



Clinical trial paper

Randomised, double-blind, placebo-controlled, cross-over single dose study of the bronchodilator duration of action of combination fluticasone furoate/vilanterol inhaler in adult asthma



Irene Braithwaite^{a,*}, Mathew Williams^a, Sharon Power^a, Janine Pilcher^a, Mark Weatherall^b, Amanda Baines^c, Jackie Moynihan^d, Rodger Kempsford^c, Richard Beasley^{a,e}, on behalf of FF/VI Study Team

^a Medical Research Institute of New Zealand, Wellington, New Zealand

^b Rehabilitation Teaching and Research Unit, University of Otago Wellington, Wellington, New Zealand

^c Medicines Research Centre, GlaxoSmithKline Research and Development, Stevenage, UK

^d Synergy Clinical, Langley, UK

^e Capital and Coast District Health Board, Wellington, New Zealand

ARTICLE INFO

Article history:

Received 18 February 2016

Received in revised form

16 August 2016

Accepted 2 September 2016

Available online 4 September 2016

Keywords:

Asthma

Bronchodilation

Duration of action

Randomised placebo-controlled trial

Fluticasone furoate/vilanterol

ABSTRACT

Background: Fluticasone furoate (FF)/vilanterol (VI) is a once-daily maintenance treatment for asthma and chronic obstructive pulmonary disease. The duration of bronchodilation beyond 24 h has not been determined previously.

Methods: Adults aged 18–65 ($n = 32$), with asthma and reversibility to salbutamol ($\geq 15\%$ and ≥ 200 mL increase in forced expiratory volume in 1 s [FEV₁]) participated in a double-blind, placebo-controlled, crossover study. Patients were admitted to a clinical trials unit for 72 h, and inhaled, in random order, placebo or FF/VI 100/25 mcg via ELLIPTA dry powder inhaler on two occasions 7–14 days apart. FEV₁ was measured at baseline, 15 and 30 min, 1, 2, 4, 12, 24, 36, 48, 60, and 72 h. The differences in change in FEV₁ from baseline between treatments and corresponding two-sided 95% confidence intervals (CI) were calculated at each time point.

Findings: FF/VI produced a rapid onset of bronchodilation (adjusted mean difference in change from baseline in FEV₁ versus placebo at 15 min, 252 mL [95% CI 182–322]). Maximum bronchodilation was observed at 12 h (adjusted mean difference in the change from baseline in FEV₁, 383 mL [95% CI 285–481]). Bronchodilation was maintained throughout the 72-h assessment period (adjusted mean difference in the change in FEV₁ from baseline at 72 h, 108 mL [95% CI 15–200]). FF/VI was well tolerated and no serious side effects were reported.

Interpretation: A single dose of FF/VI 100/25 mcg showed evidence of a 72-h bronchodilator duration of action in adults with asthma.

© 2016 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

International asthma guidelines recommend the use of combination inhaled corticosteroid (ICS)/long-acting β_2 agonist (LABA) therapy as the preferred maintenance treatment in moderate to severe asthma [1]. However, current ICS/LABA products require twice-daily dosing and treatment adherence represents a potential

problem [2–5]. This has led to the development of the next generation of inhaled LABA and corticosteroid medications with a longer duration of action to enable once-daily dosing, with the potential to improve patient convenience and enhance compliance [4–6].

Vilanterol trifenate (VI) is a member of the next generation of LABAs with at least a 24-h duration of bronchodilator action [7–10]. *In-vitro* studies have shown it to be more potent and to have greater intrinsic activity than salmeterol, with a similar selectivity profile for the β_2 -adrenoceptor (AR) over both the β_1 - and β_3 -AR subtypes compared with salbutamol, and superior to the other β -agonists

* Corresponding author. Medical Research Institute of New Zealand, PO Box 7902, Wellington, 6242, New Zealand.

E-mail address: Irene.Braithwaite@mrnz.ac.nz (I. Braithwaite).

tested [7]. In human airways, VI has a faster onset and longer duration of action than salmeterol, exhibiting significant bronchodilation 22 h after treatment [7]. Fluticasone furoate (FF) is a novel glucocorticoid that has enhanced affinity for the glucocorticoid receptor, with fast association and slow dissociation [11]. These properties result in a longer duration of action and prolonged retention in the lung, compared with fluticasone propionate (FP), and have enabled its use as a once-daily medication in asthma [12–15].

The combination FF/VI inhaler (Relvar/Breo ELLIPTA®; ELLIPTA® is a trademark of the GSK group of companies) is efficacious as a once-daily treatment in asthma [16–18] and COPD [19–23]. The bronchodilator effects of FF/VI are well characterised up to 24 h in patients with asthma [17,18] and COPD [19,21–23]. However, there is still significant bronchodilation at 24 h [17–23] and persistence of bronchodilation beyond this dosing interval time point has not been determined. The aim of this study was to investigate the duration of the bronchodilator effect over a 72-h period following a single dose of the combination FF/VI 100/25 mcg inhaler administered in the morning in adult patients with asthma. The secondary objective was to investigate the onset of bronchodilation.

2. Methods

2.1. Patients

Volunteers for this study were recruited from the Medical Research Institute of New Zealand database of asthma volunteers and local newspaper advertising. The first patient was screened in October 2013 and the last patient completed the study in September 2014. Adults aged 18–65 years with a diagnosis of asthma by a doctor were eligible for inclusion if at screening they demonstrated a pre-bronchodilator predicted forced expiratory volume in 1 s (FEV_1) $\geq 60\%$, an increase $\geq 15\%$ over baseline and an absolute change of ≥ 200 mL within 30 min following four inhalations of salbutamol 100 mcg via metered dose inhaler through a spacer device. Patients were required to be on an ICS for at least 12 weeks prior to screening and be clinically stable on a daily dose of ICS (FP 100–500 mcg or equivalent), with or without a short-acting β_2 -agonist (SABA) for 4 weeks prior to the screening visit. Patients were also required to be able to replace their current asthma treatments with a SABA inhaler from 7 days prior to randomisation until study completion and withhold their SABA for at least 6 h prior to study visits. Important exclusion criteria included a history of life-threatening asthma, current smoker or a pack year history of ≥ 10 years, other significant pulmonary diseases, respiratory infection within 1 month of entry to the study, any asthma exacerbation that required oral corticosteroids or that resulted in hospitalisation within 12 weeks of screening, LABA use in the 12 weeks prior to screening, or a significant electrocardiograph abnormality. More detailed inclusion and exclusion criteria can be found in a summary of the protocol at http://www.gsk-clinicalstudyregister.com/study/116592?study_ids=116592#ps.

2.2. Study design

This was a randomised, double-blind, placebo-controlled, cross-over study (ClinicalTrials.gov ID: NCT01837316; Supplementary Fig. S1). Patients were admitted to the Clinical Trials Unit (CTU) at Wellington Regional Hospital for 72 h on two occasions to receive the randomised treatments, FF/VI 100/25 mcg inhalation powder administered via the ELLIPTA dry powder inhaler (DPI) and placebo (first strip lactose, second strip lactose, and magnesium stearate) administered via the ELLIPTA DPI.

Within 21 days of the screening visit, eligible patients attended

on Day 1 of the treatment period. Spirometry was undertaken at baseline (pre-medication) and then at 15 and 30 min, 1, 2, 4, 12, 24, 36, 48, 60, and 72 h post-medication administration. Spirometry was performed using a body plethysmograph (Masterscreen Body, Erich-Jaeger, Friedberg, Germany). The highest value of three technically acceptable manoeuvres was retained as per American Thoracic Society/European Respiratory Society guidelines [24]. Between 7 and 14 days later, patients returned to the clinic for treatment period 2 and the procedures were repeated with whichever study medication they had not already received (Supplementary Fig. S1). Patients attended again within 10 days for a final follow-up assessment.

Maintenance ICS was stopped 24 h prior to study medication dosing until 72 h after dosing. Smoking and caffeine or xanthine-containing products were forbidden for 8 h prior to the study medication administration until completion of the 72-h assessments.

Patients were required to avoid SABA use as a rescue medication for 8 h prior to screening. Patients were also requested to avoid SABA use during the 72-h study periods in the CTU unless absolutely necessary and, if possible, not within 8 h of the next lung function assessment. SABA use was recorded, and if used within 8 h prior to any lung function assessment, the data from that time point were excluded from the analysis.

2.3. Randomisation and masking

Patients were assigned to one of two treatment sequences (AB or BA, where A was placebo and B was FF/VI 100/25 mcg) in accordance with the randomisation schedule, which was generated by the study statistician prior to the start of the study, using validated internal software. The investigators and patients were blinded to the treatment assignments.

2.4. Sample size

The sample size was based on feasibility, with some justification derived from a previous study in this subject population, in which the standard deviation (SD) of the paired difference in FEV_1 between a combination ICS/LABA medication and placebo was 190 mL [25]. This was used to obtain an estimate of within subject SD to assess the width of the confidence interval (CI) for the difference between treatments based on the proposed sample size of 32 patients. Based on the within patient SD of 270 mL and a sample size of 32 patients, this equates to a half width of a 95% CI of 138 mL. This calculation is based on a symmetric two-tailed procedure and a type I error rate of 5%.

2.5. Statistical methods

The primary objective of the study was to estimate the bronchodilator effect over 72 h following a single dose of FF/VI 100/25 mcg compared with placebo. Changes from baseline in FEV_1 at time points 15, 30 min, 1, 2, 4, 12, 24, 36, 48, 60, and 72 h post dose were the main endpoints. Baseline was defined as Day 1 pre-dose measurement for FEV_1 for each treatment period. A mixed effects repeated measures analysis of covariance model was fitted, with fixed effect terms for treatment, period, time, time by treatment interaction, patient baseline, period baseline, sex, and age fitted as covariates, with subject as a random effect. From these analyses, point estimates and their associated 95% CIs were constructed for each treatment at each time point and the difference between adjusted means and the corresponding two-sided 95% CI was calculated at each time point. In a post-hoc assessment, the adjusted mean change in FEV_1 from baseline following FF/VI, and

associated 95% CIs, were evaluated for the clinical significance of the bronchodilation, defined as change from baseline of 200 mL or greater.

The secondary endpoint, time to onset of bronchodilator effect (defined as the time point when FEV₁ first met or exceeded 12% and 200 mL over baseline during the 0–4 h serial measurements), was described by a frequency table showing how many patients achieved onset in the first 4 h, median times of the event and a Kaplan–Meier plot showing the cumulative incidence curves for each treatment.

Safety data were presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. The study was registered with clinicaltrials.gov (NCT01837316) and was approved by the New Zealand Health and Disability Ethics Committee (13/CEN/70). All patients provided written informed consent prior to undertaking any study-related procedures.

The statistical analyses were conducted using SAS version 9.3.

3. Results

The baseline characteristics of the 32 randomised patients are shown in Table 1. Patients had moderately severe asthma with a mean pre-bronchodilator FEV₁ of 79% predicted and marked bronchodilator reversibility with a mean increase in FEV₁ after bronchodilator of 21%. One patient withdrew consent 4 h after receiving FF/VI during the first treatment period, and one was withdrawn by the investigators due to worsening asthma 48 h after receiving placebo during the second treatment period (Fig. 1). On nine occasions in patients receiving placebo treatment, rescue SABA was used within 8 h of the next FEV₁ measurement and for this reason the FEV₁ measurement was excluded from the analyses.

3.1. Efficacy

3.1.1. Main endpoints (Tables 2 and 3, Figs. 2 and 3, Supplementary Tables S1, S2)

FF/VI 100/25 mcg was associated with a rapid onset of bronchodilation with an increase in adjusted mean FEV₁ change from baseline compared with placebo of 252 mL (95% CI 182–322) after 15 min, the first post-dose time point assessment (Table 2, Fig. 2). Higher FEV₁ values were observed in patients receiving FF/VI versus placebo throughout the 72-h post-dose assessment period, resulting in an adjusted mean difference in FEV₁ change from baseline of 108 mL (95% CI 15–200) compared with placebo at 72 h. The maximum bronchodilation was seen at the 12-h post-dose time point, with an adjusted mean difference in FEV₁ change from baseline of 383 mL (95% CI 285–481) compared with placebo (Table 3, Fig. 3). The difference in FEV₁ change from baseline between FF/VI and placebo progressively reduced from this time point. At the 48-h time point, the adjusted mean difference in FEV₁

change from baseline was 200 mL (95% CI 101–299) compared with placebo. For FF/VI the mean change from baseline at 48 h was 268 mL (95% CI 194–342) (Table 2, Fig. 2).

3.1.2. Secondary endpoints (Supplementary Tables S3, S4)

More patients achieved 'onset of bronchodilator effect' (defined as an increase in FEV₁ of >12% or 200 mL) within the first 4 h following FF/VI 100/25 mcg treatment, 21/32 (66%), compared with placebo treatment, 5/31 (16%) (Supplementary Table S3).

Use of SABA rescue medication during the 72-h treatment period was higher following administration of placebo than following FF/VI (Supplementary Table S4). Following placebo, 15/31 (48%) patients took rescue SABA on at least one occasion, with 13/31 (42%) taking it on two or more occasions (Supplementary Table S4). Following FF/VI, 2/32 (6%) patients took rescue SABA on one occasion, with none taking it on two or more occasions.

3.1.3. Safety results (Supplementary Tables S5, S6)

No serious adverse events (SAEs) were reported during the study. The incidence of adverse events (AEs) was high in both study groups (72% [FF/VI] and 81% [placebo]; Supplementary Table S5). The most frequently reported AEs (≥2 events in any treatment group) were headache (19 patients) and asthma (10 patients). Asthma, chest discomfort, and wheezing were all reported more frequently on placebo compared with FF/VI. Back pain was more frequent following FF/VI treatment compared with placebo (6% [FF/VI] and 3% [placebo]). All other AEs were only reported by one or two patients on either placebo, FF/VI, or both treatments. Overall, there were similar or lower incidences of AEs following FF/VI administration compared with placebo. Headache was the most common drug-related AE with similar incidence between treatments, occurring in 8 (25%) patients receiving FF/VI versus 7 (23%) patients receiving placebo (Supplementary Table S6). An episode of asymptomatic sinus tachycardia was recorded in one patient 72 h after FF/VI dosing.

4. Discussion

This randomised, double-blind, placebo-controlled trial demonstrated that a single dose of FF/VI 100/25 mcg has a bronchodilator duration of action of at least 72 h in adults with asthma. The combination FF/VI resulted in a rapid onset of bronchodilation, with a maximum bronchodilator effect at 12 h versus placebo.

To our knowledge, this is the first study demonstrating that the bronchodilator duration of action of a LABA (either alone or in an ICS/LABA combination) lasts beyond 36 h [26]. The maximum bronchodilation was achieved at the 12-h time point (adjusted mean difference in FEV₁ from placebo: 383 mL [95% CI 285–481]), which is the normal dosing interval for twice-daily LABAs such as salmeterol and formoterol fumarate. This magnitude of bronchodilation was maintained through to the 24-h time point (adjusted

Table 1
Characteristics of randomised participants (n = 32).

Characteristic	Mean (SD)	Minimum–maximum
Age (years)	38.5 (12.26)	18–64
BMI (kg/m ²)	27.3 (4.28)	19.7–34.7
ICS dose (mcg/day) ^a	248 (133)	100–500
Pre-bronchodilator FEV ₁ (% predicted)	78.7 (11.4)	59.9–101.0
Post-bronchodilator FEV ₁ reversibility (% change from baseline)	20.9 (6.26)	15.1–46.5
Screening FEV ₁ (L)	2.98 (0.84)	1.78–5.09
	n (%)	
Sex (female)	13 (41)	

BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FP, fluticasone propionate; ICS, inhaled corticosteroid; SD, standard deviation.

^a ICS dose: FP mcg/day or equivalent.

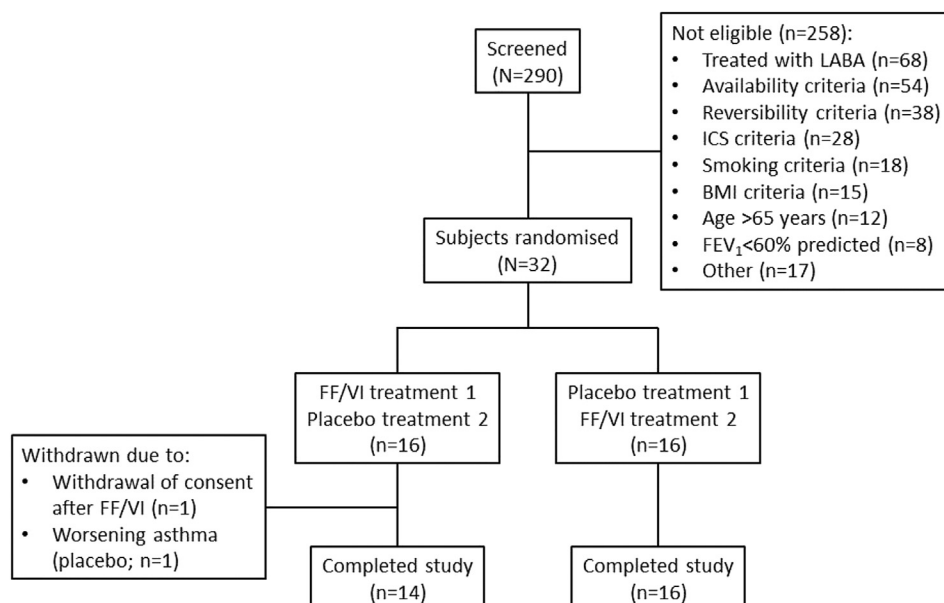


Fig. 1. Treatment flow.

Table 2Change from baseline FEV₁ (mL) 0–72 h after administration of FF/VI 100/25 mcg and placebo.

Treatment	N	Planned relative time (h)	n	Adjusted mean change in FEV ₁ (mL)	95% CI of adjusted mean change
Placebo	31	0.25	31	17	–40–74
		0.5	31	8	–48–65
		1	31	74	11–137
		2	31	131	65–196
		4	31	85	16–154
		12	29	–56	–131–19
		24	30	32	–34–98
		36	29	61	–1–122
		48	31	67	–7–142
		60	28	64	–8–137
		72	28	117	46–187
FF/VI 100/25 mcg	32	0.25	32	269	213–325
		0.5	31	313	257–368
		1	32	345	282–407
		2	32	428	364–493
		4	32	420	352–488
		12	31	327	254–401
		24	31	376	311–441
		36	31	298	238–358
		48	31	268	194–342
		60	31	196	126–267
		72	31	225	156–293

CI, confidence interval; FEV₁, forced expiratory volume in 1 s; FF, fluticasone furoate; VI, vilanterol.The scheduled FEV₁ reading was not performed in one patient in period 1 at 0.5 h.

mean difference from placebo in FEV₁: 344 mL [95% CI 258–429]), which is the normal dosing interval for FF/VI. At the final 72-h time point, bronchodilation produced by FF/VI was still apparent with an adjusted mean difference from placebo in FEV₁ of 108 mL (95% CI 15–200). By comparison, we and others have previously shown that under similar controlled conditions the LABAs salmeterol and formoterol, either administered separately or as salmeterol/FP or formoterol/budesonide combination inhalers, have bronchodilator durations of action of up to 24 h [25,27–29].

Although FF/VI 100/25 was shown to have a bronchodilator duration of action of up to 72 h, the extent of this effect at the later time-points was probably below what would be considered to be of clinical significance. Assessment of the minimally clinically important increase in FEV₁ requires determination of change from

baseline following treatment administration rather than the treatment difference compared with placebo. The minimal clinically important difference in FEV₁ has not been rigorously established for asthma. Although in a validation study [30], the average minimal perceivable improvement in FEV₁ (change from baseline) of 230 mL corresponded to a reduction of inhaled SABA of 0.81 puffs per day. The corresponding measure for moderate improvement for FEV₁ response and associated reduction in SABA use were 250 mL and 1.47 puffs per day, respectively [30]. An increase in FEV₁ of 200 mL compared with baseline during a single testing session suggests a “significant” bronchodilation [31], and is used to demonstrate an individual’s responsiveness to a bronchodilator. Based on a limit of 200 mL, the duration of bronchodilation (as change from baseline) produced by FF/VI 100/25 mcg was longer

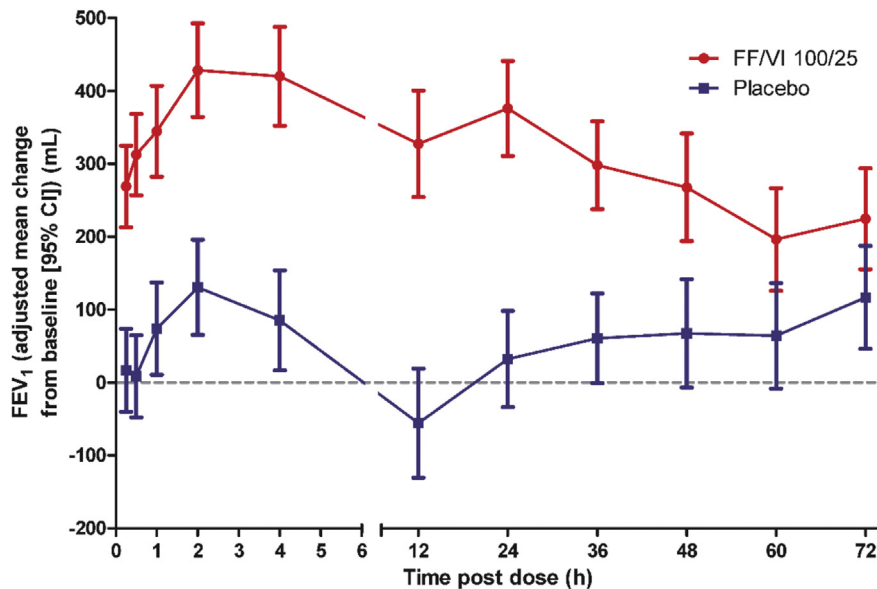


Fig. 2. Adjusted mean FEV1 (mL; change from baseline) and 95% CIs 0–72 h after administration of FF/VI 100/25 ($n = 32$) and placebo ($n = 31$) in patients with asthma.

Table 3

Adjusted mean differences in FEV₁: FF/VI 100/25 mcg minus placebo from 0.25 to 72 h.

Planned relative time (h)	FF/VI minus placebo adjusted ^a mean difference FEV ₁ (mL) (95% CI)
0.25	252 (182–322)
0.5	304 (235–374)
1	271 (190–351)
2	298 (214–382)
4	335 (245–424)
12	383 (285–481)
24	344 (258–429)
36	237 (159–316)
48	200 (101–299)
60	132 (38–227)
72	108 (15–200)

CI, confidence interval; FEV₁, forced expiratory volume in 1 s; FF, fluticasone furoate; VI, vilanterol.

^a Adjusted for treatment, period, time, time by treatment interaction, subject baseline, period baseline, sex and age.

than 48 h with a mean FEV₁ change from baseline of 268 mL at the 48 h time point. As a result, we propose that the duration of clinically relevant bronchodilation produced by single dose FF/VI 100/25 mcg is in the region of at least 48 h.

No new safety concerns were identified, although as a single-dose study, it was not designed to assess safety. No SAEs were reported during the study and the most frequently reported AEs were headache (19 patients) and asthma (10 patients) in total. The number of patients with drug-related AEs was similar between groups.

There are a number of methodological issues relevant to the interpretation of this study. Firstly, participants were admitted to a CTU for the 72-h study period to provide a controlled environment to avoid provoked bronchoconstriction secondary to everyday exposures such as exercise and cold air. This also ensured that patients did not take caffeine-containing products and that SABA use for relief of asthma symptoms was fully documented by the investigators. If participants experienced worsening asthma to the extent that they required rescue SABA medication, the investigator supervised and documented the administration of salbutamol via a

metered dose inhaler, preferably after a lung function measurement. If rescue salbutamol was administered within 8 h of the next lung function measurement, the FEV₁ at that time point was not included in the analysis. In the event, there were only nine occasions in five patients when rescue salbutamol was administered within 8 h of the next lung function measurement, all of these were following placebo administration, and so such rescue bronchodilator use is unlikely to have influenced the results reported here.

Patients were required to demonstrate bronchodilator reversibility at screening, with an increase in FEV₁ of $\geq 15\%$ and an absolute change of ≥ 200 mL from baseline within 30 min following 400 mcg of salbutamol. This criterion enabled inclusion of suitable patients to ensure that both the onset and duration of bronchodilation could be assessed. LABA use in the last 3 months prior to study entry was an exclusion criterion that ensured participants were LABA free. However, we acknowledge that these criteria resulted in the exclusion of a proportion of patients with moderate-to-severe asthma in whom ICS/LABA therapy is indicated, thereby reducing the generalisability of the study findings. Patients were all taking maintenance ICS prior to randomised treatment administration, suggesting that the observed bronchodilator response is likely to have been due mainly to the VI component.

VI was administered in the combination FF/VI ELLIPTA DPI, as this is the formulation in which VI will be available for use in adults with asthma; there is no separate VI inhaler product available for use in adults with asthma, thereby avoiding possible LABA monotherapy, if ICS and LABA therapy is prescribed as separate inhalers [32]. Although both the FF/VI 100/25 mcg and 200/25 mcg preparations are the once-daily doses recommended in asthma, based on the clinical trials in which efficacy has been demonstrated [16–18], we examined the FF/VI 100/25 mcg preparation as this is the dose likely to be most commonly used in clinical practice. However the results are likely to be generalisable to the FF/VI 200/25 mcg preparation, as it contains the same VI dose. Placebo was administered as a control treatment, due to the significant placebo bronchodilator response in asthma [8,10] and the circadian variation in lung function in asthma [33].

FF/VI was administered in the morning to enable the onset of action to be determined with five measurements of lung function within the initial 4 h period, which would have been difficult if

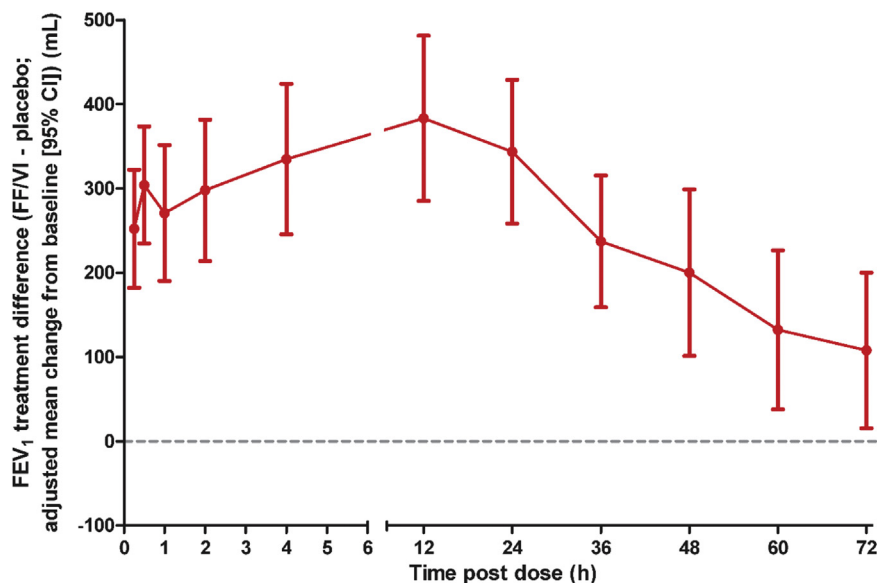


Fig. 3. Adjusted mean FEV1 (mL, change from baseline) treatment differences and 95% CIs 0–72 h after administration of FF/VI 100/25 (n = 32) and placebo (n = 31) in patients with asthma.

administered in the evening. However, in patients with asthma there is no difference in bronchodilator response to FF/VI with morning or evening dosing [34], and the study results are considered generalisable to afternoon dosing.

The rapid onset and prolonged bronchodilator duration of action of FF/VI is consistent with its known pharmacological properties *in vitro*. In human airways, VI has been shown to have a faster onset and longer duration of action than salmeterol [7]. It would be interesting to now determine the duration of action of other LABAs such as indacaterol, abediterol, and olodaterol, which are also recommended for once-daily use in asthma.

There are two main clinical implications of the findings reported here. Firstly, the study confirmed that the bronchodilator duration of action of FF/VI is sufficient to enable once-daily dosing in asthma. Secondly, it suggests that if a patient inadvertently missed a daily dose, then FF/VI may have sufficient bronchodilator effect for a further 24-h period.

In conclusion, a single dose of FF/VI 100/25 mcg showed evidence of a 72-h bronchodilator duration of action in adults with asthma. The duration of clinically relevant bronchodilation produced by this dose of FF/VI was at least 48 h.

Contributors

Conception and design: AB, IB, RB, RK, MWe.

Data collection: IB, JP, MWi, SP.

Analysis and data interpretation: AB, IB, JM, MWe, RB, RK.

The first draft of the manuscript was written by IB and RB. All authors contributed to the revision of, and approved the final version of the submitted manuscript.

Conflict of interest

The study was funded by GSK.

AB and RK are employees of GSK and hold stock in GSK.

IB, JP, MWe, MWi and SP and have no conflicts of interest to declare.

JM is employed by Synergy Clinical who was contracted by GSK to complete the analyses for this study.

RB has been a member of AstraZeneca, GSK and Novartis advisory boards, received research grants from AstraZeneca, Cephalon, Chiesi, GSK and Novartis, and received payments for lectures or support to attend meetings from AstraZeneca, Boehringer Ingelheim, GSK and Novartis.

The FF/VI study group

MRINZ: Richard Beasley, Susan Bibby, Irene Braithwaite, Amanda Burmeister, Rachel Caswell-Smith, Thom Charles, Mark Holliday, Alexander Hosking, Claire Munro, Janine Pilcher, Sharon Power, Sumeet Reddy, Judith Riley, Mathew Williams.

University of Otago: Mark Weatherall.

GSK: Amanda Baines, Rodger Kempford.

Synergy Clinical: Jackie Moynihan.

Funding

GSK (HZA116592).

Acknowledgements

We are grateful to the study participants for their involvement in the study. The MRINZ is supported by Health Research Council of New Zealand Independent Research Organisation funding. Editorial support in the form of incorporating author comments on the first draft and styling and editing before submission, was provided by Jenni Lawton, PhD and Angela Rogers PhD (Gardiner-Caldwell Communications) and funded by GSK.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2016.09.006>.

References

- [1] Global Initiative for Asthma, Global Strategy for Asthma Management and Prevention, 2014. www.ginasthma.org (accessed Jan 2016).
- [2] S.W. Stoloff, D.A. Stempel, J. Meyer, R.H. Stanford, J.R. Carranza Rosenzweig,

- Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies, *J. Allergy Clin. Immunol.* 113 (2004) 245–251.
- [3] D.A. Stempel, S.W. Stoloff, J.R. Carranza, R.H. Stanford, K.L. Ryskina, A.P. Legorreta, Adherence to asthma controller medication regimens, *Respir. Med.* 99 (2005) 1263–1267.
 - [4] N.S. Breeckveldt-Postma, J. Koerselman, J.A. Erkens, T. van der Molen, J.W. Lammers, R.M. Herings, Treatment with inhaled corticosteroids in asthma is too often discontinued, *Pharmacoepidemiol Drug Saf.* 17 (2008) 411–422.
 - [5] J.F. Guest, A.M. Davie, F.J. Ruiz, M.J. Greener, Switching asthma patients to a once-daily inhaled steroid improves compliance and reduces healthcare costs, *Prim. Care Respir. J.* 14 (2005) 88–98.
 - [6] A.J. Claxton, J. Cramer, C. Pierce, A systematic review of the associations between dose regimens and medication compliance, *Clin. Ther.* 23 (2001) 1296–1310.
 - [7] R. Slack, V. Barrett, V. Morrison, et al., In vitro characterization of vilanterol, a novel long-acting β_2 -adrenoceptor agonist with 24-hour duration of action, *J. Pharmacol. Exp. Ther.* 344 (2013) 218–230.
 - [8] R. Sterling, J. Lim, L. Frith, N.G. Snowise, L. Jacques, B. Haumann, Efficacy and optimal dosing interval of the long-acting β_2 agonist, vilanterol, in persistent asthma: a randomised trial, *Respir. Med.* 106 (2012) 1110–1115.
 - [9] J. Lotvall, E. Bateman, E. Bleecker, et al., 24-h duration of the novel LABA vilanterol trifenate in asthma patients treated with inhaled corticosteroids, *Eur. Respir. J.* 40 (2012) 570–579.
 - [10] R. Kempford, V. Norris, S. Siederer, Vilanterol trifenate, a novel inhaled long-acting beta2 adrenoceptor agonist, is well tolerated in healthy subjects and demonstrates prolonged bronchodilation in subjects with asthma and COPD, *Pulm. Pharmacol. Ther.* 26 (2013) 256–264.
 - [11] M. Salter, K. Biggadike, J.L. Matthews, et al., Pharmacological properties of the enhanced-affinity glucocorticoid fluticasone furoate in vitro and in an in vivo model of respiratory inflammatory disease, *Am. J. Physiol. Lung Cell Mol. Physiol.* 293 (2007) L660–L667.
 - [12] A. Woodcock, E.D. Bateman, W.W. Busse, et al., Efficacy in asthma of once-daily treatment with fluticasone furoate: a randomized, placebo-controlled trial, *Respir. Res.* 12 (2011) 132–142.
 - [13] E. Bateman, E. Bleecker, J. Lotvall, et al., Dose effect of once-daily fluticasone furoate in persistent asthma: a randomised trial, *Respir. Med.* 106 (2012) 642–650.
 - [14] P. O'Byrne, A. Woodcock, E. Bleecker, et al., Efficacy and safety of once-daily fluticasone furoate 50 μ g in adults with persistent asthma: a 12-week randomised trial, *Respir. Res.* 15 (2014) 88–97.
 - [15] W.W. Busse, E.R. Bleecker, E.D. Bateman, et al., Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial, *Thorax* 67 (2012) 35–41.
 - [16] W.W. Busse, P.M. O'Byrne, E.R. Bleecker, et al., Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the beta2 agonist vilanterol administered once daily for 52 weeks in patients ≥ 12 years old with asthma: a randomised trial, *Thorax* 68 (2013) 513–520.
 - [17] A. Woodcock, E.R. Bleecker, J. Lotvall, et al., Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial, *Chest* 144 (2013) 1222–1229.
 - [18] E. Bleecker, J. Lotvall, P. O'Byrne, et al., Fluticasone furoate-vilanterol 100-25 μ g compared with fluticasone furoate 100 μ g in asthma: a randomised trial, *J. Allergy Clin. Immunol. Pract.* 2 (2014) 553–561.
 - [19] J. Boscia, K. Pudi, M. Zvarich, L. Sanford, S.K. Siederer, C. Crim, Effect of once-daily fluticasone furoate/vilanterol on 24-hour pulmonary function in patients with chronic obstructive pulmonary disease: a randomised, three-way, incomplete block, crossover study, *Clin. Ther.* 34 (2012) 1655–1666.
 - [20] M. Dransfield, J. Bourbeau, P. Jones, et al., Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel group, randomised controlled trials, *Lancet Respir. Med.* 1 (2013) 210–223.
 - [21] F. Martinez, J. Boscia, G. Feldman, et al., Fluticasone furoate/vilanterol (100/25/200/25 μ g) improves lung function in COPD— a randomised trial, *Respir. Med.* 107 (2013) 550–559.
 - [22] E. Kerwin, C. Scott-Wilson, S. Sanford, et al., A randomised trial of fluticasone furoate/vilanterol (50/25 μ g; 100/25 μ g) on lung function in COPD, *Respir. Med.* 107 (2013) 560–569.
 - [23] M.T. Dransfield, G. Feldman, P. Korenblat, et al., Efficacy and safety of once-daily fluticasone furoate/vilanterol (100/25 mcg) versus twice-daily fluticasone propionate/salmeterol (250/50 mcg) in COPD patients, *Respir. Med.* 108 (2014) 1171–1179.
 - [24] M.R. Miller, J. Hankinson, V. Brusasco, et al., Standardisation of spirometry. Number 2 in the series 'ATS/ERS Task Force: standardisation of lung function testing. Edited by Brusasco V, Crapo R, and Viegi G, *Eur. Respir. J.* 26 (2005) 319–338.
 - [25] M. Masoli, M. Weatherall, J. Ayling, M. Williams, R. Beasley, The 24 h duration of bronchodilator action of the salmeterol/fluticasone combination inhaler, *Respir. Med.* 99 (2005) 545–552.
 - [26] D. Singh, H. Pujol, A. Ribera, et al., A dose ranging study of the bronchodilator effects of abediterol (LAS100977), a long acting b2-adrenergic agonist, in asthma; a Phase II randomised study, *BMC Pulm. Med.* 14 (2014) 176.
 - [27] S. Aldington, M. Williams, M. Weatherall, R. Beasley, Duration of action of the salmeterol/fluticasone combination inhaler administered in the evening: a randomized controlled trial in childhood asthma, *Respirol* 11 (2006) 638–642.
 - [28] M. Masoli, M. Williams, M. Weatherall, R. Beasley, The 24 h duration of bronchodilator action of the budesonide/formoterol combination inhaler, *Respir. Med.* 100 (2006) 20–25.
 - [29] K.F. Rabe, R. Jorres, D. Nowak, N. Behr, H. Magnussen, Comparison of the effects of salmeterol and formoterol on airway tone and responsiveness over 24 hours in bronchial asthma, *Am. Rev. Respir. Dis.* 147 (6 Pt 1) (1993) 1436–1441.
 - [30] N.C. Santanello, J. Zhang, B. Seidenberg, T.F. Reiss, B.L. Barber, What are minimal important changes for asthma measures in a clinical trial? *Eur. Respir. J.* 14 (1999) 23–27.
 - [31] R. Pellegrino, G. Viegi, V. Brusasco, et al., Interpretative strategies for lung function tests. Number 5 in the series 'ATS/ERS task force: standardisation of lung function testing', Edited by Brusasco V, Crapo R, and Viegi G, *Eur. Respir. J.* 26 (2005) 948–968.
 - [32] R. Beasley, K. Perrin, M. Weatherall, M. Wijesinghe, Call for withdrawal of LABA single inhaler therapy in asthma, *Lancet* 376 (2010) 750–751.
 - [33] R. Bonnet, R. Jorres, U. Heitmann, H. Magnussen, Circadian rhythm in airway responsiveness and airway tone in patients with mild asthma, *J. Appl. Physiol.* 71 (1991) 1598–1605.
 - [34] R.D. Kempford, A. Oliver, J. Bal, L. Tombs, D. Quinn, The efficacy of once-daily fluticasone furoate/vilanterol in asthma is comparable with morning or evening dosing, *Respir. Med.* 107 (2013) 1873–1880.

Supplementary material

Table S1: Summary of FEV₁ (mL) 0–72 h after the administration of FF/VI 100/25 mcg and placebo

Treatment	n	Planned relative time	n	Mean FEV ₁	95% CI of mean
		(h)		(mL) (SD)	FEV ₁ (mL)
Placebo	31	PREDOSE	31	2994 (824)	(2691–3296)
		0.25	31	3031 (806)	(2735–3326)
		0.5	31	3022 (781)	(2736–3309)
		1	31	3088 (819)	(2787–3388)
		2	31	3145 (848)	(2834–3456)
		4	31	3099 (848)	(2788–3410)
		12	29	2950 (832)	(2634–3267)
		24	30	2994 (790)	(2699–3289)
		36	29	3094 (863)	(2766–3423)
		48	31	3081 (841)	(2773–3390)
		60	28	3072 (860)	(2738–3405)
		72	28	3160 (851)	(2830–3490)
FF/VI 100/25 mcg	32	PREDOSE	32	3032 (896)	(2708–3355)
		0.25	32	3284 (894)	(2962–3606)
		0.5	31	3343 (926)	(3003–3682)
		1	32	3360 (918)	(3029–3691)
		2	32	3443 (908)	(3116–3771)
		4	32	3435 (920)	(3103–3767)
		12	31	3378 (888)	(3052–3703)
		24	31	3427 (894)	(3099–3755)
		36	31	3344 (892)	(3017–3671)

48	31	3318 (865)	(3000–3635)
60	31	3239 (878)	(2917–3561)
72	31	3272 (830)	(2967–3576)

CI, confidence interval; FEV₁, forced expiratory volume in 1 s; FF, fluticasone furoate; SD, standard deviation; VI, vilanterol.

Table S2: Summary of change from baseline FEV₁ (mL) 0–72 h after the administration of FF/VI 100/25 mcg and placebo

Treatment	n	Planned	n	Mean change from	95% CI of mean
		relative time (h)		baseline FEV ₁ (mL) (SD)	change from baseline FEV ₁ (mL)
Placebo	31	0.25	31	37 (136)	(-13–87)
		0.5	31	29 (138)	(-22–79)
		1	31	94 (183)	(27–161)
		2	31	151 (200)	(78–224)
		4	31	105 (220)	(25–186)
		12	29	-46 (252)	(-141–50)
		24	30	54 (206)	(-23–131)
		36	29	69 (229)	(-18–156)
		48	31	88 (273)	(-12–188)
		60	28	61 (277)	(-46–169)
		72	28	156 (250)	(59–253)
FF/VI 100/25 mcg	32	0.25	32	253 (154)	(197–308)
		0.5	31	300 (165)	(239–361)
		1	32	328 (165)	(269–388)
		2	32	412 (191)	(343–481)
		4	32	403 (182)	(338–469)
		12	31	319 (188)	(250–388)
		24	31	368 (192)	(298–438)
		36	31	285 (159)	(227–344)
		48	31	259 (176)	(195–324)
		60	31	180 (163)	(121–240)
		72	31	213 (199)	(140–286)

CI, confidence interval; FEV₁, forced expiratory volume in 1 s; FF, fluticasone furoate; SD, standard deviation; VI, vilanterol.

Table S3: Summary of time to onset of bronchodilator effect (defined as the time point when FEV₁ first met or exceeded 12% and 200 mL over baseline during 0–4 h serial measurements) after administration of FF/VI 100/25 mcg or placebo

	Placebo (n=31)	FF/VI 100/25 mcg (n=32)
Time (h)	n (%)	n (%)
0.25	2 (6%)	11 (34%)
0.5	0	2 (6%)
1	1 (3%)	4 (13%)
2	1 (3%)	4 (13%)
4	1 (3%)	0
Censored*	26 (84%)	11 (34%)
Median time (h)	4:01	1:00

*Subjects who did not achieve bronchodilation (0–4 h).

FEV₁, forced expiratory volume in 1 second; FF, fluticasone furoate; VI, vilanterol.

Table S4: Summary of rescue salbutamol medication use

Rescue medication use per (number of occasions)	Placebo (n=31) n (%)	FF/VI (n=32) n (%)
None	16 (52)	30 (94)
1	2 (6)	2 (6)
2	8 (26)	0
3	1 (3)	0
4	2 (6)	0
5	0	0
>5	2 (6)	0

FF, fluticasone furoate; VI, vilanterol.

Table S5: Frequency of AEs during treatment periods (≥2 events in any treatment group)

	Placebo	FF/VI 100/25 mcg	Total
	(n=31)	(n=32)	(n=32)
Most frequent AEs	n (%)	n (%)	n (%)
Any AE	25 (81)	23 (72)	30 (94)
Most Common AEs: (≥2 events in any treatment group):			
Headache	15 (48)	12 (38)	19 (59)
Asthma	8 (26)	4 (13)	10 (31)
Chest discomfort	6 (19)	2 (6)	6 (19)
Wheezing	4 (13)	0	4 (13)
Dizziness	1 (3)	2 (6)	3 (9)
Nasal obstruction	2 (6)	2 (6)	4 (13)
Cough	0	2 (6)	2 (6)
Upper respiratory tract infection	2 (6)	0	2 (6)
Back pain	1 (3)	2 (6)	2 (6)
Laceration	2 (6)	0	2 (6)

All AEs were of mild or moderate intensity.

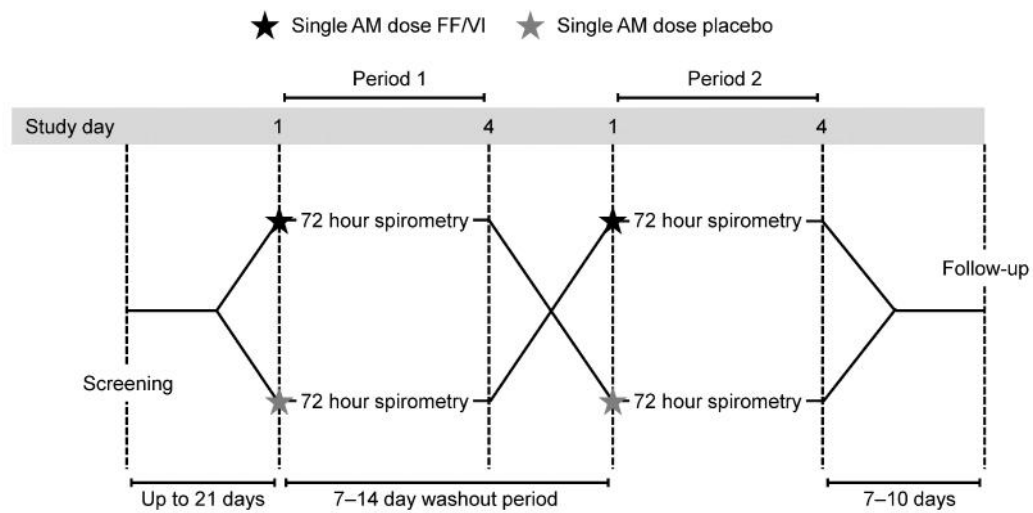
AE, adverse event; FF, fluticasone furoate; VI, vilanterol.

Table S6: Number of patients with drug-related AEs during treatment periods

	Placebo (n=31)	FF/VI 100/25 mcg (n=32)	Total (n=32)
All drug-related AEs	n (%)	n (%)	n (%)
Any AE	10 (32)	11 (34)	18 (56)
Headache	7 (23)	8 (25)	12 (38)
Dizziness	0	2 (6)	2 (6)
Nasal obstruction	1 (3)	1 (3)	2 (6)
Asthma	1 (3)	0	1 (3)
Cough	0	1 (3)	1 (3)
Nasal congestion	0	1 (3)	1 (3)
Oropharyngeal pain	0	1 (3)	1 (3)
Rhinorrhoea	1 (3)	0	1 (3)
Tachycardia	0	1 (3)	1 (3)
Salivary hypersecretion	0	1 (3)	1 (3)
Feeling abnormal	0	1 (3)	1 (3)
Urinary tract infection	1 (3)	0	1 (3)

AE, adverse event; FF, fluticasone furoate; VI, vilanterol.

Figure S1: Schematic figure of the study design



FF, fluticasone furoate; VI, vilanterol.