in 1 second (FEV_1; mL) *versus* placebo at Day 28 (intent-to-treat population).

Error bars are 95% confidence intervals.

VI: vilanterol trifenatate.

FIGURE 3. Change from baseline serial forced expiratory volume in 1 second (FEV_1) adjusted treatment differences from placebo (mL) from a repeated measures model (left panels) and adjusted treatment differences from placebo of weighted mean 24-hour serial FEV_1 (right panels) on Day 1 (a) and Day 28 (b) (intent-to-treat population).

Panel (a), left-hand graph standard errors: 44 mL at 4 hours (all doses); 46 mL (25 µg) and 47 mL (all other doses) at 16 hours; 46 mL at 24 hours (all doses).

Panel (b), left-hand graph standard errors: 48 mL (25 µg, 50 µg), 49 mL (6.25 µg, 12.5 µg), and 50 mL (3 µg) at 0 hours; 46 mL (50 µg), 48 mL (3 µg), and 47 mL (all other doses) at 4 hours; 49 mL (25 µg, 50 µg), 50 mL (6.25 µg, 12.5 µg), and 51 mL (3 µg) at 16 hours; 48 mL (50 µg), 49 mL (6.25 µg, 25 µg), and 50 mL (3 µg, 12.5 µg) at 24 hours.

Error bars in right-hand panels are 95% confidence intervals.

VI: vilanterol trifenatate.

FIGURE 4. Daily mean change in peak expiratory flow (PEF; L/min) from baseline (left panels) and adjusted treatment differences from placebo of change from baseline in PEF over Days 1–28 (right panels) for morning (a) and evening (b) PEF (intent-to-treat population). Error bars in right-hand panels are 95% confidence intervals.

AM: morning; PM: evening; VI: vilanterol trifenatate.

FIGURE 5. Response to salbutamol 24 hours after administration of placebo or each dose of VI for 1 day or 28 days (absolute values) (intent-to-treat population). Error bars are standard errors.

Figures

FIGURE 1

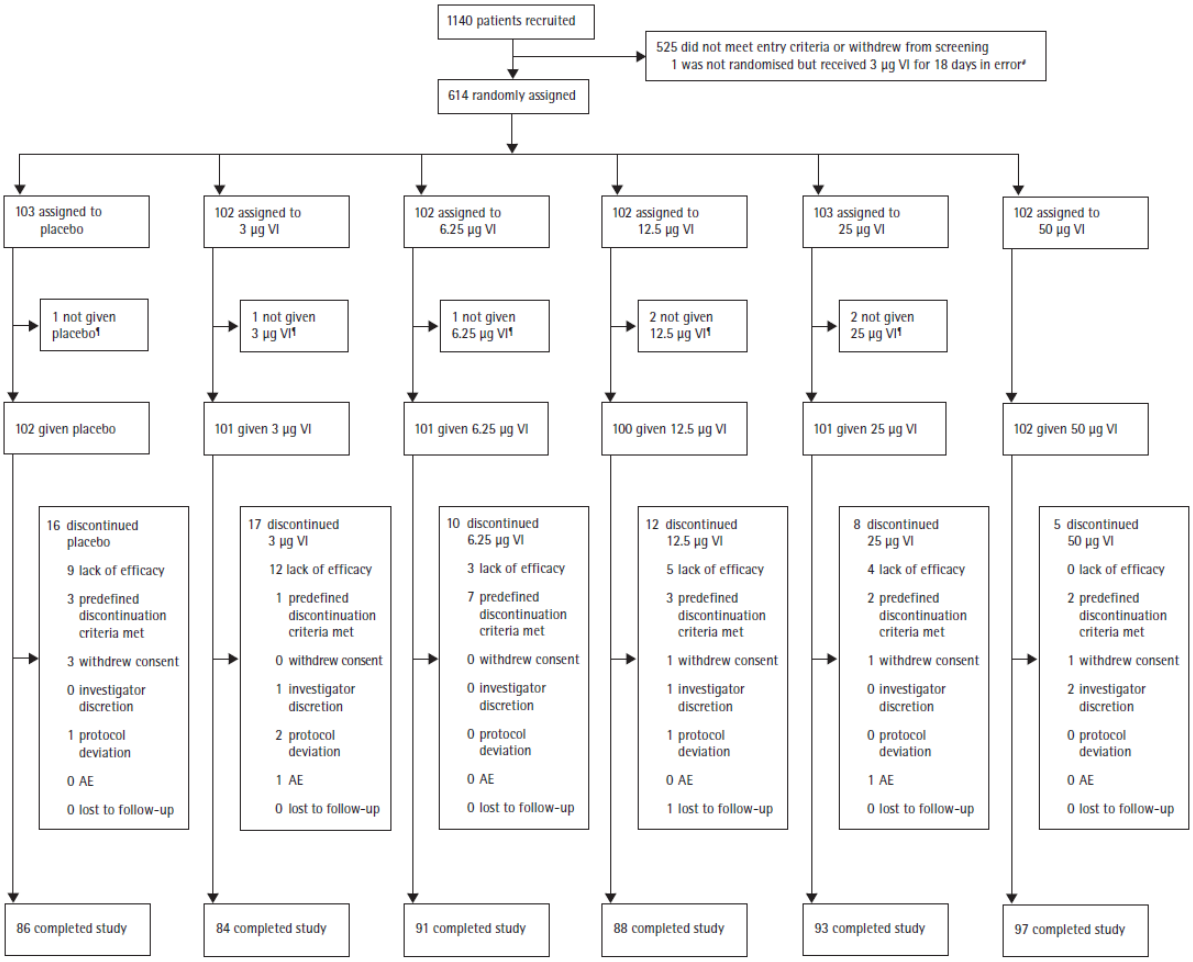


FIGURE 2

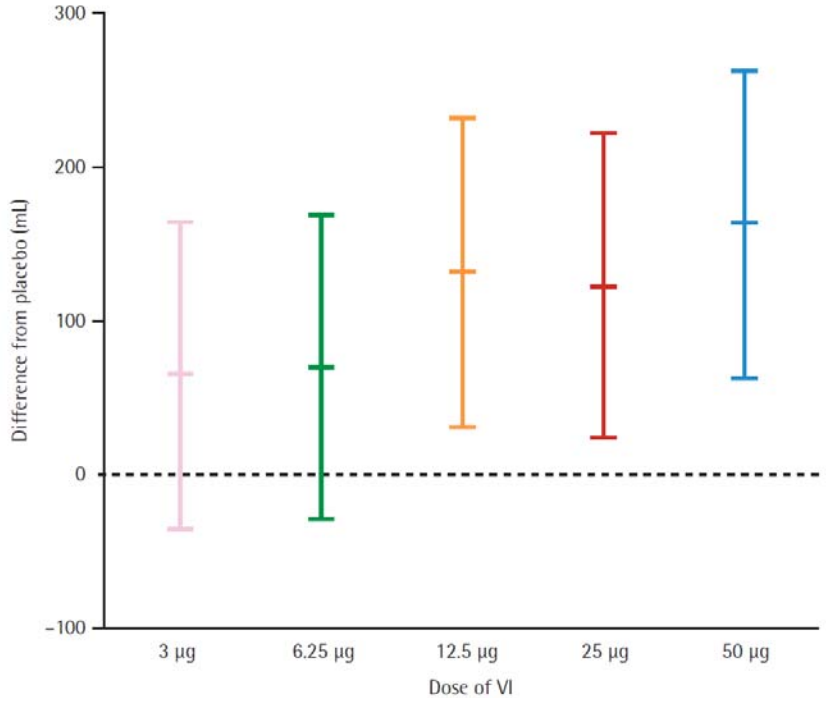

300
200
100
0
−100
Difference from placebo (mL)
3 µg
6.25 µg
12.5 µg
25 µg
50 µg
Dose of VI

FIGURE 3

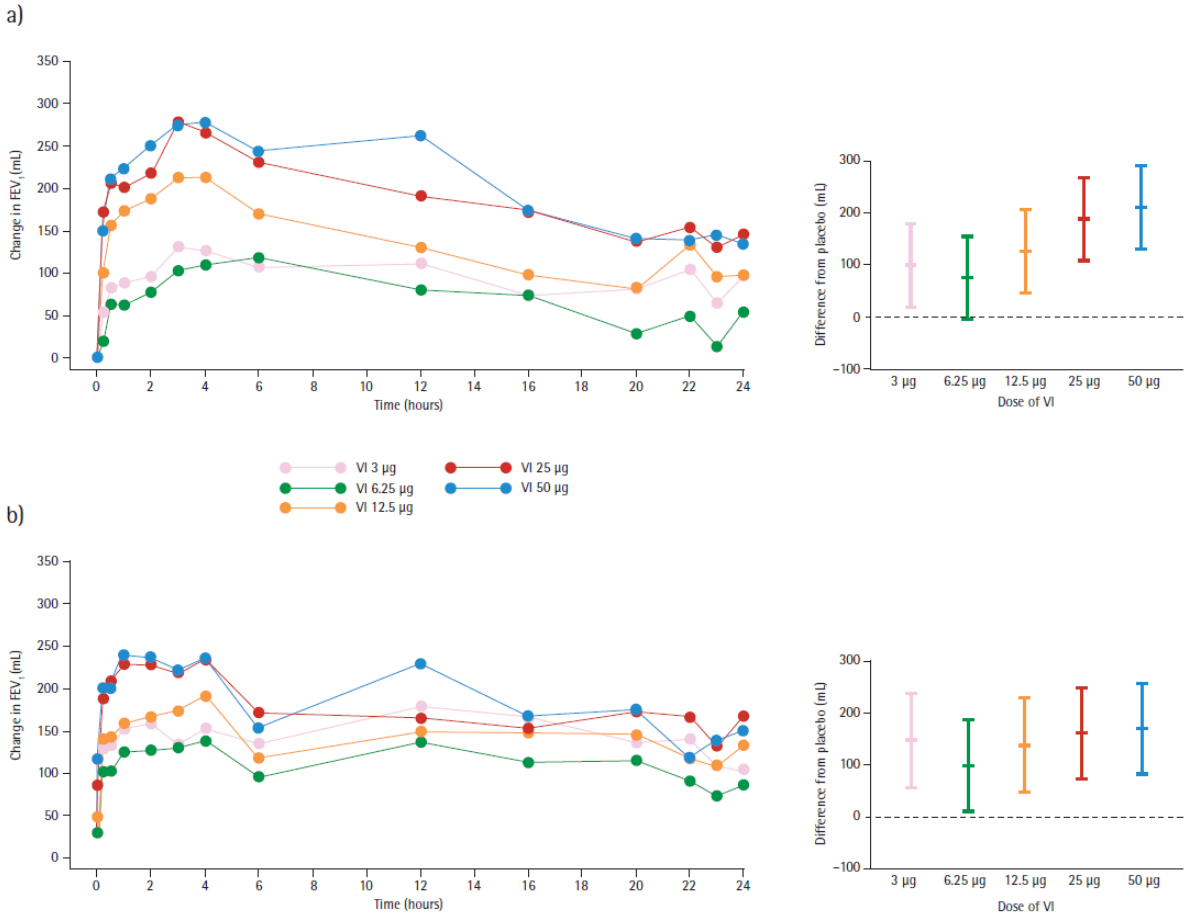

a)
Change in FEV1 (mL)
Time (hours)
Difference from placebo (mL)
3 µg
6.25 µg
12.5 µg
25 µg
50 µg
Dose of VI
VI 3 µg
VI 6.25 µg
VI 12.5 µg
VI 25 µg
VI 50 µg
b)
Change in FEV1 (mL)
Time (hours)
Difference from placebo (mL)
3 µg
6.25 µg
12.5 µg
25 µg
50 µg
Dose of VI

FIGURE 4:

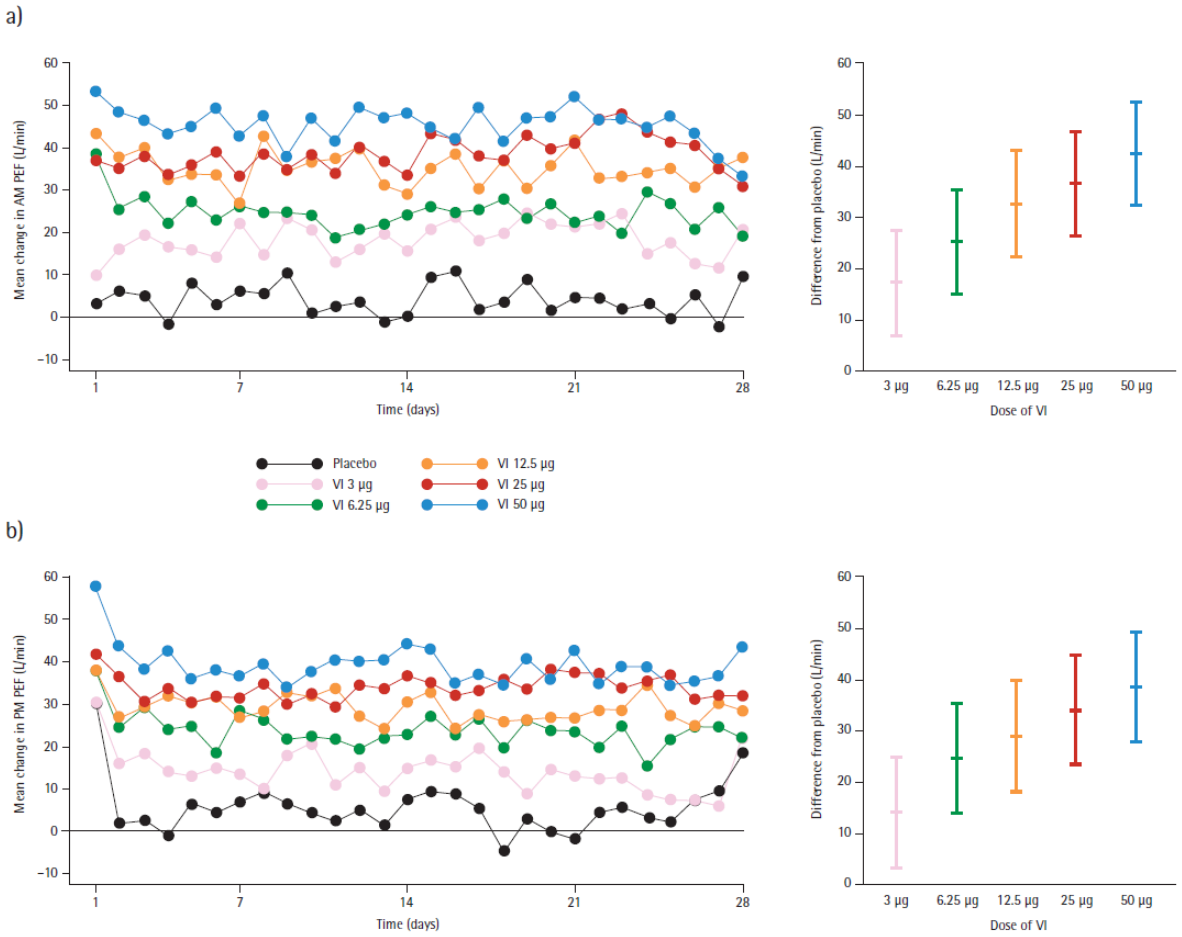
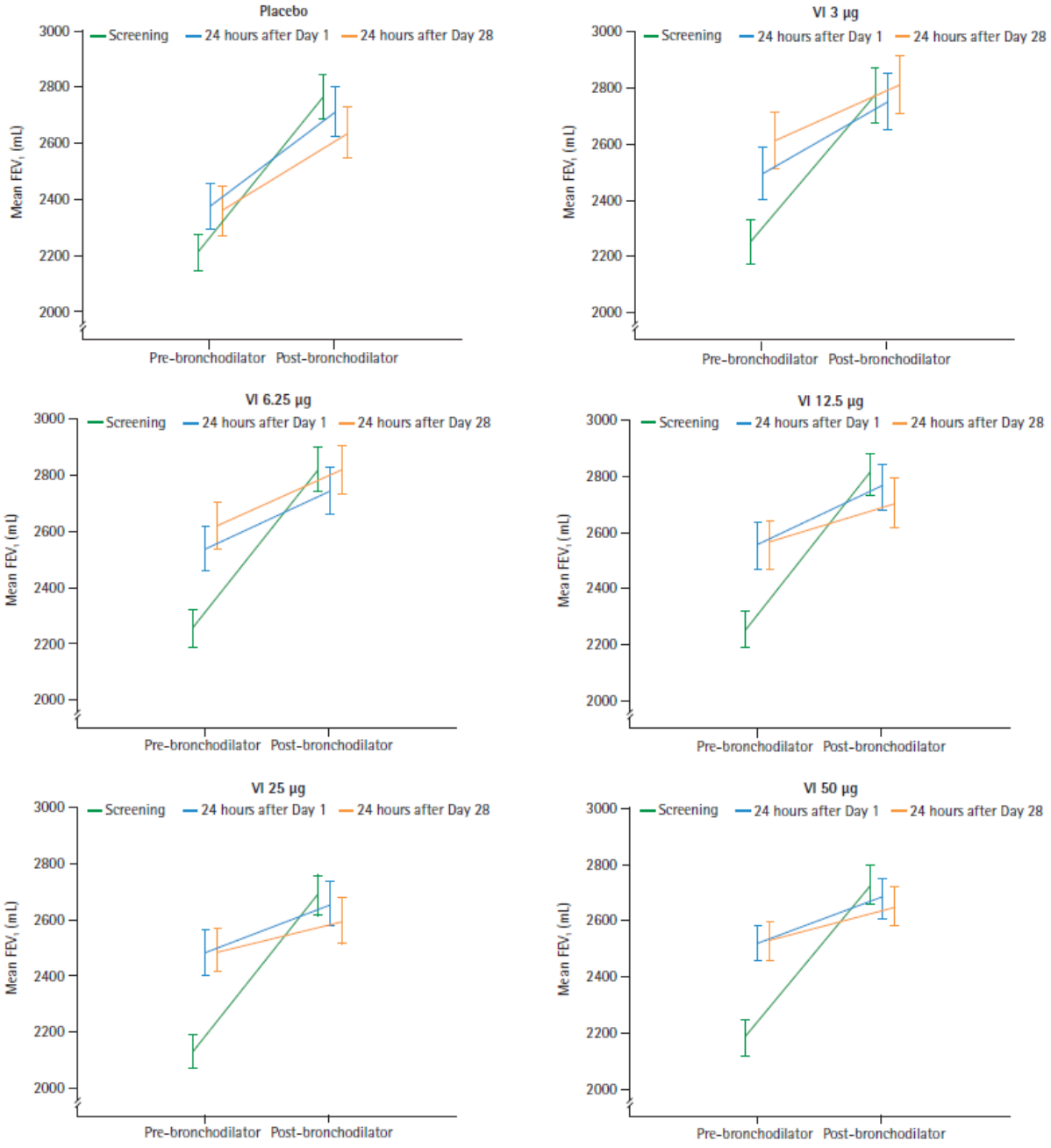

a)
Mean change in AM PEF (L/min)
Time (days)
Difference from placebo (L/min)
Dose of VI
3 µg
6.25 µg
12.5 µg
25 µg
50 µg
Placebo
VI 3 µg
VI 6.25 µg
VI 12.5 µg
VI 25 µg
VI 50 µg
b)
Mean change in PM PEF (L/min)
Time (days)
Difference from placebo (L/min)
Dose of VI

FIGURE 5


Placebo
Screening
24 hours after Day 1
24 hours after Day 28
Mean FEV1 (mL)
3000
2800
2600
2400
2200
2000
Pre-bronchodilator
Post-bronchodilator
VI 3 µg
VI 6.25 µg
VI 12.5 µg
VI 25 µg
VI 50 µg