



# 24-h duration of the novel LABA vilanterol trifenate in asthma patients treated with inhaled corticosteroids

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**ABSTRACT:** Current guidelines recommend adding a long-acting inhaled  $\beta_2$ -agonist (LABA) to inhaled corticosteroids (ICS) in patients with uncontrolled asthma. This study evaluated the novel, once-daily LABA vilanterol trifenate (VI) in asthma patients who remained symptomatic despite existing ICS therapy.

The study involved a randomised, double-blind, placebo-controlled trial of VI (3, 6.25, 12.5, 25 and 50  $\mu\text{g}$ ), administered once daily in the evening by dry powder inhaler for 28 days, in asthma patients aged  $\geq 12$  yrs symptomatic on current ICS therapy. The primary end-point was trough (24 h post-dose) forced expiratory volume in 1 s (FEV<sub>1</sub>); secondary end-points were weighted mean FEV<sub>1</sub>, 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<sub>1</sub> ( $p=0.037$ ). Statistically significant increases in mean trough FEV<sub>1</sub>, relative to placebo, were documented for VI 12.5–50  $\mu\text{g}$  (121–162 mL;  $p\leq 0.016$ ). Dose-related effects of VI were observed on weighted mean (0–24 h) FEV<sub>1</sub>, 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 12.5–50  $\mu\text{g}$  resulted in prolonged bronchodilation of at least 24 h 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 25  $\mu\text{g}$ .

**KEYWORDS:** Add-on therapy, asthma management, bronchodilator

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 health-care 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 trifenate (VI; GW642444M) is a LABA with inherent 24 h activity that is being

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developed as a once-daily clinical treatment for asthma in combination with fluticasone furoate, a novel ICS also active for 24 h [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 conducted between December 2007 and September 2008.

### Patients

Patients were aged  $\geq 12$  yrs with asthma [19] first diagnosed  $\geq 6$  months prior to screening, with reversibility to salbutamol (400  $\mu\text{g}$ ; increase in baseline forced expiratory volume in 1 s (FEV<sub>1</sub>) of  $\geq 12\%$  and  $\geq 200$  mL), pre-bronchodilator FEV<sub>1</sub> of  $\geq 40\%$  to  $\leq 90\%$  of predicted [20], and maintained on a stable dose of an ICS for  $\geq 4$  weeks prior to screening. Complete inclusion and exclusion criteria are provided in the online supplementary material, appendix S1.

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) 3  $\mu\text{g}$ , 6.25  $\mu\text{g}$ , 12.5  $\mu\text{g}$ , 25  $\mu\text{g}$  or 50  $\mu\text{g}$ , 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 noninferior 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 h prior to or during clinic visits.

Patients visited the clinic on days 1, 7, 14 and 28 for FEV<sub>1</sub> measurements. On days 1 and 28, serial FEV<sub>1</sub> measurements were made pre-dose and at various intervals up to 24 h post-dose. Peak expiratory flow (PEF), symptom and rescue medication data were recorded daily in an electronic diary.

### 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<sub>1</sub> ( $\geq 40\%$  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 end-point was change from baseline in trough FEV<sub>1</sub> (defined as the mean of the evening pre-bronchodilator FEV<sub>1</sub> values obtained 23 and 24 h after dosing) at day 28.

Secondary end-points were: change from baseline in weighted mean 24 h serial FEV<sub>1</sub> 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 h periods during the 28 day treatment period; and difference in post-salbutamol FEV<sub>1</sub> between 24 h after dosing on days 1 and 28, between screening and 24 h after dosing on day 1, and between screening and 24 h after dosing on day 28.

The proportion of patients obtaining both  $\geq 200$  mL and  $\geq 12\%$  increase from baseline in FEV<sub>1</sub> was calculated over 0–24 h on days 1 and 28. The change over 0–4 h was an “other” end-point, while the change after 4–24 h 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 ECG and potassium and glucose levels.

### Statistical analysis

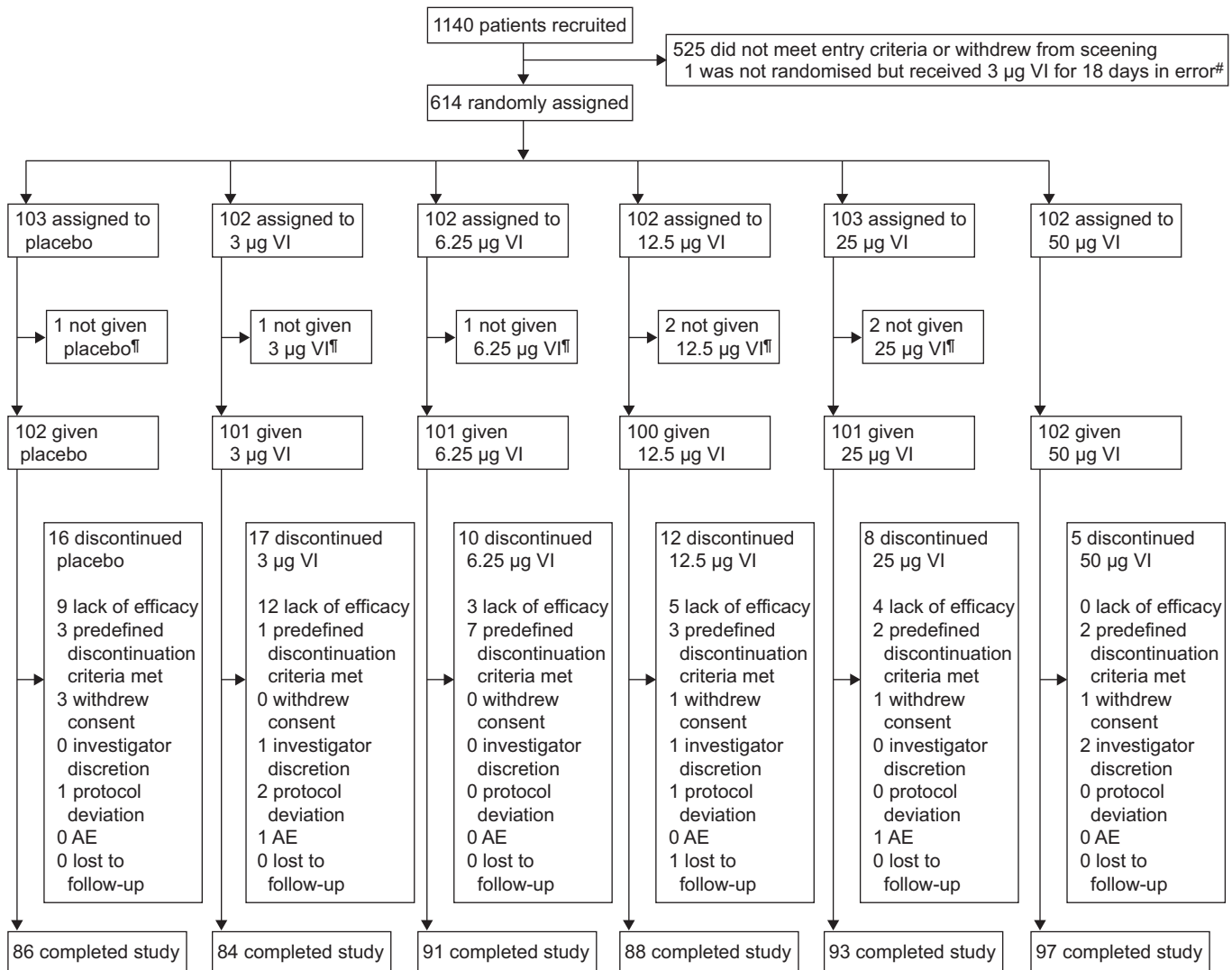
All efficacy analyses were pre-specified in the intent-to-treat population. It was estimated that 594 patients (99 per group) would be needed to provide 97% power (two-sided  $\alpha=0.05$ ) to detect a dose-response effect of 200 mL improvement in FEV<sub>1</sub> per 50  $\mu\text{g}$  of VI, assuming a standard deviation of 430 mL (GlaxoSmithKline; data on file).

The primary analyses were performed using SAS software (SAS Institute Inc., Cary, NC, USA) in a step-wise approach. First, 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<sub>1</sub>, country amalgamation, age, sex, baseline % pred FEV<sub>1</sub> stratum and treatment group, using a last observation carried forward approach.

Serial FEV<sub>1</sub> 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 S2 of the online supplementary material.

### Further information

Further methodological details can be found in appendix S2 of the online supplementary material.



**FIGURE 1.** Patient enrolment and completion of the study. AE: adverse event; VI: vilanterol trifenate. #: 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.

**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 yrs in 64–74% of patients) and most (67%) patients had a history of atopy. Per cent predicted pre-bronchodilator FEV<sub>1</sub> (65–68%), absolute reversibility (518–563 mL), and per cent reversibility (24–27%) in FEV<sub>1</sub> 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; beclometasone-equivalent doses in each treatment group (mean ± SD) were as

follows: placebo: 814.4 ± 537.5 µg; VI 3 µg: 698.3 ± 405.53 µg; VI 6.25 µg: 747.6 ± 467.68 µg; VI 12.5 µg: 736.3 ± 473.29 µg; VI 25 µg: 736.4 ± 411.78 µg; and VI 50 µg: 709.8 ± 517.24 µg.

**Efficacy**

The mean change from baseline in trough (23–24 h post-dose) FEV<sub>1</sub> at day 28 in the placebo group was 147 mL. There was a significant relationship between the dose of VI and trough FEV<sub>1</sub> response (p=0.037, excluding placebo). Direct comparisons of each VI dose *versus* placebo showed statistically significant improvements in trough FEV<sub>1</sub> for 12.5 µg, 25 µg and 50 µg VI, but not for the lower doses of 3 µg and 6.25 µg (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<sub>1</sub> data on days 1 and 28 (fig. 3) show an onset of action at the first measurement time point (15 min) and a sustained duration of response over the 24 h of observation, for all doses of VI. The ratio of peak post-dose FEV<sub>1</sub> (over the first 4 h) *versus* trough FEV<sub>1</sub> on day 28 was approximately one in all

**TABLE 1** Patient baseline demographics

Characteristic	Placebo	3 µg VI	6.25 µg VI	12.5 µg VI	25 µg VI	50 µg VI
<b>Subjects n</b>	102	101	101	100	101	102
<b>Age at enrolment yrs</b>	39.9±15.6	44.4±13.5	42.4±14.1	41.3±15.3	42.2±14.3	44.0±15.2
<b>Female sex n (%)</b>	61 (60)	52 (51)	51 (50)	56 (56)	61 (60)	57 (56)
<b>Race n (%)</b>						
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)
<b>Duration of asthma</b>						
≥6 months to <1 yr	0 (0)	2 (2)	1 (<1)	1 (1)	2 (2)	1 (<1)
≥1 yr to <5 yrs	14 (14)	11 (11)	19 (19)	16 (16)	11 (11)	16 (16)
≥5 yrs to <10 yrs	20 (20)	13 (13)	11 (11)	12 (12)	14 (14)	20 (20)
≥10 yrs	68 (67)	75 (74)	70 (69)	71 (71)	74 (73)	65 (64)
<b>Lung function<sup>#</sup></b>						
Pre-bronchodilator FEV <sub>1</sub> 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
Pre-bronchodilator FEV <sub>1</sub> % pred	66.9±12.0	65.8±13.5	66.5±10.8	67.6±11.8	65.3±12.1	65.9±12.3
Absolute reversibility mL	556±300	518±271	563±291	537±280	540±339	537±254
Reversibility % pred	26.6±15.4	24.2±13.5	26.3±15.4	25.2±16.2	27.4±20.7	26.4±15.5
<b>Use of asthma medication n (%)</b>						
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)

Data are presented as mean ± SD, unless otherwise stated. VI: vilanterol trifenatate; FEV<sub>1</sub>: forced expiratory volume in 1 s; % pred: % predicted. #: screening values.

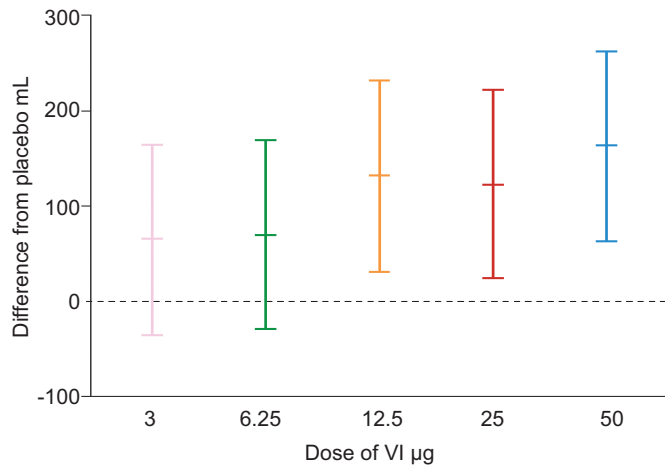
VI groups and placebo (the ratio varied between 1.04 and 1.06, standard deviation varied between 0.053 and 0.091). The change from baseline in weighted mean for 24 h serial FEV<sub>1</sub>

(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 6.25 µg dose on day 1). A dose-related effect

**TABLE 2** Mean trough forced expiratory volume in 1 s (FEV<sub>1</sub>) and change from baseline at day 28 (intent-to-treat and FEV<sub>1</sub> strata populations)

	Placebo	3 µg VI	6.25 µg VI	12.5 µg VI	25 µg VI	50 µg VI
<b>Total subjects n</b>	102	101	101	100	101	102
Intent-to-treat population						
Subjects n	95	98	99	97	99	100
LS mean mL	2388	2452	2458	2518	2509	2550
LS mean change mL	147±36	212±36	217±35	278±36	269±35	309±35
Difference versus placebo mL (95% CI)		64 (-36–164)	69 (-29–168)	130 (30–230)	121 (23–220)	162 (62–261)
p-value		0.208	0.169	0.011	0.016	0.001
<b>Lower stratum (FEV<sub>1</sub> ≥40 to ≤65% pred)</b>						
Subjects n	43	44	41	40	46	45
LS mean mL	2450	2402	2487	2559	2522	2590
LS mean change mL	210±57	161±56	247±57	319±57	281±54	349±55
Difference versus placebo mL (95% CI)		-49 (-198–100)	37 (-113–188)	109 (-44–262)	72 (-75–218)	139 (-9–287)
<b>Upper stratum (FEV<sub>1</sub> &gt;65 to ≤90% pred)</b>						
Subjects n	52	54	58	57	53	55
LS mean mL	2338	2495	2435	2488	2499	2517
LS mean change mL	98±49	254±51	194±48	247±49	259±49	276±49
Difference versus placebo mL (95% CI)		156 (22–291)	97 (-35–228)	149 (18–281)	161 (27–295)	178 (45–312)

Data are presented as mean ± SE, unless otherwise stated. VI: vilanterol trifenatate; LS: least square; FEV<sub>1</sub>: forced expiratory volume in 1 s.



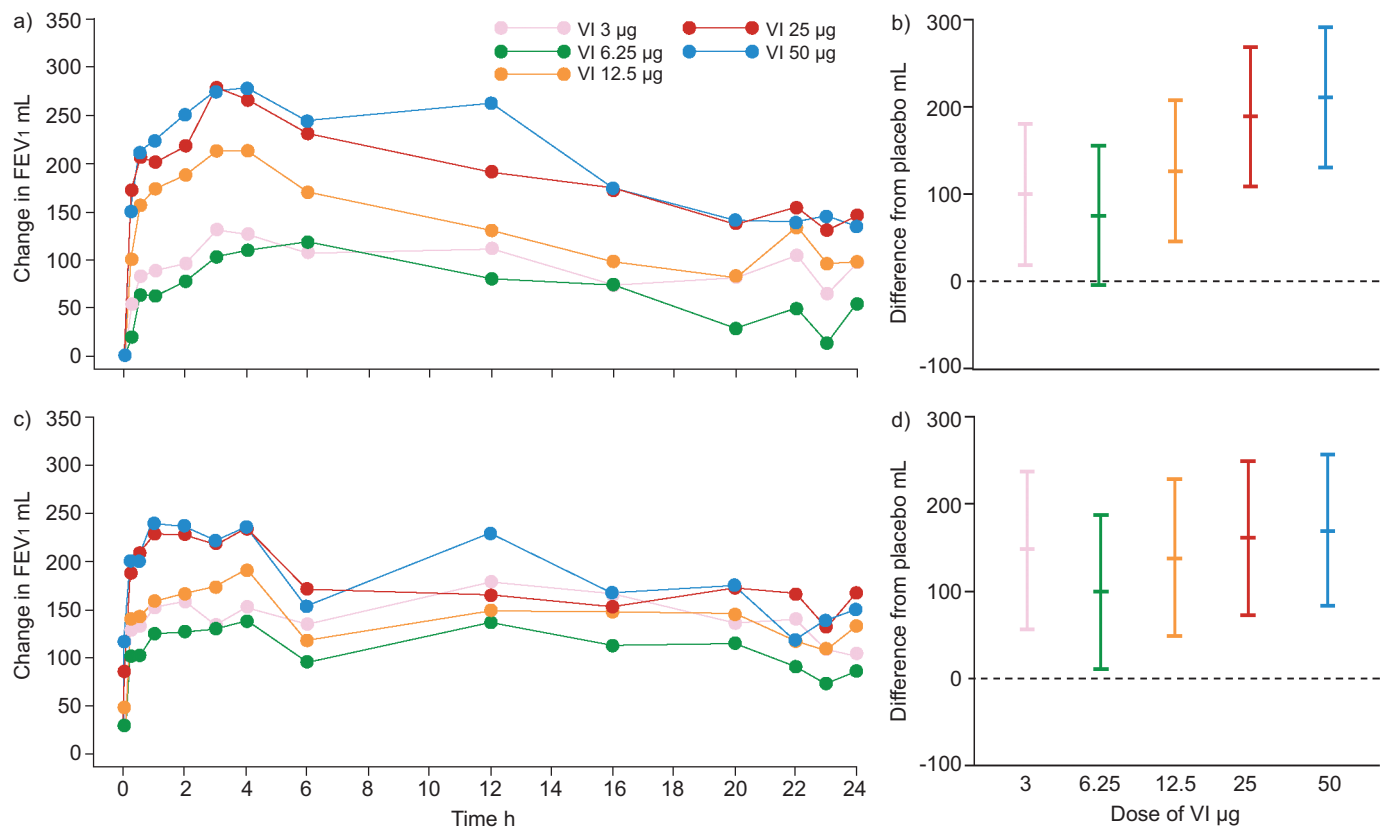
**FIGURE 2.** Adjusted mean change from baseline in trough forced expiratory volume in 1 s (mL) versus placebo at day 28 (intent-to-treat population). Error bars represent 95% confidence intervals. VI: vilanterol trifenate.

of VI was observed on both days 1 and 28, with greatest improvements *versus* placebo seen for the 25 µg (day 1 and day 28 data, respectively: 193 mL and 165 mL) and 50 µg (215 mL and 172 mL) doses (fig. 3).

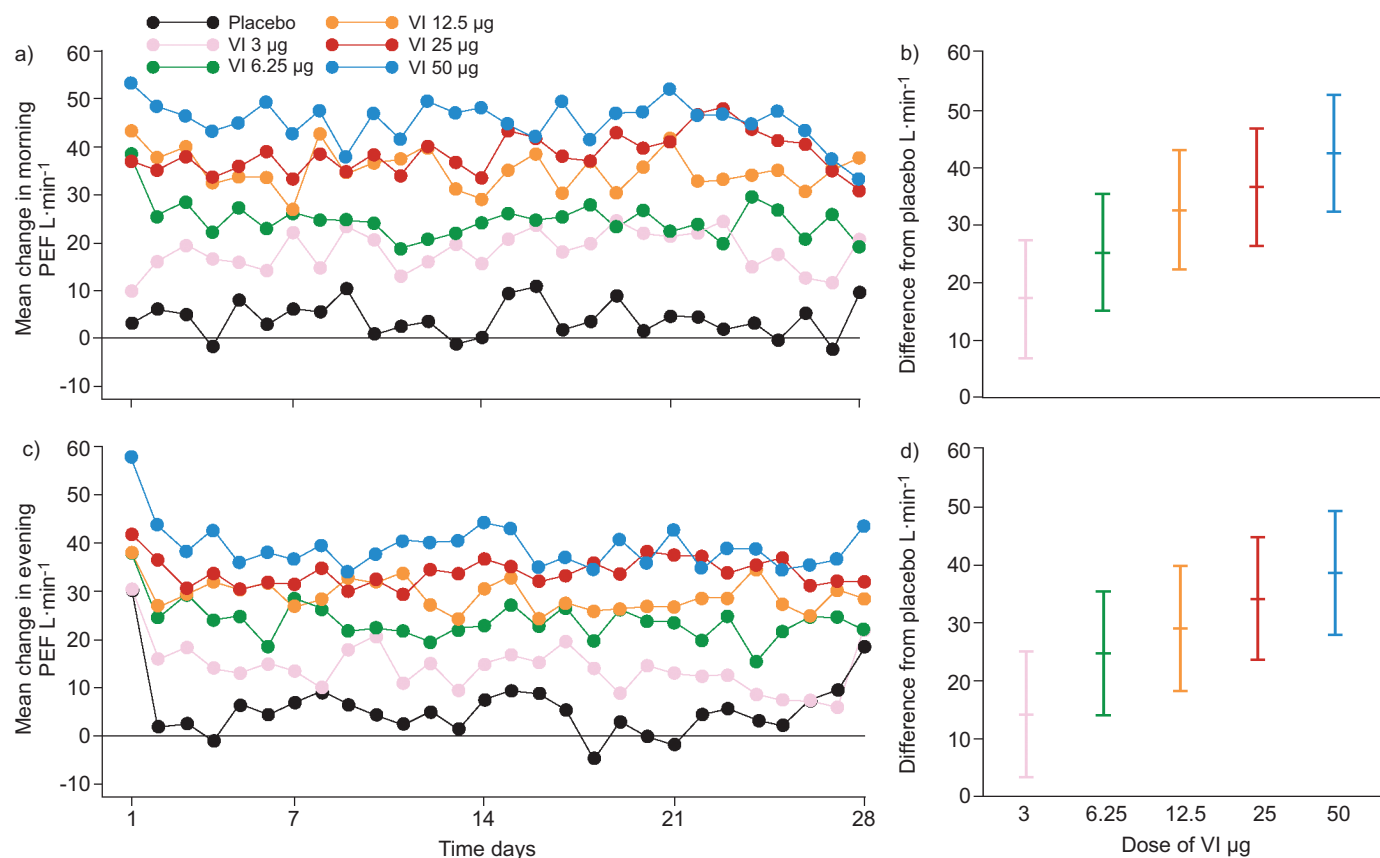
The study design also allowed for patients to be stratified according to baseline lung function (upper strata >65% to ≤90%; lower strata ≥40% to ≤65% pred FEV<sub>1</sub>). In the upper strata absolute mean reversibility ranged from 542.3 mL to 616.7 mL and from 22.4% to 26.4%. In comparison, mean absolute reversibility was slightly lower across the treatment groups (447.4 mL to 542.8 mL) in the lower strata, while mean per cent reversibility was slightly higher (26.4–31.1%). In the upper strata there was little evidence of a dose response at doses of 12.5 µg or greater; there appeared to be a reasonable response to the 3 µg dose that was not evident at the 6.25 µg dose. In contrast, in the lower strata (table 2), there was some evidence of a dose-related effect ranging from no effect with 3 µg (-49 mL difference relative to placebo) to a 139 mL increase with the 50 µg 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 significantly greater than placebo for all doses of VI (fig. 4), with the greatest increases recorded for 12.5 µg, 25 µg and 50 µg VI, respectively, in morning PEF (32.3 L·min<sup>-1</sup>, 36.2 L·min<sup>-1</sup>, 42.1 L·min<sup>-1</sup>) and evening PEF (28.5 L·min<sup>-1</sup>, 33.6 L·min<sup>-1</sup>, 38.0 L·min<sup>-1</sup>; all p<0.001).

VI increased the percentage of symptom-free 24 h periods *versus* placebo by 8–22% in a dose-dependent manner; the effect was statistically significant for all doses of VI, except 3 µg (table 3). VI



**FIGURE 3.** Change from baseline serial forced expiratory volume in 1 s (FEV<sub>1</sub>) adjusted treatment differences from placebo (mL) from a repeated measures model (a, c) and adjusted treatment differences from placebo of weighted mean 24 h serial FEV<sub>1</sub> (b, d) on (a, b) day 1 and (c, d) day 28 (intent-to-treat population). a) SE: 44 mL at 4 h (all doses); 46 mL (25 µg) and 47 mL (all other doses) at 16 h; 46 mL at 24 h (all doses). c) SE: 48 mL (25 µg, 50 µg), 49 mL (6.25 µg, 12.5 µg), and 50 mL (3 µg) at 0 h; 46 mL (50 µg), 48 mL (3 µg), and 47 mL (all other doses) at 4 h; 49 mL (25 µg, 50 µg), 50 mL (6.25 µg, 12.5 µg), and 51 mL (3 µg) at 16 h; 48 mL (50 µg), 49 mL (6.25 µg, 25 µg), and 50 mL (3 µg, 12.5 µg) at 24 h. Error bars represent 95% confidence intervals. VI: vilanterol trifenate.



**FIGURE 4.** Daily mean change in peak expiratory flow (PEF; L·min<sup>-1</sup>) from baseline (a, c) and adjusted treatment differences from placebo of change from baseline in PEF over days 1–28 (b, d) for (a, b) morning and (c, d) evening PEF (intent-to-treat population). VI: vilanterol trifenate. Error bars represent 95% confidence intervals.

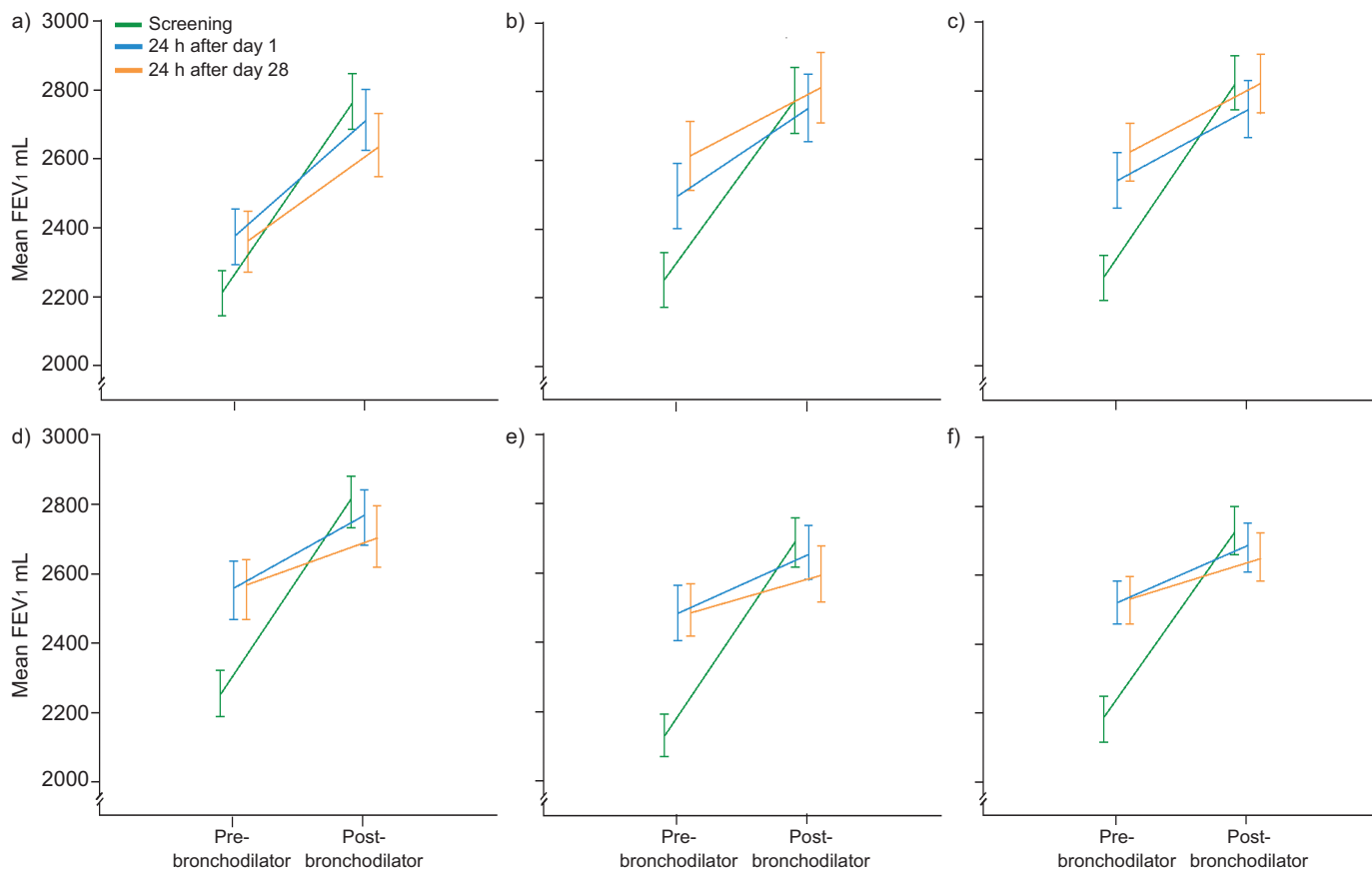
also dose-dependently increased the percentage of rescue-free 24 h periods *versus* placebo by 11–28% (*p*<0.05 for all doses), with the greatest increases seen with the 25 µg dose (table 3).

Comparable improvements in absolute FEV<sub>1</sub> 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

**TABLE 3** Change from baseline in percentage of symptom-free and rescue-free 24 h periods averaged over the 28 day treatment period (intent-to-treat population)

	Placebo	3 µg VI/p>	6.25 µg VI	12.5 µg VI	25 µg VI	50 µg VI
<b>Total subjects n</b>	102	101	101	100	101	102
<b>Symptom-free 24 h periods</b>						
Subjects n	98	99	101	98	101	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 versus 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
<b>Rescue-free 24 h periods</b>						
Subjects 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 versus 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

Data are presented as mean ± SE unless otherwise stated. VI: vilanterol trifenate; LS: least square.



**FIGURE 5.** Response to salbutamol 24 h after administration of placebo or each dose of vilanterol trifenatate (VI) for 1 day or 28 days (absolute values) (intent-to-treat population). a) Placebo; b) VI 3 µg; (c) VI 6.25 µg; d) VI 12.5 µg; e) VI 25 µg; f) VI 50 µg. FEV1: forced expiratory volume in 1 s. Error bars represent standard errors.

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

	Placebo	3 µg VI	6.25 µg VI	12.5 µg VI	25 µg VI	50 µg VI
<b>Total subjects n</b>	102	101	101	100	101	102
<b>Any on-treatment AE</b>	37 (36)	37 (37)	34 (34)	25 (25)	23 (23)	31 (30)
<b>Any post-treatment AE<sup>#</sup></b>	6 (6)	4 (4)	5 (5)	0	5 (5)	2 (2)
<b>Any drug-related AE</b>	7 (7)	8 (8)	8 (8)	5 (5)	4 (4)	7 (7)
<b>Any AE leading to permanent discontinuation of drug or withdrawal<sup>†</sup></b>	1 (<1)	1 (<1)	2 (2)	1 (1)	1 (<1)	0
<b>SAEs</b>	0	0	0	0	0	0
<b>Most frequent on-treatment AEs (≥3% in any treatment group)</b>						
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

Data are presented as n (%). VI: vilanterol trifenatate; SAE: serious adverse event. <sup>#</sup>: during the week following the 28-day dosing period; <sup>†</sup>: two patients were withdrawn due to AEs; four patients were withdrawn primarily due to protocol-defined stopping criteria, with AEs as a sub-reason.

any dose of VI (fig. 5). There were no statistically significant differences between time points or active treatment and placebo ( $p > 0.05$ ; online supplementary table S1).

The proportion of patients obtaining  $\geq 200$  mL and  $\geq 12\%$  increase from baseline in FEV<sub>1</sub> (0–4 h) on days 1 and 28 increased with VI dose (online supplementary fig. S1). When measured over 0–24 h,  $>50\%$  of patients in the 25  $\mu\text{g}$  and 50  $\mu\text{g}$  VI groups maintained the  $\geq 200$  mL and  $\geq 12\%$  improvement in FEV<sub>1</sub> 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 four patients (two 3  $\mu\text{g}$  VI, one 12.5  $\mu\text{g}$  VI, one 25  $\mu\text{g}$  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 6.25  $\mu\text{g}$  VI; one occurred on day 1 and one on day 6; one event was considered to be possibly treatment-related). Palpitations considered to be possibly treatment-related were reported by four patients (one placebo, two 3  $\mu\text{g}$  VI, one 6.25  $\mu\text{g}$  VI). One patient reported impaired glucose tolerance (12.5  $\mu\text{g}$  VI; considered to be possibly treatment related) and one patient had increased blood glucose levels (50  $\mu\text{g}$  VI; considered to be 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  $\mu\text{g}$  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 (online supplementary material, appendix S3). There was no evidence of a statistically significant difference in weighted mean change in pulse rate *versus* placebo 0–4 h 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 50  $\mu\text{g}$  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<sub>1</sub> (the primary end-point), showing a sustained duration of action of at least 24 h at doses  $\geq 12.5$   $\mu\text{g}$ . Significant improvements were also observed on the end-points of trough FEV<sub>1</sub> analysed by baseline FEV<sub>1</sub>, weighted mean (0–24 h) FEV<sub>1</sub>, morning and evening PEF, and symptom-free and rescue-free 24 h 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 3  $\mu\text{g}$  dose would have no or little effect and the 50  $\mu\text{g}$  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 3  $\mu\text{g}$  dose of VI resulted in no significant effect,

the 12.5  $\mu\text{g}$  dose caused intermediate effects, and the bronchodilator responses with 25  $\mu\text{g}$  and 50  $\mu\text{g}$  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<sub>1</sub>. Overall, slightly more pronounced effects were observed with VI 25  $\mu\text{g}$  *versus* 12.5  $\mu\text{g}$ , for example on end-points of morning and evening PEF, as well as symptom-free and rescue-free 24 h 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 end-point of trough FEV<sub>1</sub>, as measured 24 h after the previous dose, confirms a 24 h duration of effect of VI on lung function in asthma patients concomitantly being treated with maintenance ICS. The serial FEV<sub>1</sub> profiles also provide evidence of the 24 h duration of VI at 12.5  $\mu\text{g}$  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<sub>1</sub> were observed at the first time point measured (15 min after inhalation) and maximum effect was documented at 3–4 h on day 1, and within 1–2 h 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<sub>1</sub> values were similar between screening and day 28 in all VI treatment groups, despite the increase in pre-bronchodilator FEV<sub>1</sub> observed 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, hypokalaemia, 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 (50  $\mu\text{g}$ ), which 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 50  $\mu\text{g}$  have limited side-effects. Clearly, the influence of 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 µg, 100 µg and 200 µg) 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 6 µg, 12 µg, and 24 µg showed incremental dose-related efficacy on FEV<sub>1</sub> [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 12.5 µg and/or 25 µg 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<sub>1</sub> and was sufficiently large to determine the frequency of recognised side-effects. The placebo effect on FEV<sub>1</sub> 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<sub>1</sub> 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 h at doses of 12.5 µg and greater, with a favourable therapeutic ratio at doses of 12.5 µg and 25 µg, with the greatest benefit seen at the 25 µg 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.

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#### CLINICAL TRIAL

This study is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) with identifier number NCT00600171.

#### STATEMENT OF INTEREST

Statements of interest for all authors of this manuscript can be found at [www.erj.ersjournals.com/site/misc/statements.xhtml](http://www.erj.ersjournals.com/site/misc/statements.xhtml)

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