UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 8-K

Current Report Pursuant
to Section 13 or 15(d) of the
Securities Exchange Act of 1934

Date of Report (Date of earliest event Reported): **September 19, 2010**

THERAVANCE, INC.

(Exact Name of Registrant as Specified in its Charter)

Delaware	**000-30319**	**94-3265960**
(State or Other Jurisdiction of Incorporation)	(Commission File Number)	(I.R.S. Employer Identification Number)

901 Gateway Boulevard
South San Francisco, California 94080
(650) 808-6000
(Addresses, including zip code, and telephone numbers, including area code, of principal executive offices)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 8.01 Other Events.

On September 19, 2010, at the European Respiratory Society Annual Congress in Barcelona, Spain, GlaxoSmithKline (GSK) presented six posters on the components of RELOVAIR™, fluticasone furoate (FF), the inhaled corticosteroid (ICS), and vilanterol trifenatate (VI), the long-acting beta$_2$ agonist (LABA). These posters contained information from a Phase 2 study of FF, and Phase 2b studies with the individual components, FF and VI. RELOVAIR™ is a once-daily combination medicine of FF and VI under development for the treatment of patients with chronic obstructive pulmonary disease (COPD) or asthma under the LABA collaboration between GSK and Theravance, Inc. The six posters are attached hereto as Exhibits 99.1 to 99.6 and are incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit	Description
Exhibit 99.1	Fluticasone furoate (FF), a novel inhaled corticosteroid (ICS), demonstrates once-daily efficacy in asthma when dosed in the evening
Exhibit 99.2	Fluticasone furoate (FF) a once-daily inhaled corticosteroid (ICS), demonstrates dose-response efficacy in patients symptomatic on non-steroidal asthma therapy
Exhibit 99.3	Fluticasone furoate (FF), an inhaled corticosteroid (ICS), is efficacious in asthma patients symptomatic on low doses of

	ICS therapy
Exhibit 99.4	Fluticasone furoate (FF), an inhaled corticosteroid (ICS), demonstrates efficacy in asthma patients symptomatic on moderate doses of ICS therapy
Exhibit 99.5	Safety of vilanterol trifenatate (VI) in a chronic obstructive pulmonary disease (COPD) dose-ranging study
Exhibit 99.6	Dose-related efficacy of vilanterol trifenatate (VI) in chronic obstructive pulmonary disease (COPD)

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

THERAVANCE, INC.

Date: September 20, 2010

By: /s/ **Michael W. Aguiar**
Michael W. Aguiar
Chief Financial Officer

EXHIBIT INDEX

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POSTER P1170

Fluticasone furoate (FF), a novel inhaled corticosteroid (ICS), demonstrates once-daily efficacy in asthma when dosed in the evening

Woodcock A(1), Bleecker ER(2), Bateman ED(3), Busse W(4), Lötvall J(5), Snowise N(6), Forth R(7), Jacques L(6), Haumann B(6)

(1)School of Translational Medicine, University Hospital of Manchester, Manchester, UK; (2)Translational Sciences, Wake Forest University Health Sciences Winston-Salem, USA (3)Department of Medicine, University of Cape Town, Cape Town, South Africa; (4)Department of Medicine, University of Wisconsin, Madison, USA; (5)Krefting Research Centre, Gothenburg, Sweden (6)Respiratory Medicine Development Centre, GlaxoSmithKline, Uxbridge, UK; (7)Respiratory Medicine Development Center, GlaxoSmithKline, North Carolina, USA

ABSTRACT

Introduction: FF (GW685698X) is a novel ICS still active at 24h and under development as an once-daily treatment.

Objectives: To evaluate the efficacy and safety of once- and twice-daily dosing and of morning (AM) and evening (PM) dosing of FF in asthma patients ≥12 years.

Methods: Multicentre, randomised, double-blind, parallel group, placebo-controlled study to evaluate FF 200mcg twice daily, FF 200mcg and 400mcg once daily in the morning and FF 200mcg and 400mcg once daily in the evening compared with placebo. 652 patients were randomised to 8 weeks of treatment, with a mean age of 45 years, 65% female, baseline mean pre-bronchodilator forced expiratory volume in 1 second (FEV_1) mean 67% predicted and 29% mean FEV_1 reversibility. The primary endpoint was the mean change from baseline at Week 8 in trough (AM or PM) FEV_1.

Results: FF 400mcg once daily in the evening and FF 200mcg twice daily resulted in comparable, placebo-adjusted improvements in PM trough FEV_1 after 8 weeks of dosing (240mL and 235mL, respectively). FF 200mcg twice daily resulted in greater improvements in placebo-adjusted AM trough FEV_1 than FF 400mcg once daily in the morning after 8 weeks of dosing (315mL and 202mL, respectively). FF was well tolerated in this study with a low incidence of adverse events (AEs), comparable across treatment groups. Urinary cortisol was comparable with placebo for all groups.

Conclusion: Efficacy of FF 400mcg once daily in the evening was comparable with 200mcg twice daily supporting FF as a well tolerated and efficacious once-daily ICS.

INTRODUCTION

- ICS are considered the most effective anti-inflammatory treatment for all severities of persistent asthma. Most current ICS formulations for asthma are indicated for twice-daily dosing; however, once-daily treatments offer the advantage of increased convenience with the subsequent potential for improved adherence and asthma control.(1)
- FF is a novel ICS, still active 24h after dosing,(2) which is under development for use as the ICS component of a new once-daily ICS/long-acting $beta_2$ agonist combination for treatment of asthma and chronic obstructive pulmonary disease.

OBJECTIVES

- To assess the efficacy and tolerability of FF administered using a DISKUS™/ACCUHALER™ once daily in the morning and evening, or twice daily, in asthma patients aged ≥12 years and symptomatic on low-dose ICS therapy.

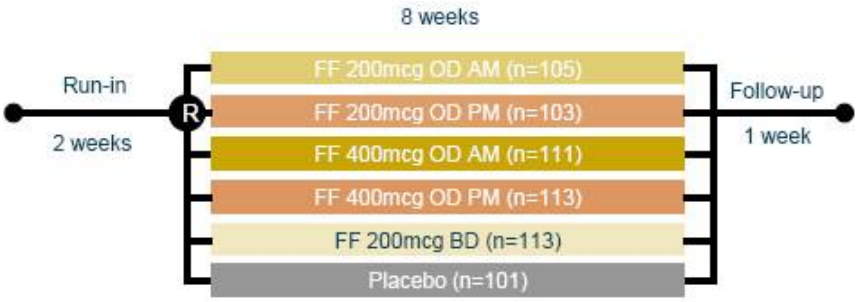
PATIENTS AND METHODS

Study design

- This phase IIa, randomised, double-blind, placebo-controlled, parallel group study was conducted at 70 centres in 16 countries around the world.
- Patients were randomised to one of six treatments for 8 weeks (Figure 1). All treatments were administered using a DISKUS™/ ACCUHALER™.

- The study was conducted in accordance with Good Clinical Practice and the principles of the Declaration of Helsinki. Patients provided written informed consent.

Figure 1. Study design.



Design:	652 randomised patients 646 patients in intent-to-treat (ITT) population 2-week run-in Remained on current ICS until day before randomisation 8-week treatment period
Randomisation:	AM pre-dose FEV_1 50–80% predicted Reversability FEV_1 ≥12% predicted following albuterol Symptoms or short-acting beta agonist (SABA) use on 4 of 7 days

OD = once daily; BD = twice daily

Eligible patients

- Persistent asthma with use of an ICS for ≥3 months prior to study entry and maintained on a stable dose for 4 weeks prior to study visit 1.
- Baseline FEV_1 50–80% of predicted normal value during visit 1 and demonstrating ≥12% and 200mL reversibility of FEV_1 within 30min following inhalation of 200–400mcg albuterol/salbutamol aerosol (2–4 puffs) or one nebulised albuterol/salbutamol treatment at visit 1.
- All patients had to be able to replace SABAs with albuterol/salbutamol aerosol for use as needed during the study period and to be able to withhold all inhaled short-acting beta sympathomimetic bronchodilators for ≥6h prior to study visits. (Note: use of nebulised albuterol/salbutamol was not permitted during the study except at visit 1).

Endpoints

- The single efficacy endpoint was the mean change from baseline at Week 8 (last assessment on treatment using last observation carried forward [LOCF]) in the trough (morning or evening pre-dose and pre-rescue bronchodilator) FEV_1.
- Safety endpoints included incidence of AEs (defined using the MedDRA dictionary), oropharyngeal examinations, haematology and clinical chemistry, urinalysis, 24h urinary cortisol excretion, vital signs and withdrawals due to worsening asthma.

RESULTS

- In total, 646 patients were included in the ITT population. 126 patients withdrew from the ITT population
  - in the placebo group, 36% (n=36) of patients withdrew overall (21% lack of efficacy, 13% exacerbation and 2% other [decided to withdraw, AE, non-compliance, lost to follow-up, protocol violation, liver function test abnormality or other reason])

  - in the FF 200mcg once-daily morning and evening groups, 19% (n=20) and 20% (n=21) of patients, respectively, withdrew overall (10% lack of efficacy, 2% exacerbation, 8% other and 13% lack of efficacy, 3% exacerbation, 5% other, respectively)
  - in the FF 400mcg once-daily morning and evening groups, 14% (n=15) and 15% (n=17) of patients, respectively, withdrew overall (6% lack of efficacy, 2% exacerbation, 5% other and 8% lack of efficacy, 3% exacerbation, 4% other, respectively)
  - in the FF 200mcg twice-daily group, 15% (n=17) of patients withdrew overall (12% lack of efficacy, 0 exacerbation and 3% other).
- Patient baseline characteristics were similar in the six treatment groups (Table 1).

Table 1. Patient baseline characteristics (ITT population).

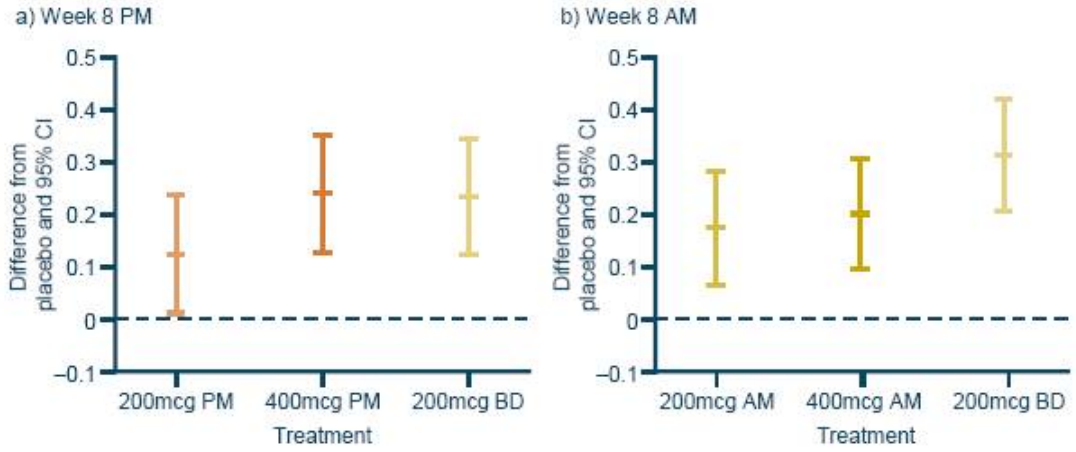
		FF dose				
Demographic characteristics	**Placebo (n=101)**	**200mcg OD/AM (n=105)**	**200mcg OD/PM (n=103)**	**400mcg OD/AM (n=111)**	**400mcg OD/PM (n=113)**	**200mcg BD (n=113)**
Gender, n (%)						
Female	62 (61)	62 (59)	74 (72)	73 (66)	70 (62)	78 (69)
Age (years), mean	44.4	45.0	43.7	46.9	45.0	45.6
Race, n (%)						
White	60 (60)	67 (64)	67 (66)	74 (67)	75 (68)	76 (67)
Asian	16 (16)	14 (13)	15 (15)	16 (15)	15 (14)	17 (15)
Other	24 (24)	23 (22)	20 (20)	20 (18)	21 (19)	20 (18)
Asthma history, n (%)						
<6 month	0	0	0	1 (<1)	0	1 (<1)
≥6 months to <1 year	3 (3)	1 (<1)	3 (3)	1 (<1)	3 (3)	2 (2)
≥1 to <5 years	16 (16)	12 (11)	19 (18)	14 (13)	19 (17)	17 (15)
≥5 to <10 years	24 (24)	26 (25)	26 (25)	30 (27)	24 (21)	35 (31)
≥10 years	58 (57)	66 (63)	55 (53)	65 (59)	67 (59)	58 (51)
Lung function, mean						
Pre-bronchodilator FEV_1, L	1.966	1.969	1.986	1.931	1.995	1.976
% predicted FEV_1 (%)	66.37	66.52	68.24	67.23	67.69	68.14

% reversibility FEV_1 (%)	30.16	29.25	29.29	27.94	30.90	26.32

Efficacy (ITT population)

- There were statistically significant improvements in trough FEV_1 with each FF treatment group compared with placebo (Figure 2, Table 2).
- FF 400mcg once daily dosed in the evening showed similar placebo-adjusted improvements in evening trough FEV_1 at Week 8 versus FF 200mcg twice daily (240mL vs 235mL).

Figure 2. Adjusted treatment difference in trough FEV_1 (L) (LOCF; ITT population).



CI = confidence interval

Table 2. Change from baseline in trough FEV_1 (L) (LOCF) at Week 8, by PM versus AM FEV_1 and treatment group (ITT population).

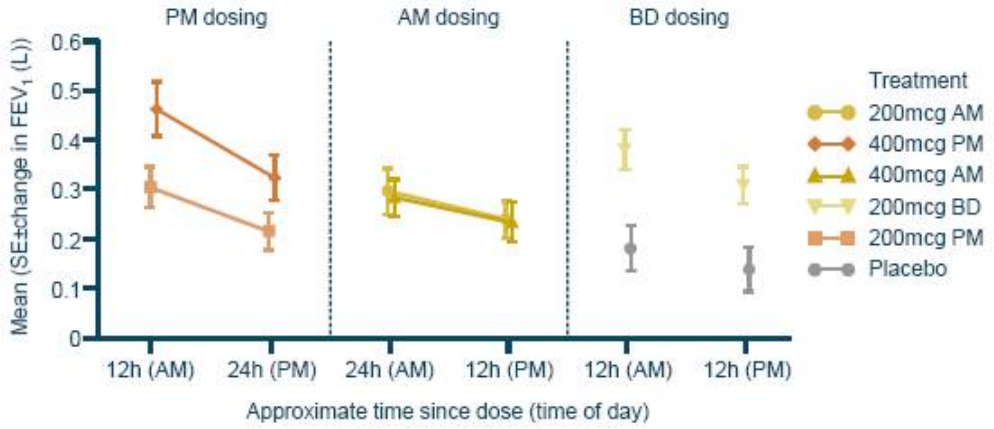
		FF dose		
Week 8 PM FEV_1	**Placebo (n=101)**	**200mcg OD (n=103)**	**400mcg OD (n=113)**	**200mcg BD (n=113)**
Trough FEV_1 (n)	77	92	103	100
LSM	2.198	2.322	2.438	2.432
LSM change (SE)	0.084 (0.0458)	0.208 (0.0437)	0.324 (0.0398)	0.319 (0.0411)
Difference from placebo	—	0.124	0.240	0.235
95% CI	—	0.010-0.238	0.129-0.351	0.123-0.346
p value	—	0.033	<0.001	<0.001

		FF dose		
Week 8 AM FEV_1	**Placebo (n=101)**	**200mcg OD (n=105)**	**400mcg OD (n=111)**	**200mcg BD (n=113)**
Trough FEV_1 (n)	85	100	106	102
LSM	2.029	2.203	2.230	2.344
LSM change (SE)	0.053 (0.0434)	0.228 (0.0389)	0.255 (0.0397)	0.368 (0.0400)
Difference from placebo	—	0.174	0.202	0.315
95% CI	—	0.067-0.282	0.096-0.307	0.208-0.421
p value	—	0.002	<0.001	<0.001

LSM = least square mean; SE = standard error

- FF 400mcg once daily dosed in the morning produced a smaller improvement in placebo-adjusted trough morning FEV_1 at Week 8 than FF 200mcg twice daily (202mL vs 315mL).
- A ≥200mL increase in trough FEV_1 versus placebo was seen with FF 400mcg once daily dosed morning or evening and with FF 200mcg twice daily, but not with the two FF 200mcg once-daily groups.
- Week 8 morning and evening FEV_1 responses for each treatment group are shown in Figure 3.

Figure 3. Comparison of AM and PM FEV_1 at Week 8 following once-daily dosing in the PM or AM, or twice-daily dosing (ITT population).



Safety

- FF treatment was well tolerated, with a similar incidence of on-treatment AEs in the placebo (28%) and FF treatment groups (31–39%).
- The most common AEs are listed in Table 3. The frequency of AEs did not appear to be related to FF dose.

- Of four serious AEs reported (two during and two post-treatment), only one case of angioedema in the FF 200mcg once-daily morning group was considered to be possibly related to study treatment; the three other serious AEs were recurrent paroxysm of atrial fibrillation (FF 400mcg once-daily morning group), and cerebrovascular accident and spontaneous abortion (both FF 200mcg twice-daily group). Eleven patients withdrew due to AEs (three on FF 200mcg once-daily morning dosing, one on 200mcg once-daily evening, three on 400mcg once-daily morning, three on 400mcg once-daily morning and one on FF 200mcg twice-daily).
- There were no safety concerns with regard to vital signs, oropharyngeal examinations, or laboratory parameters. Oral candidiasis (coded as oral candidiasis, oropharyngeal candidiasis or candidiasis) occurred at an incidence of 0–4% across all treatment arms.
- The incidence of asthma exacerbations was low with FF treatment (<1–4% vs 14% for placebo).
- 24h urinary cortisol excretion ratios (Week 8/baseline) were similar for all FF treatment groups (range 0.78–1.03) and placebo (0.87), between morning and evening dosing, and between once- and twice-daily dosing.

Table 3. Most common on-treatment AEs (≥3% incidence in any treatment group; ITT population).

		FF dose				
AEs, n (%)	**Placebo (n=101)**	**200mcg OD/AM (n=105)**	**200mcg OD/PM (n=103)**	**400mcg OD/AM (n=111)**	**400mcg OD/PM (n=113)**	**200mcg BD (n=113)**
Patients with any AE	28 (28)	36 (34)	32 (31)	43 (39)	35 (31)	38 (34)
Headache	6 (6)	8 (8)	7 (7)	10 (9)	7 (6)	9 (8)
Nasopharyngitis	4 (4)	8 (8)	8 (8)	3 (3)	7 (6)	6 (5)
Bronchitis	2 (2)	1 (<1)	3 (3)	4 (4)	4 (4)	0
Pharyngolaryngeal pain	1 (<1)	2 (2)	3 (3)	2 (2)	1 (<1)	3 (3)
Upper respiratory tract infection	2 (2)	3 (3)	2 (2)	2 (2)	1 (<1)	1 (<1)
Dysphonia	0	1 (<1)	1 (<1)	1 (<1)	2 (2)	3 (3)
Rhinitis	0	4 (4)	1 (<1)	0	1 (<1)	2 (2)
Rhinitis allergic	1 (<1)	2 (2)	3 (3)	0	0	1 (<1)
Dizziness	0	3 (3)	0	2 (2)	1 (<1)	0
Influenza	2 (2)	0	1 (<1)	3 (3)	0	0
Pharyngitis	4 (4)	2 (2)	0	0	0	0
Respiratory tract infection	0	1 (<1)	0	3 (3)	1 (<1)	0

CONCLUSIONS

- Once-daily treatment with FF 400mcg dosed in the evening or morning showed clinically and statistically significant improvements in trough FEV_1 (≥200mL).
- FF 400mcg administered in the morning provided a smaller improvement in efficacy compared with FF 200mcg twice daily.
- FF 400mcg administered in the evening provided similar efficacy to FF 200mcg twice daily.
- The data support FF as an effective and well-tolerated once-daily ICS for patients with mild-to-moderate asthma.

REFERENCES

(1) Price D, et al. BMC Pulm Med 2010;10:1.
(2) van den Berge M, et al. Allergy 2010. Epub ahead of print.

ACKNOWLEDGEMENTS

- This study was sponsored by GlaxoSmithKline (ClinicalTrials.gov: NCT00398645; protocol number: FFA106783).
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Presented at the Annual Conference of the European Respiratory Society (ERS), Barcelona, Spain, 18–22 September 2010

POSTER P1166

Fluticasone furoate (FF), a once-daily inhaled corticosteroid (ICS), demonstrates dose-response efficacy in patients symptomatic on non-steroidal asthma therapy

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ABSTRACT

Introduction: FF (GW685698X) is an ICS still active at 24h, in development as a once-daily treatment in combination with the long-acting beta$_2$ agonist (LABA), vilanterol trifenatate (VI; GW642444M) for asthma and chronic obstructive pulmonary disease (COPD).

Objectives: To compare the efficacy and safety of FF (dry powder) at four doses administered via a novel single-step activation inhaler in patients ≥12 years old with persistent uncontrolled asthma. Fluticasone propionate (FP) served as an active control.

Methods: In a randomised, double-blind, placebo-controlled, parallel group study, 598 patients received one of six treatments: FF (25, 50, 100 or 200mcg) once daily, FP 100mcg twice daily or placebo for 8 weeks. The primary endpoint was change from baseline in trough (pre-dose) forced expiratory volume in 1 second (FEV_1) at Week 8.

Results: A dose response was observed for trough FEV_1 between FF 25–200mcg once daily including and excluding placebo (linear trend analysis $p<0.001$ and $p=0.03$, respectively). At Week 8, relative to placebo FF 50–200mcg once daily had significantly greater increases in trough FEV_1 from baseline ($p<0.05$) with FF 100mcg and 200mcg achieving a >200mL increase. Secondary endpoints peak expiratory flow (PEF), symptom-free and rescue-free 24h periods supported the efficacy of FF 50–200mcg once daily doses and FP. Overall, FF was well tolerated. The incidence of oral candidiasis was low (0–4%). 24h urinary cortisol excretion ratios (Week 8/baseline) were similar across treatments (FF 0.98–1.21 and placebo 1.04).

Conclusion: The data support the use of FF (100 and 200mcg) as a once-daily treatment in persistent uncontrolled asthma.

INTRODUCTION

- FF is an ICS with a pharmacological profile that demonstrates greater retention in the lung and a longer duration of action than FP.(1)
- FF is under development as a once-daily inhaled asthma therapy, administered in a novel dry powder inhaler (DPI) formulation in combination with VI, a new LABA with 24h activity.(2)

OBJECTIVE

- To compare the efficacy and safety of FF (dry powder) versus placebo at four doses administered via a novel single-step activation inhaler in patients ≥12 years old with persistent uncontrolled asthma. FP served as an active control.

PATIENTS AND METHODS

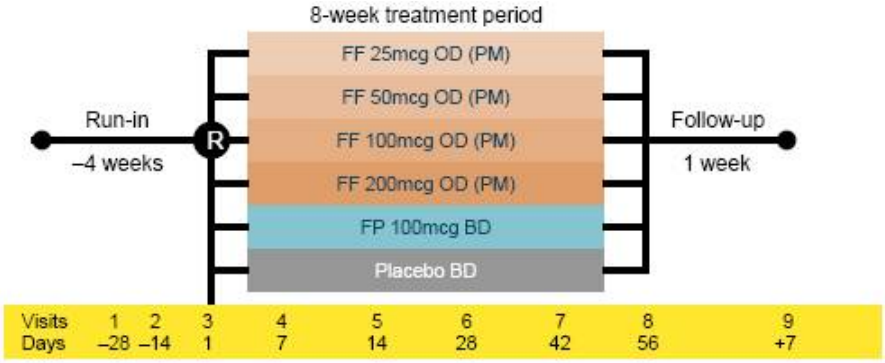
Study design

- A phase IIb, randomised, double-blind, double-dummy, parallel-group, placebo- and active-controlled study conducted at 142 centres in 14 countries.
- Eligible patients had: persistent asthma (defined by the National Institutes of Health criteria)(3) and were symptomatic on short-acting beta$_2$ agonists (SABAs) or other non-steroid agents; FEV_1 (% of predicted normal) 40–90% (evening; PM) or 40–85% (morning; AM); reversibility of FEV_1 of ≥12% and ≥200mL with albuterol/salbutamol aerosol inhaler. All patients had to be able to replace their current SABAs with albuterol/salbutamol aerosol for use as needed during the study period.
- After 4-weeks run-in (on usual medications), patients entered the treatment period if they were symptomatic (combined daily asthma symptom score ≥1 or albuterol/ salbutamol use on ≥4 of the last 7 days of run-in) and their evening pre-dose FEV_1 was 40–90% of predicted normal.
- Eligible patients were randomised to one of six treatment groups for 8 weeks using a double dummy design (Figure 1): one of four doses of FF (25–200mcg once daily PM using a novel single-step DPI; these patients also took placebo twice daily via Diskus™/Accuhaler™); FP (twice daily via Diskus™/Accuhaler™; these patients also took placebo once daily via the novel DPI); or placebo (every evening via the novel DPI and twice daily via Diskus™/Accuhaler™). Patients were assessed at 1, 2, 4, 6 and 8 weeks during treatment.

Endpoints

- Primary: the mean change from baseline in trough (pre-dose, pre-rescue bronchodilator) evening FEV_1 at Week 8 in each treatment group. The main treatment comparison was to test for a linear dose response across the four FF doses.

Figure 1. Study design.



OD = once daily; BD = twice daily

- **Secondary:** mean change from baseline over the 8-week treatment period in daily trough (pre-dose, pre-rescue bronchodilator) PM PEF, daily AM PEF; % of symptom-free and rescue-free 24h periods; number of withdrawals due to lack of efficacy.
- **Safety:** incidence of adverse events (AEs) during treatment; evidence of oral candidiasis (visits 1, 3–8); haematology, clinical chemistry and urinalysis parameters before and end of study; 24h urinary cortisol excretion; vital signs (visits 1, 3–8).

RESULTS

- Of 601 patients randomised, 598 received at least one dose of study treatment (intent-to-treat [ITT] population). The demographics and baseline characteristics were similar across groups (Table 1): the patients' mean age was 37–41 years; over half of them had a ≥10-year history of asthma, and around 20% had suffered an exacerbation during the last 6 months.

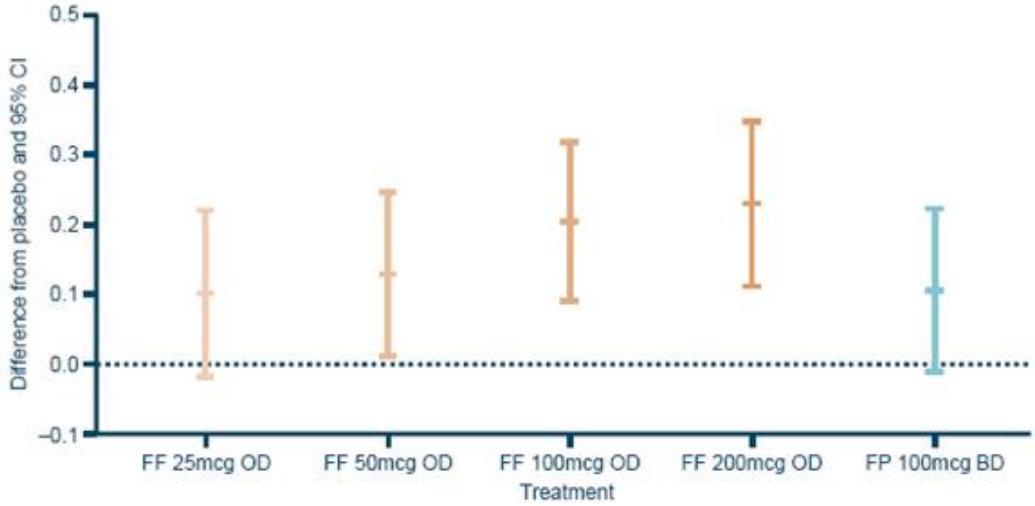
Table 1. Demographics and baseline characteristics (ITT population).

		FF dose				FP dose
	Placebo (n=94)	25mcg OD (n=97)	50mcg OD (n=100)	100mcg OD (n=110)	200mcg OD (n=95)	100mcg BD (n=102)
Mean age (years)	39.2	37.7	38.3	36.8	40.7	39.9
Gender, n (%)						
Female	47 (50)	57 (59)	59 (59)	60 (55)	60 (63)	56 (55)
Duration of asthma, n (%)						
0 to <5 years	16 (17)	19 (19)	20 (20)	26 (24)	22 (23)	19 (19)
5 years to <10 years	13 (14)	20 (21)	15 (15)	19 (17)	22 (23)	16 (16)
³10 years	65 (69)	58 (60)	65 (65)	65 (59)	51 (54)	67 (66)
History of atopy, n (%)	45 (48)	38 (39)	50 (50)	47 (43)	34 (36)	39 (38)
FEV_1 at screening, mean						
Pre-bronchodilator (L)	2.320	2.394	2.335	2.279	2.163	2.238
Pre-bronchodilator (% predicated)	67.03	69.69	69.20	67.16	66.56	67.35
Reversibility (%)	28.09	26.43	29.84	31.60	29.32	29.05
FEV_1 at baseline, mean (L)	2.373	2.456	2.427	2.419	2.210	2.343
DRC data at baseline, mean						
PM PEF (L)	355.4	370.8	364.5	372.9	337.3	347.2
AM PEF (L)	342.7	359.0	356.3	362.2	326.0	337.2
Rescue-free 24h periods (%)	10.5	9.5	13.1	15.4	9.0	9.8
Symptom-free 24h periods (%)	13.5	11.0	9.5	14.2	8.3	9.2

Efficacy (ITT population)

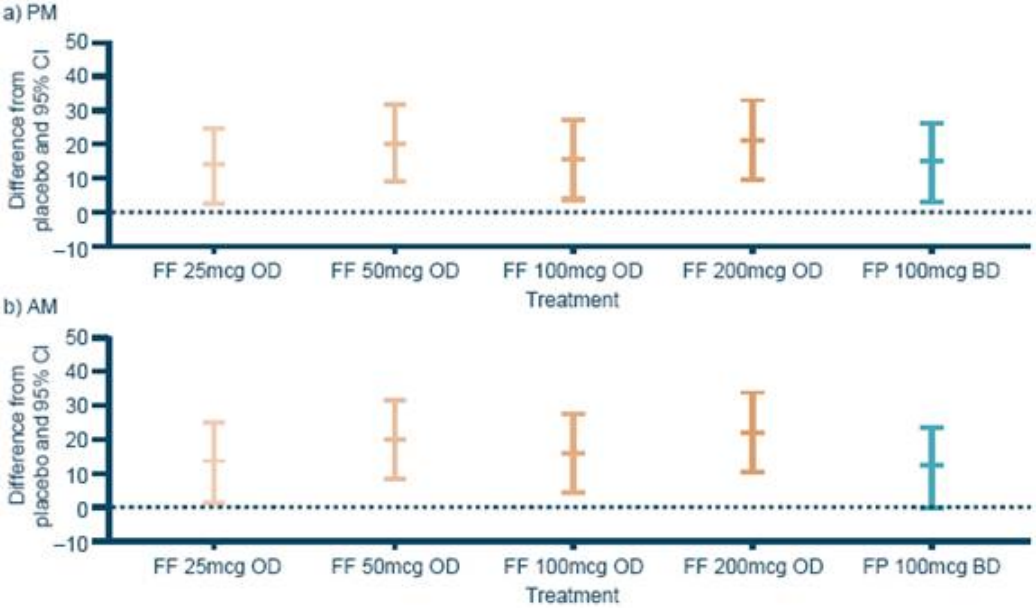
- At Week 8, all active treatment groups showed a >200mL improvement in trough FEV_1 from baseline; the FF 100mcg and 200mcg doses achieved a >200mL difference compared with placebo ($p<0.001$). FF 50mcg was also significantly better than placebo (129mL; $p<0.05$). A difference of 101mL was achieved with FF 25mcg, but this was not significantly better than placebo ($p=0.095$; Figure 2).
- There was a significant dose-response relationship for the baseline–Week 8 change in trough PM FEV_1 across FF dose groups (25–200mcg), both with placebo ($p<0.001$) and without ($p=0.03$).
- Both AM and PM PEF values (Figure 3) were increased from baseline at Week 8 in all FF treatment groups. There were significantly greater improvements in PEF values versus placebo in all active treatment groups ($p=0.041$ to $p<0.001$).

Figure 2. Adjusted treatment differences of change from baseline in trough FEV_1 (LOCF) at Week 8 (ITT population).



Note: analysis performed using analysis of covariance (ANCOVA) with covariates of baseline, country, sex, age and treatment

Figure 3. Change from baseline in PM and AM PEF over Weeks 1–8 (ITT population).



- The percentage of symptom-free 24h periods over Weeks 1–8 was significantly higher versus placebo for all treatment groups ($p \leq 0.005$) except the FF 25mcg group ($p=0.128$); similarly, the percentage of rescue-free 24h periods over Weeks 1–8 was significantly higher versus placebo for all treatment groups ($p \leq 0.031$) except the FF 25mcg group ($p=0.110$) (Figure 4).

- Withdrawal rates due to lack of efficacy were 15% and 11% for placebo and FP, respectively, and ranged from 3–9% for FF dose groups; there was a statistically significant difference for lower withdrawal rates due to lack of efficacy with the 50mcg ($p=0.004$) and 100mcg ($p=0.032$) FF dose groups versus placebo (Figure 5).

SAFETY

- FF therapy was generally well tolerated (Table 2). The most common AEs were headache, oropharyngeal pain and nasopharyngitis (Table 2). There was no evidence of a relationship between FF dose and the incidence of any of the most common AEs.

- Incidence of candidiasis was low (0–4%), but occurred at a higher incidence in the 50mcg (4%) and 100mcg (3%) FF once-daily PM dose groups.

Figure 4. Symptom-free and rescue-free 24h periods over Weeks 1–8.

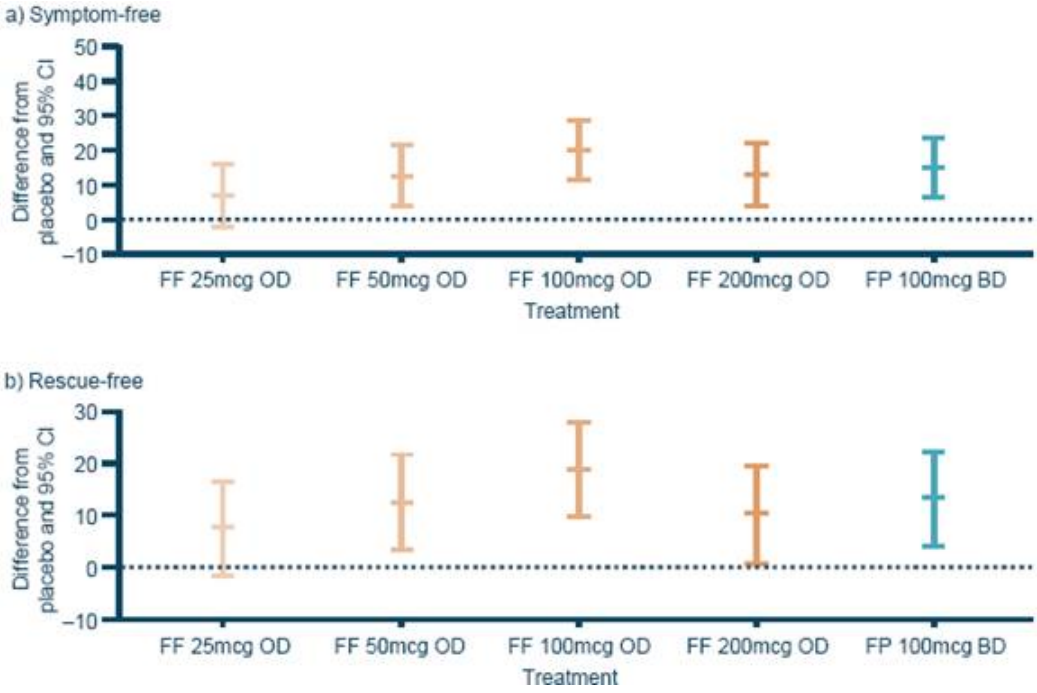
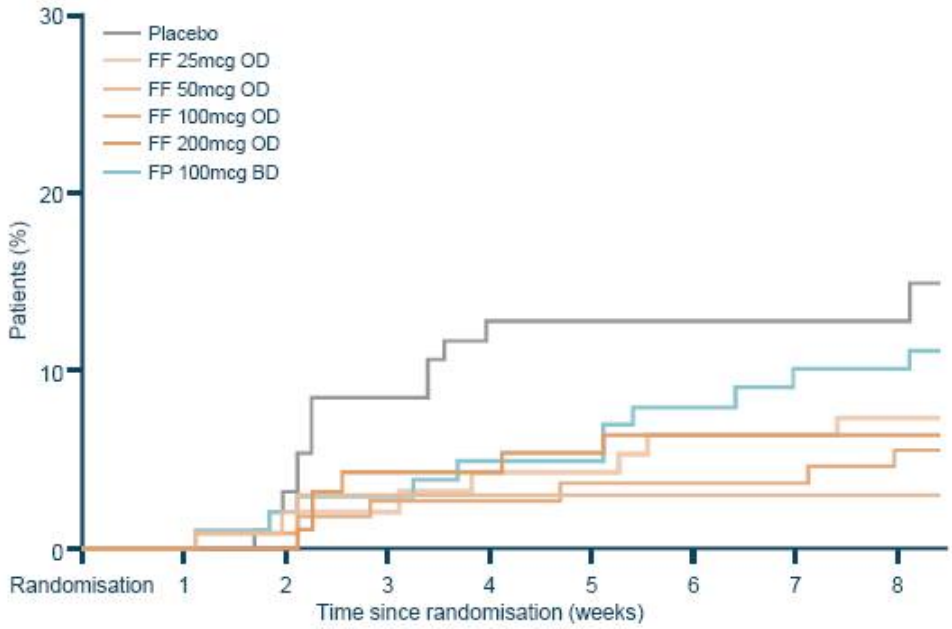


Figure 5. Treatment discontinuation due to lack of efficacy (cumulative incidence).



Note: patients are represented from their date of randomisation to their date of withdrawal due to lack of efficacy

- None of the six on-treatment serious AEs reported by four patients (snake bite [FF 25mcg], depression [FF 100mcg], gastritis, chest pain, hyperhidrosis, hypertension [all FP]) were considered to be study drug-related and there were no deaths or hospitalisations associated with AEs.

- There were no statistically significant differences in urinary cortisol excretion between placebo and any of the FF groups or FP (Figure 6) and no events attributable to systemic corticosteroid effects were reported. No clinically important changes in laboratory parameters or vital signs were recorded.

Table 2. Summary of AEs and most common on-treatment AEs (≥3% incidence in any treatment group; ITT population).*

		FF dose				FP dose
AE, n (%)	Placebo (n=94)	25mcg OD (n=97)	50mcg OD (n=100)	100mcg OD (n=110)	200mcg OD (n=95)	100mcg BD (n=102)
Patients with any on-treatment AE, n (%)	24 (26)	19 (20)	28 (28)	35 (32)	27 (28)	35 (34)
Patients with drug-related AE, n (%)	2 (2)	0	3 (3)	7 (6)	4 (4)	6 (6)
Patients with on-treatment SAEs, n (%)	0	1 (1)	0	1 (<1)	0	2 (2)
Patients with AEs leading to withdrawal, n (%)	0	1 (1)	1 (1)	2 (2)	1 (1)	2 (2)
Most common on-treatment AEs						
Headache	10 (11)	6 (6)	6 (6)	12 (11)	5 (5)	12 (12)
Oropharyngeal pain	1 (1)	0	1 (1)	4 (4)	3 (3)	2 (2)
Nasopharyngitis	1 (1)	0	0	4 (4)	3 (3)	2 (2)
Sinusitis	1 (1)	2 (2)	0	0	2 (2)	3 (3)
Upper respiratory	0	2 (2)	1 (1)	3 (3)	0	1 (<1)
tract infection Insomnia	1 (1)	0	1 (1)	3 (3)	0	1 (<1)

Back pain	0	0	3 (3)	0	1 (1)	1 (<1)

*Oral candidiasis was diagnosed in 1 (1%), 1 (<1%) and 2 (2%) of patients in the FF 50, 100 and 200mcg OD arms, respectively when coded as 'oropharyngeal candidiasis', and in 1 (<1%) patients in the FP 100mcg BD arm. It was diagnosed in 1 (1%) and 2 (2%) of patients in the FF 50 and 100mcg OD arms, respectively when coded as 'candidiasis', and in 2 (2%) patients in the FF 50mcg OD arm when coded as 'oral candidiasis'

Figure 6. Adjusted treatment ratios for 24h urinary cortisol excretion (urinary cortisol population).*

Note: analysis performed using ANCOVA with covariates of country, sex, age, treatment and the log of the baseline values; *The urinary cortisol population consisted of 425 (71%) patients in the ITT population who had urine samples with no factors that would confound the analysis of urinary cortisol

CONCLUSIONS

- A dose-response was observed for trough FEV_1 between FF 25–200mcg once daily, including ($p<0.001$) and excluding ($p=0.03$) placebo; at Week 8 the 50–200mcg FF doses were all significantly better than placebo with the 100 and 200mcg FF doses resulting in a >200mL difference in FEV_1 from baseline compared with placebo.
- Secondary endpoints, including PM and AM PEF and symptom-free and rescue-free 24h periods, further supported the efficacy of FF 50–200mg once-daily doses.
- The incidence of on-treatment AEs was low across the treatment groups and there was no evidence of FF dose impacting on incidence of AEs. 24h urinary cortisol excretion ratios (Week 8/baseline) were similar across treatment groups.
- FF 50–200mcg given once daily in the evening provided effective asthma control and was well tolerated in patients symptomatic on non-steroid asthma therapy. The data support the 100mcg FF once-daily dose as the optimal dose for further evaluation in phase III studies.

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POSTER P1167 **Fluticasone furoate (FF), an inhaled corticosteroid (ICS), is efficacious in asthma patients symptomatic on low doses of ICS therapy**

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ABSTRACT

Introduction: FF (GW685698X) is a novel ICS still active at 24h and under development as a once-daily treatment in combination with the long-acting beta$_2$ agonist (LABA) vilanterol trifenatate (GW642444M) for asthma and chronic obstructive pulmonary disease (COPD).

Objectives: To compare the relative efficacy and safety of four doses of FF (dry powder), administered using a novel single-step activation inhaler in patients ≥12 years with moderate asthma uncontrolled on low doses of ICS (fluticasone propionate [FP] 200mcg/day or equivalent). FP was used as an active control.

Methods: This randomised, double-blind, double-dummy, placebo-controlled, parallel group study, randomised 622 patients to one of six treatments: FF (100, 200, 300 or 400mcg) once daily, FP 250mcg twice daily or placebo for 8 weeks. The primary endpoint was change in 24h trough (pre-dose) forced expiratory volume in 1 second (FEV_1) from baseline at Week 8.

Results: Primary: at Week 8 relative to placebo, all doses of FF and FP demonstrated significantly greater increases from baseline in trough FEV_1 ($p<0.001$) and >200mL increase. There was no evidence of a dose response between FF doses. Secondary: withdrawals due to lack of efficacy were low, and peak expiratory flow (PEF) results supported the efficacy of FF 100–400mcg and FP. Oral candidiasis was low (0–4%) and the range of 24h urinary cortisol excretion ratios (Week 8/baseline) was similar across treatments, including placebo.

Conclusion: This dose-ranging study supports the use of FF as once-daily treatment for patients with asthma uncontrolled on low ICS doses.

INTRODUCTION

- ICS are the most effective anti-inflammatory medications currently available for long-term control of all severities of persistent asthma.(1)–(3)
- Most current inhaled steroids are more effective when taken twice daily rather than once daily.(3)
- Patients not controlled on low-dose ICS may require combination therapy with a LABA or twice-daily therapy with a higher dose of ICS.(1)–(3)
- FF is a novel ICS, still active 24h after dosing, which is under development for use as the ICS component of a new once-daily ICS/LABA combination for asthma and COPD.

OBJECTIVE

- To evaluate the dose response, efficacy and safety of four dose regimens of FF administered once daily in the evening in patients aged ≥12 years with persistent asthma uncontrolled on low-dose ICS therapy, in order to identify the appropriate dose of FF for further investigation.

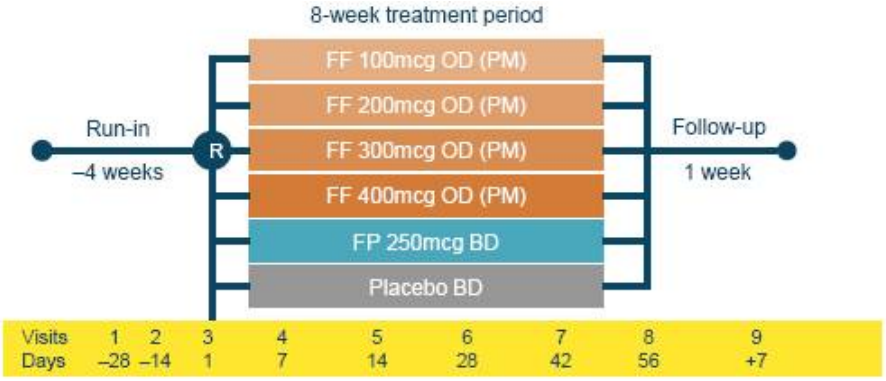
METHODS

- Phase IIb, multicentre, randomised, double-blind, double-dummy, parallel-group, placebo-controlled study, involving nine clinic visits (Figure 1).
- Eligible patients had an FEV_1 of 40–90% (for PM visit) or 40–85% (for AM visit) of the predicted normal value at visit 1 and demonstrated a ≥12% and ≥200mL reversibility of FEV_1 within ~30min following four inhalations of albuterol/salbutermol inhalation aerosol. Patients had been using an inhaled ICS for ≥8 weeks prior to visit 1 and were able to replace their current short-acting beta$_2$ agonist with albuterol/salbutamol at visit 1 for use during the study.
- FF once daily was administered in the evening via a novel dry powder inhaler given at doses of 100, 200, 300 and 400mcg versus placebo.
- FP 250mcg twice daily was administered via DISKUS™/ACCUHALER™ inhaler and was included for assay sensitivity and compared against placebo for the relative magnitude of response with FF doses investigated.

Efficacy and safety measures methods

- Primary efficacy endpoint: mean change from baseline in trough (PM pre-dose and pre-rescue bronchodilator) FEV_1 at the end of the 8-week treatment period.

Figure 1. Study design.



OD = once daily; BD = twice daily

- Secondary efficacy endpoints: mean change from baseline in daily trough (pre-dose and pre-rescue bronchodilator) PM PEF and daily AM PEF averaged over the treatment period; mean change from baseline in the percentage of symptom-free 24h periods and rescue-free 24h periods during the treatment period; and number of withdrawals due to lack of efficacy during the treatment period.
- Safety assessments included: incidence of adverse events (AEs); incidence of oral candidiasis at clinic visits 1 and 3–8; urinary cortisol excretion; and laboratory tests and vital signs, before and at the end of the 8-week treatment period.

RESULTS

Efficacy study design

- Patient characteristics were comparable across the groups (Table 1).

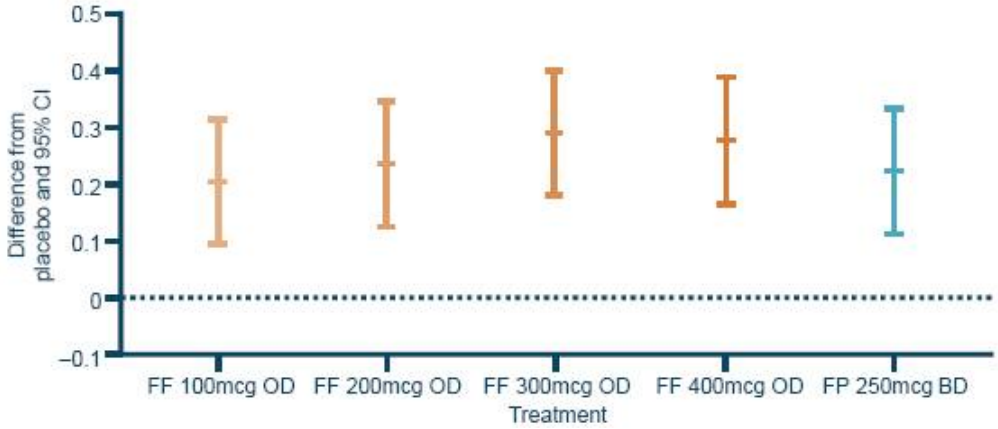
Table 1. Demographic and baseline clinical characteristics (ITT population).

		FF				FP
	Placebo (n=107)	100mcg OD (n=105)	200mcg OD (n=101)	300mcg OD (n=103)	400mcg OD (n=99)	250mcg BD (n=100)
Age (years)						
Mean±SD	39.1±16.19	38.3±16.76	38.8±15.97	39.9±15.57	40.7±15.87	39.8±16.70
Range	12–75	12–77	12–72	12–80	12–78	12–79
Gender, n (%)						
Female	74 (69)	72 (69)	63 (62)	67 (65)	64 (65)	62 (62)
Race, n (%)						
White	62 (58)	64 (61)	65 (64)	63 (62)	56 (57)	61 (61)
Asian	26 (24)	25 (24)	23 (23)	23 (23)	25 (25)	23 (23)
Other	19 (18)	16 (15)	13 (13)	16 (16)	18 (18)	16 (16)
FEV_1 at baseline, mean (L)	2.228	2.284	2.296	2.251	2.315	2.300
% predicted FEV_1 at screening, mean±SD	66.59±12.571	66.68±11.744	66.38±12.581	66.74±11.251	66.92±10.733	69.26±10.793
% reversibility in FEV_1 at screening, mean±SD	29.15±19.972	26.42±12.689	29.25±16.631	26.10±13.623	28.94±17.146	25.70±14.310

ITT = intent-to-treat

- All dosages of FF demonstrated significant ($p<0.001$) mean increases in FEV_1 from baseline compared with placebo (Figure 2).
- There was no evidence of a dose response for the four FF groups.

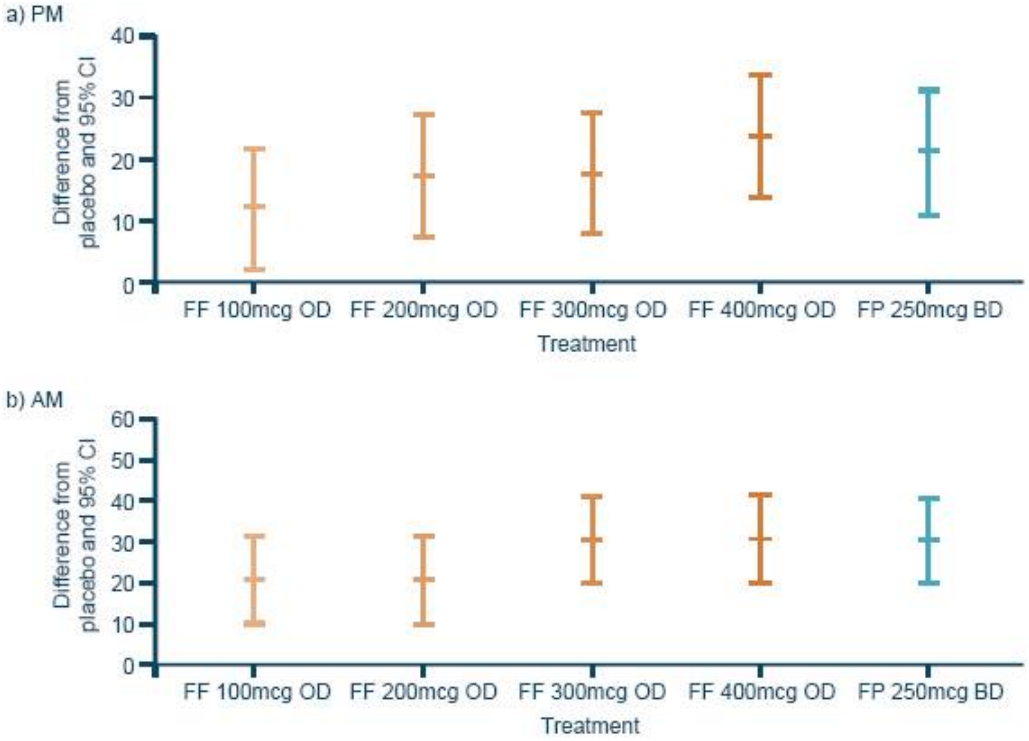
Figure 2. Adjusted treatment differences of change from baseline in trough FEV_1 (LOCF) at Week 8 (ITT population).



Note: analysis performed using an analysis of covariance (ANCOVA) with covariates of baseline, country, sex, age and treatment

- The results of a test of linear trend in dose response, excluding placebo group showed no significant relationship between response and dose of FF (p>0.05; 95% CI: –0.060 to 0.616). The estimate of the slope was 0.278mL/mcg. The results of the test for linear trend in dose response, including placebo were significant (p<0.001; 95% CI: 0.391 to 0.900). The estimate of the slope was 0.646mL/mcg.
- FF once daily PM and FP twice daily produced significantly different (improved) changes relative to placebo in daily trough (pre-dose and pre-rescue bronchodilator) PM PEF and daily AM PEF (p=0.018 to p<0.001; Figure 3).

Figure 3. PEF over Weeks 1–8
a) PM and b) AM.



- The change in percentage of symptom-free 24h periods were significantly different from placebo for FF 400mcg once daily PM (p=0.010) and FP 250mcg twice daily (p=0.002), but not for FF 100, 200 and 300mcg once daily PM (p=0.311, p=0.592 and p=0.097, respectively; Figure 4a). The change in percentage of rescue-free 24h periods were significantly different from placebo for FF 100, 300 and 400mcg once daily PM, and FP 250mcg twice daily (p=0.030, p=0.031, p=0.045 and p<0.001, respectively) but not for FF 200mcg once daily (p=0.06; Figure 4b).
- Significantly higher withdrawals due to lack of efficacy were observed with placebo (33%) compared with the active treatment groups (p<0.001 for all FF doses and p=0.002 for FP; Figure 5).

Figure 4. Symptom-free and rescue-free 24h periods over Weeks 1–8.

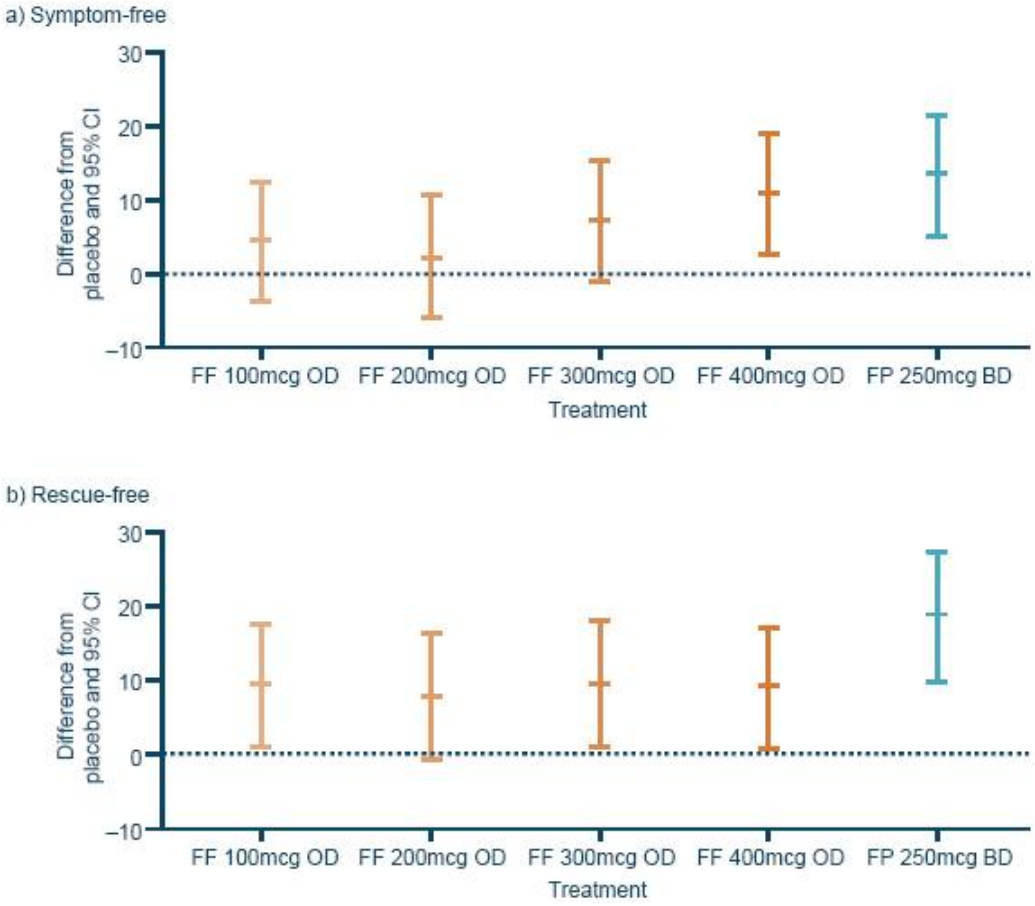
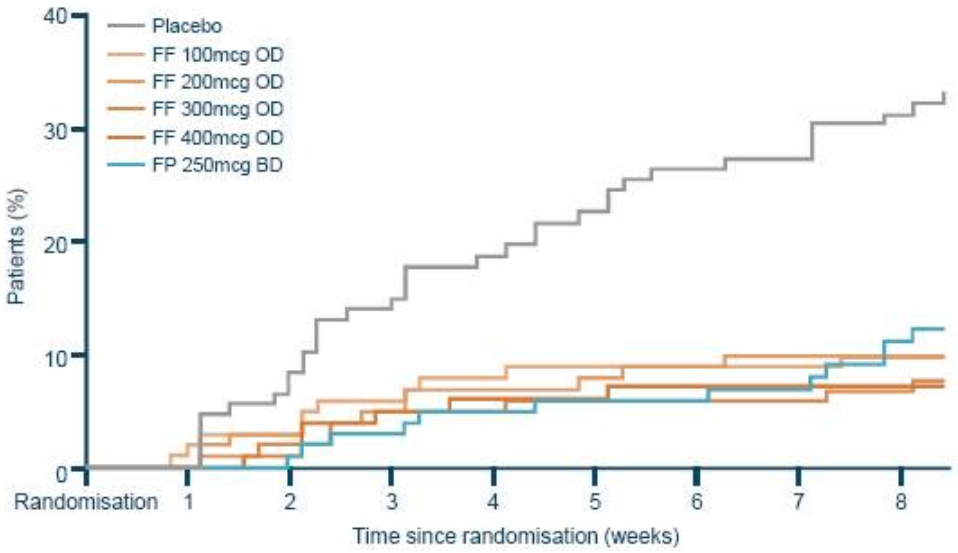


Figure 5. Treatment discontinuation due to lack of efficacy (cumulative incidence).



Note: patients are represented from their date of randomisation to their date of withdrawal due to lack of efficacy

Safety

- Overall, FF was well tolerated, with no apparent dose-related increase in the frequency of the most commonly reported AEs across the four doses of FF (Table 2).
- Seven patients withdrew due to AEs, including one serious AE (asthma exacerbation); three of these events were considered treatment-related (pharyngitis and throat infection [both in the FF 100mcg group]; bilateral thigh pain [FF 400mcg group]).
- The urinary cortisol excretion ratios were not significantly different between placebo and any dose groups of FF or FP 250mcg twice daily (Figure 6).

Table 2. Most common on-treatment AEs (≥3% incidence in any treatment group; ITT population).

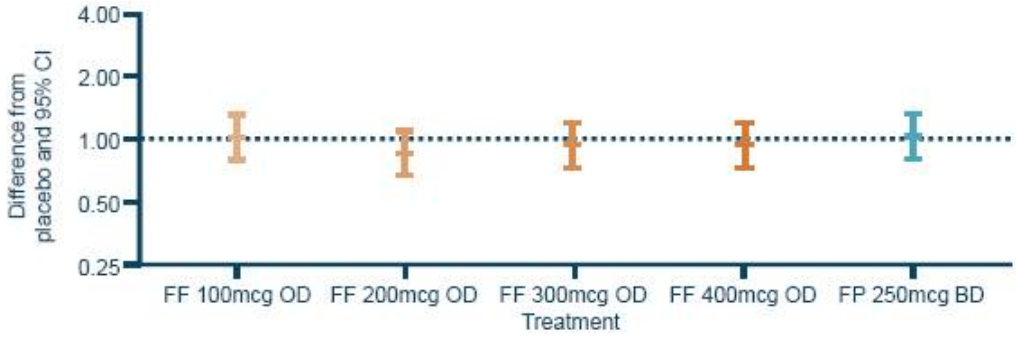
		FF				FP
AE, n (%)	**Placebo (n=107)**	**100mcg OD (n=105)**	**200mcg OD (n=101)**	**300mcg OD (n=103)**	**400mcg OD (n=99)**	**250mcg BD (n=100)**
Number (%) of patients with any AE	32 (30)	43 (41)	33 (33)	41 (40)	35 (35)	42 (42)
Headache	6 (6)	9 (9)	8 (8)	8 (8)	9 (9)	8 (8)
Nasopharyngitis	8 (7)	9 (9)	5 (5)	7 (7)	4 (4)	7 (7)
Upper respiratory tract infection	3 (3)	2 (2)	3 (3)	1 (<1)	0	6 (6)
Oral candidiasis*	0	3 (3)	1 (<1)	3 (3)	3 (3)	3 (3)

Cough	1 (<1)	2 (2)	0	2 (2)	4 (4)	2 (2)
Back pain	0	1 (<1)	1 (<1)	3 (3)	3 (3)	2 (2)
Dysphonia	1 (<1)	1 (<1)	0	2 (2)	2 (2)	4 (4)
Oropharyngeal pain	0	2 (2)	1 (<1)	1 (<1)	3 (3)	3 (3)
Hypertension	2 (2)	0	3 (3)	2 (2)	2 (2)	0
Diarrhoea	0	4 (4)	1 (<1)	1 (<1)	1 (1)	1 (1)
Pain in extremity	3 (3)	1 (<1)	1 (<1)	0	2 (2)	1 (1)
Abdominal pain upper	0	2 (2)	1 (<1)	1 (<1)	3 (3)	0
Sinusitis	1 (<1)	2 (2)	0	0	1 (1)	3 (3)
Abdominal pain	0	3 (3)	1 (<1)	0	1 (1)	1 (1)
Rhinitis	3 (3)	0	2 (2)	1 (<1)	0	0
Pharyngitis	1 (<1)	1 (<1)	0	3 (3)	0	0
Toothache	0	1 (<1)	1 (<1)	0	0	3 (3)

*Two additional patients, 1 (<1%) in the FF 300mcg OD arm and 1 (1%) in the FP 250mcg BD arm were diagnosed as having oral candidiasis, coded as 'oropharyngeal candidiasis'

- No treatment-related clinically important changes were apparent for the mean and median laboratory values noted at Week 1 and Week 8 for haematology and clinical chemistry analytes, or vital signs.

Figure 6. Adjusted 24h urinary cortisol excretion ratios.*



Note: analysis performed using ANCOVA with covariates of baseline, country, sex, age and treatment and the log of baseline values;

*The urinary cortisol population consisted of 417 (68%) patients in the ITT population who had urine samples with no factors that would confound the analysis of urinary cortisol

CONCLUSIONS

- These results support FF as an effective and well-tolerated ICS at doses ranging from 100 to 400mcg administered once daily in the evening, in patients with asthma uncontrolled on low doses of ICS.
- On the basis of the efficacy and safety data, FF 100mcg and 200mcg are likely to be the most effective doses for this population of asthma patients.

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Presented at the Annual Conference of the European Respiratory Society (ERS), Barcelona, Spain, 18–22 September 2010

POSTER P1168

Fluticasone furoate (FF), an inhaled corticosteroid (ICS), demonstrates efficacy in asthma patients symptomatic on moderate doses of ICS therapy

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UPDATED ABSTRACT

Introduction: FF (GW685698X) is a novel ICS still active at 24h, in development as a once-daily treatment in combination with the long-acting $beta_2$ agonist (LABA) vilanterol trifenatate (VI; GW642444M) for asthma and chronic obstructive pulmonary disease.

Objectives: To evaluate the efficacy and safety of FF administered using a novel single-step activation dry powder inhaler (DPI) in patients ≥12 years uncontrolled on moderate doses of ICS (fluticasone propionate [FP] 500mcg/day or equivalent). FP was used as an active control.

Methods: In this randomised, double-blind, placebo-controlled, double-dummy, parallel group study, 627 patients were randomised to FF (200, 400, 600 or 800mcg) once daily, FP 500mcg twice daily or placebo for 8 weeks. Primary endpoint: change in trough (pre-dose) forced expiratory volume in 1 second (FEV_1) at Week 8.

Results: Primary: the test of linear trend in FF dose response relative to placebo for trough FEV_1 at Week 8 was significant ($p<0.001$). However, no dose response between FF doses was observed. Secondary: peak expiratory flow (PEF), symptom-free and rescue medication-free 24h periods, and withdrawals due to lack of efficacy supported the efficacy of FF 200–800mcg doses and FP. Incidence of oral candidiasis was highest for FF 800mcg (12%). 24h urinary cortisol excretion ratios (Week 8/baseline) for FF were similar to placebo except for FF 800mcg, which was significantly lower.

Conclusion: This study supports the use of FF as a once-daily treatment for patients with asthma uncontrolled on moderate ICS doses.

INTRODUCTION

- ICS are the most effective anti-inflammatory treatment for persistent asthma(1)–(3) and play a critical role in first-line treatment.
- There is a need for improved treatment options for patients with uncontrolled disease; most ICS are dosed twice daily, but once-daily dosing can improve treatment adherence,(4) and may improve outcomes for patients.(5),(6)
- FF a novel ICS still active at 24h, is currently in development as the ICS component of a new ICS/LABA once daily inhaled combination treatment for asthma.

OBJECTIVE

- Evaluate the efficacy and safety of four doses of FF dosed once daily in the evening for 8 weeks, using a novel single-step activation DPI, in patients ≥12 years whose symptoms were uncontrolled on moderate doses of ICS (FP 500mcg/day or equivalent).

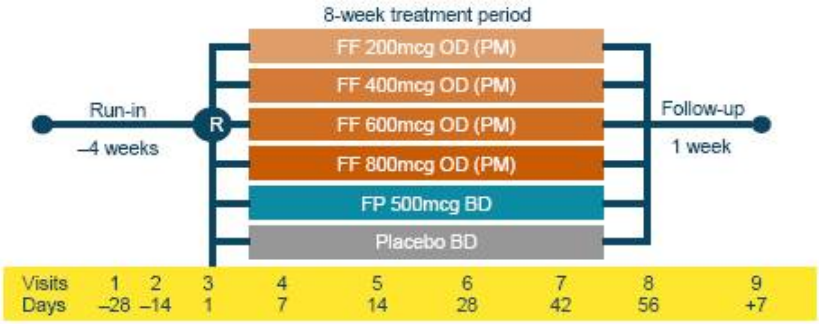
METHODS

- A phase IIb, randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multicentre, dose-ranging study in adolescent and adult patients with persistent asthma (Figure 1).
- Eligible patients (≥12 years old) had persistent asthma,(2) with an evening pre-dose % predicted FEV_1 of 40–90% of their predicted normal value, and ≥12% and ≥200mL reversibility of FEV_1 following albuterol/salbutamol inhalation. They had been using an ICS for ≥8 weeks prior to their first visit (at a stable dose for ≥4 weeks).
- All patients replaced their short-acting $beta_2$ agonists with albuterol/salbutamol inhalation aerosol at visit 1, for use as needed during the study.
- Following a 28-day run-in (to assess baseline asthma status, daily diary compliance, and for safety evaluations) during which patients continued their prior ICS therapy at a fixed dose, they were randomly assigned to receive
  - FF (200, 400, 600 or 800mcg once daily [evening; PM]) via novel DPI plus placebo twice daily (morning [AM] and PM) via DISKUS™/ACCUHALER™
  - FP (500mcg twice daily AM and PM) via DISKUS™/ACCUHALER™ plus placebo once daily (PM) via novel DPI
  - placebo once daily (PM) via novel DPI plus placebo twice daily (AM and PM) via DISKUS™/ACCUHALER™.
- All medications were blinded to investigators and patients, and each patient received two devices at each visit (novel DPI and DISKUS™/ACCUHALER™).
- Patients stopped their maintenance ICS therapy for the duration of treatment (visit 3–8), and received study medication for 56 days (8 weeks). A follow-up clinic visit or phone contact was conducted 1 week after completing treatment.

Efficacy and safety measures

- The primary endpoint was the mean change from baseline in PM trough FEV_1 (pre-dose and pre-rescue bronchodilator) at Week 8
  - the primary comparison was the test for linear dose response in FEV_1 across the four doses of FF and placebo (intent-to-treat [ITT] population; analysis of covariance [ANCOVA] with last observation carried forward [LOCF]).
- Secondary endpoints
  - mean change from baseline in daily PM trough (pre-dose and pre-rescue bronchodilator) PEF and daily AM PEF, averaged over the treatment period
  - mean change from baseline in % symptom-free and % rescue medication-free 24h periods
  - withdrawals due to lack of efficacy.

Figure 1. Study design.



OD = once daily; BD = twice daily

- Safety assessments included
  - incidence of adverse events (AEs; categorised using the MedDRA coding dictionary, Version 11)
  - oropharyngeal examination for oral candidiasis
  - laboratory tests (haematology, clinical chemistry, urinalysis parameters [pre- and post-treatment]) and vital signs
  - 24h urinary cortisol excretion (pre- and post-treatment).

RESULTS

- 627 patients were randomised to FF (200, 400, 600 or 800mcg) once daily PM, FP 500mcg twice daily or placebo for 8 weeks; 622 patients received one or more doses (the ITT population).
- 82–92% of the FF groups and 88% of the FP group completed the study, vs 63% of the placebo group (Table 1).

Table 1. Patient disposition.

		FF dose				FP dose
	Placebo n (%)	200mcg OD n (%)	400mcg OD n (%)	600mcg OD n (%)	800mcg OD n (%)	500mcg BD n (%)
Received study medication	103	99	101	107	102	110
Completed	65 (63)	81 (82)	93 (92)	94 (88)	85 (83)	97 (88)
Discontinued	38 (37)	18 (18)	8 (8)	13 (12)	17 (17)	13 (12)
Lack of efficacy	34 (33)	11 (11)	6 (6)	11 (10)	12 (12)	8 (7)
AE	2 (2)	3 (3)	0	1 (<1)	0	4 (4)
Withdrew consent	1 (<1)	0	0	1 (<1)	3 (3)	1 (<1)
Protocol deviation	0	3 (3)	1 (<1)	0	1 (<1)	0
Investigator discretion	1 (<1)	0	0	0	1 (<1)	0
Lost to follow-up	0	1 (1)	1 (<1)	0	0	0

- Demographic characteristics were evenly matched between treatment groups, as were clinical characteristics and measures of pulmonary function at screening, indicating a similar severity of illness between groups (Table 2).

Table 2. Demographic and clinical characteristics (ITT population).

		FF dose				FP dose
	Placebo (n=103)	200mcg OD (n=99)	400mcg OD (n=101)	600mcg OD (n=107)	800mcg OD (n=102)	500mcg BD (n=110)
Age, years (range)*	47.2±14.03 (16–78)	45.7±15.02 (12–77)	47.2±14.39 (13–70)	45.7±14.38 (13–75)	46.6±14.09 (12–76)	46.1±13.86 (12–74)
Gender, n (%)						
Females	64 (62)	63 (64)	62 (61)	67 (63)	63 (62)	68 (62)
Race, n (%)						
White	83 (81)	74 (75)	80 (79)	77 (72)	80 (78)	83 (76)
Asian	6 (6)	9 (9)	7 (7)	11 (10)	7 (7)	7 (6)
Other	14 (14)	16 (16)	14 (14)	19 (18)	15 (15)	19 (17)
Lung function at screening*						
Pre-bronchodilator FEV_1 (L)	2.043±0.6022	2.046±0.6387	2.066±0.6358	2.043±0.6076	2.057±0.5865	2.064±0.5644
% predicted FEV_1 (%)	64.12±11.133	65.08±11.684	66.59±12.771	64.33±11.983	66.00±12.118	65.43±12.353
Post-bronchodilator FEV_1	2.557±0.7454	2.603±0.7591	2.566±0.7522	2.597±0.7176	2.639±0.7355	2.592±0.6413
Reversibility of FEV_1 (%)	26.14±14.448	28.93±17.305	25.53±13.892	28.55±14.005	29.32±15.409	27.02±15.013
Reversibility of FEV_1 (mL)	513.4±278.54	556.1±305.62	500.9±258.55	553.5±260.75	582.4±316.95	528.5±253.20

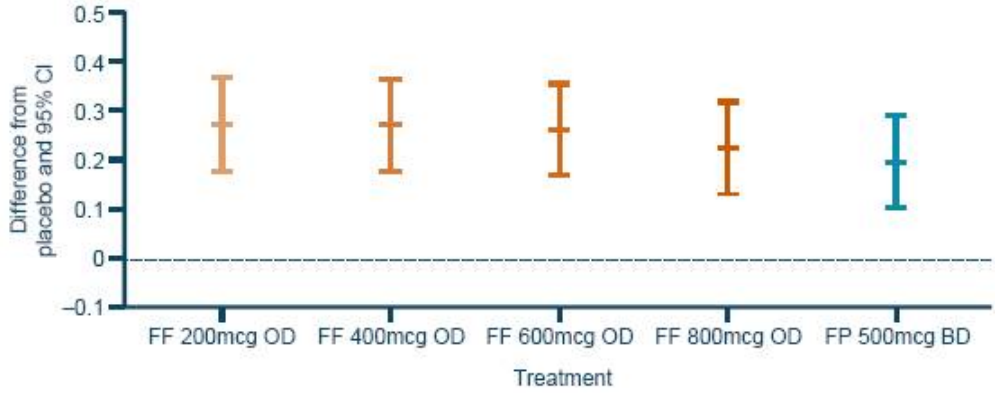
*Values are mean ± standard deviation

Efficacy

Primary outcome

- At baseline, PM trough FEV_1 was similar between the six treatment groups; between baseline and Week 8 there was a reduction in trough FEV_1 with placebo, but an increase with all FF once daily PM doses, and FP twice daily (Figure 2).
- The results of a test of linear trend in dose response, excluding the placebo group showed no significant relationship between response and dose of FF (p=0.306; 95% CI: –0.229 to 0.072). The estimate of slope was –0.078mL/mcg. The results of the test for linear trend in dose response, including placebo were significant (p<0.001; 95% CI: 0.112 to 0.333). The estimate of the slope was 0.223mL/mcg.
- Results for the per-protocol population were consistent with those for the ITT population.

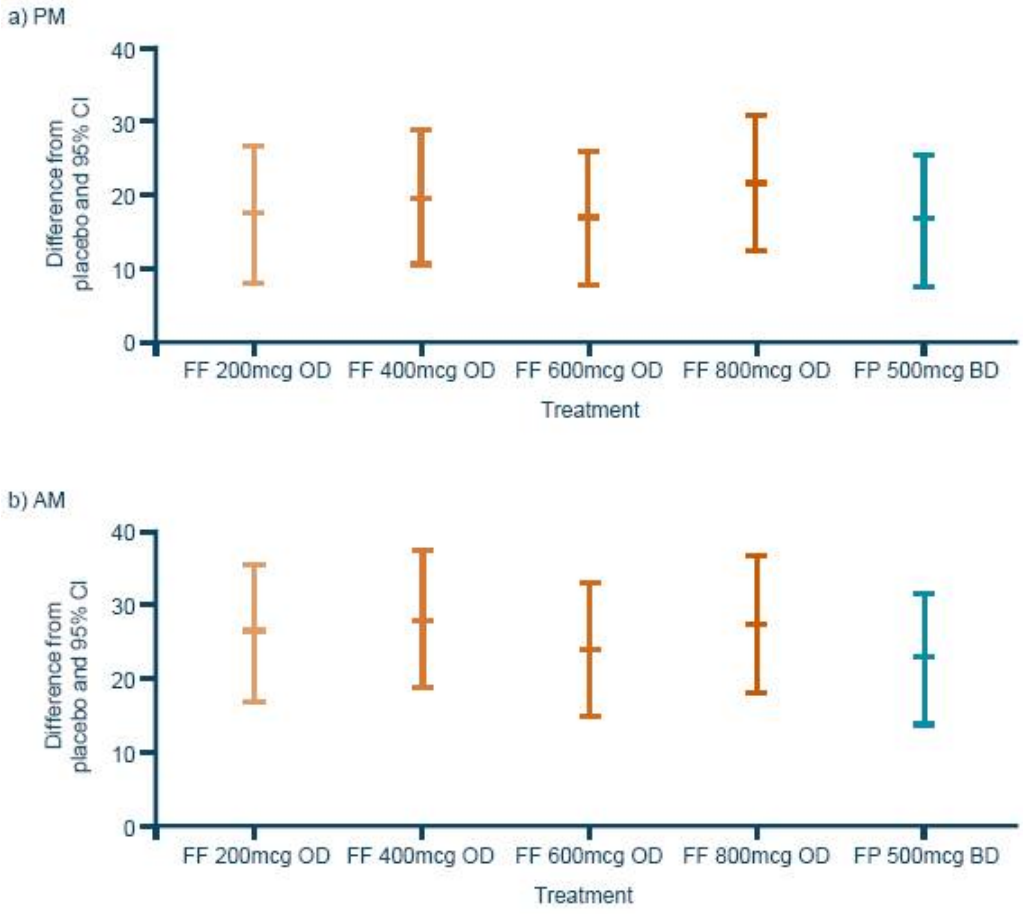
Figure 2. Adjusted treatment differences of change from baseline in trough FEV_1 (LOCF) at Week 8 (ITT population).



PEF

- All FF once daily PM doses and FP twice daily had greater improvements in PM and AM trough PEF (LSM change between baseline and Weeks 1–8) than placebo (p<0.001; Figure 3).

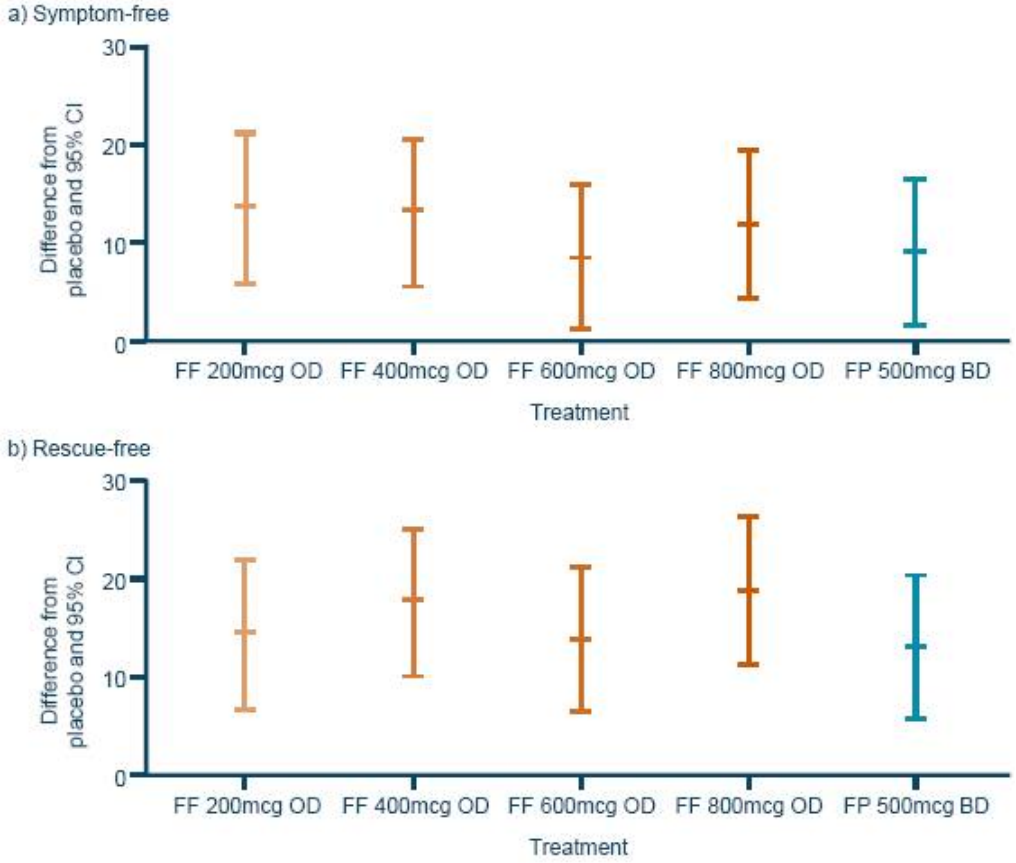
Figure 3. PEF over Weeks 1–8
a) PM and b) AM.



Symptom-free and rescue medication-free periods

- Differences in the percentage of symptom-free 24h periods (LSM change between baseline and Weeks 1–8) were greater for FF 200mcg and 400mcg (p<0.001), 600mcg (p=0.022), 800mcg (p=0.002) once daily PM and FP twice daily (p=0.017) than for placebo (Figure 4a). Differences in the percentage of rescue medication-free 24h periods (LSM change between baseline and Weeks 1–8) were greater for all FF once daily PM doses and FP twice daily than for placebo (p<0.001; Figure 4b).

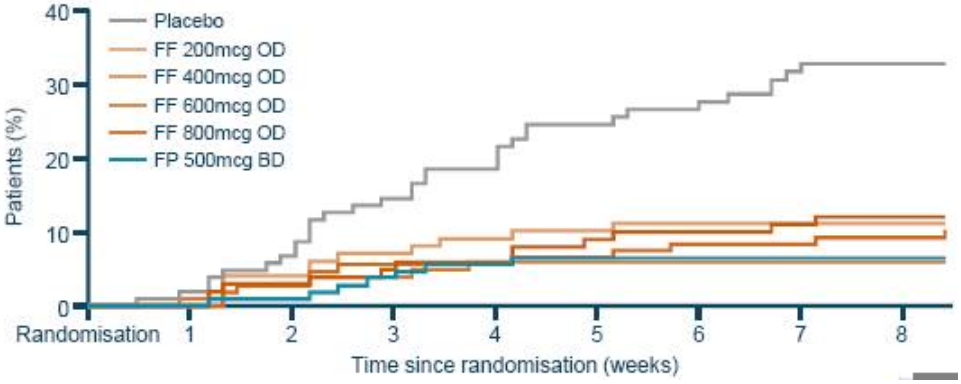
Figure 4. Symptom-free (a) and rescue-free (b) 24h periods over Weeks 1–8.



Treatment discontinuation

- More patients on placebo (33%) than on active treatment (6–12%) discontinued treatment due to lack of efficacy (p<0.001, Figure 5).

Figure 5. Treatment discontinuation due to lack of efficacy (cumulative incidence).



Note: patients are represented from their date of randomisation to their date of withdrawal due to lack of efficacy

Safety

- A low incidence (<1–6%) of asthma exacerbations occurred during active treatment, vs 16% with placebo; most were due to lack of efficacy
  - 8% of patients receiving placebo took oral corticosteroid for exacerbations, vs 2%, 0%, 0% and <1% with FF 200, 400, 600 and 800mcg respectively, and 3% with FP.
- FF was generally well tolerated; Table 3 lists the most commonly reported AEs in each treatment group.
- Other than for oral candidiasis (higher incidence at highest dose level), the incidence of drug-related AEs was similar between FF dose groups.
- No serious AEs were related to study medication.

Table 3. Most common on-treatment AEs.

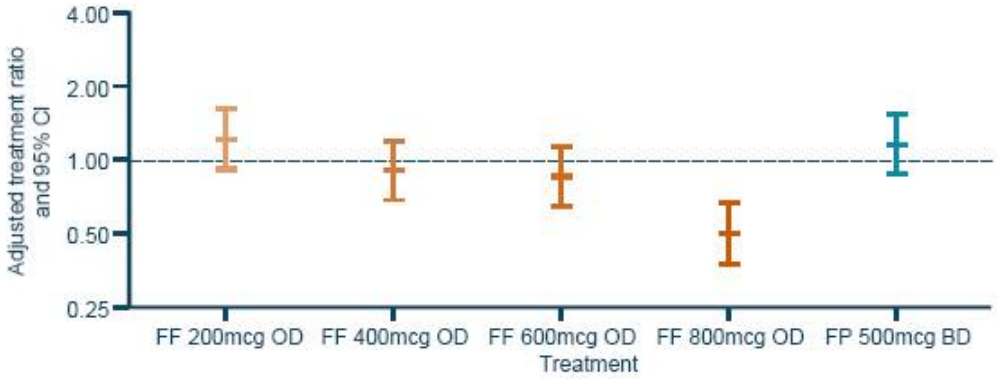
		FF dose				FP dose
	Placebo (n=103)	200mcg OD (n=99)	400mcg OD (n=101)	600mcg OD (n=107)	800mcg OD (n=102)	500mcg BD (n=110)
Patients with any on- treatment AE, n (%)	23 (22)	31 (31)	34 (34)	37 (35)	36 (35)	39 (35)
Headache	10 (10)	3 (3)	10 (10)	12 (11)	10 (10)	10 (9)
Nasopharyngitis	4 (4)	3 (3)	5 (5)	2 (2)	7 (7)	4 (4)
Oropharyngeal candidiasis*	1 (<1)	4 (4)	4 (4)	1 (<1)	4 (4)	4 (4)
Dysphonia	1 (<1)	4 (4)	5 (5)	1 (<1)	4 (4)	2 (2)
Oral candidiasis*	0	2 (2)	2 (2)	1 (<1)	7 (7)	0
Pharyngolaryngeal pain	1 (<1)	2 (2)	0	3 (3)	1 (<1)	4 (4)
URTI	1 (<1)	2 (2)	0	3 (3)	1 (<1)	3 (3)
Back pain	1 (<1)	1 (1)	1 (<1)	4 (4)	2 (2)	0

Influenza	1 (<1)	1 (1)	2 (2)	3 (3)	0	0
Nausea	0	0	3 (3)	0	2 (2)	0
Pain in extremity	0	0	0	3 (3)	1 (<1)	0

*One additional patient (<1%), in the FF 800mcg OD arm, was diagnosed as having oral candidiasis, coded as 'candidiasis' URTI = upper respiratory tract infection

- In general, 24h urinary cortisol excretion ratios (Week 8/baseline) for FF were similar to placebo (the ratio for FF 800mcg was significantly lower than for placebo [p<0.001; Figure 6]).
- No other safety concerns were raised.

Figure 6. Adjusted 24h urinary cortisol excretion ratios.*



Note: analysis performed using ANCOVA with covariates of country, sex, age, treatment and the log of the baseline values; *The urinary cortisol population consisted of 414 (67%) patients in the ITT population who had urine samples with no factors that would confound the analysis of urinary cortisol

CONCLUSIONS

- The current findings support the use of FF as a once-daily treatment for patients with asthma, uncontrolled on moderate ICS doses
  - the primary efficacy analysis was statistically significant, with all FF doses providing greater improvements in PM trough FEV_1 than placebo; the lack of FF dose dependency is typical of ICS studies in patients symptomatic on moderate doses of ICS
  - secondary efficacy endpoints consistently confirmed the findings of the primary endpoint
  - FF once daily appears to be generally well tolerated with AEs equivalent to FP (1000mcg total daily dose) except for a higher incidence of oral candidiasis and a lower urinary cortisol excretion ratio at the highest dose (800mcg once daily PM) overall, the incidence of AEs was low, with no evidence of dose dependency for the most commonly reported AEs.
- On the basis of these findings, FF 200–600mcg appears to be an appropriate once-daily dose for patients with moderate-to-severe persistent asthma.

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POSTER P1185 **Safety of vilanterol trifenatate (VI) in a chronic obstructive pulmonary disease (COPD) dose-ranging study**

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ABSTRACT

Introduction: VI (GW642444M) is a long-acting beta$_2$ agonist (LABA) with inherent 24h activity under development as a once-daily monotherapy for COPD and in combination with a novel inhaled corticosteroid (ICS; fluticasone furoate) for COPD and asthma.

Objective: To evaluate the safety of VI administered via a novel single-step activation inhaler in a COPD dose-ranging study.

Methods: Randomised, placebo-controlled, double-blind, stratified, parallel-group study of 605 COPD patients randomised to one of six treatment arms: VI (3, 6.25, 12.5, 25 or 50mcg) or placebo administered once daily for 28 days. Safety assessments included adverse events (AEs), effect on glucose and potassium, vitals (pulse rate and blood pressure) and electrocardiogram (ECG).

Results: Mean (standard deviation [SD]) age 61.9 (8.34) years; 61% were male; mean (SD) screening % predicted forced expiratory volume in 1 second (FEV_1) 50.5 (9.78). Overall incidence of on-treatment AEs in the VI arms (24–33%) was comparable with placebo (36%). Few AEs led to withdrawal with incidence similar across treatment arms (placebo 3%, 3mcg 3%, 6.25mcg 4%, 12.5mcg 2%, 25mcg 0% and 50mcg 1%). The incidence of AEs associated with LABAs was low ($\leq$3%) with no apparent treatment or dose relationship. There was no clinically relevant effect on systolic or diastolic blood pressure, pulse rate or blood glucose or potassium levels. Four patients experienced non-fatal serious AEs (SAEs) during treatment (3mcg vasovagal syncope, 6.25mcg aortic aneurysm, 12.5mcg atrial fibrillation, 12.5mcg COPD exacerbation and pneumonia), but none were considered drug related by the Investigator.

Conclusion: Once-daily administration of VI has a safety and tolerability profile comparable with placebo in COPD patients.

INTRODUCTION

- VI is a novel inhaled LABA, which shows inherent 24h activity.(1) VI is in development both as a once-daily monotherapy for COPD and, in combination with the ICS fluticasone furoate, for COPD and asthma.
- This dose-ranging study of VI in COPD patients assessed the efficacy and tolerability of five different doses of VI administered using a novel single-step activation inhaler. This poster summarises the safety data from the study; efficacy data are reported separately in poster number P1227.

PATIENTS AND METHODS

Study design

- A phase IIb, randomised, double-blind, placebo-controlled, parallel-group trial conducted at 89 centres from February to October 2008. Patients were stratified by reversibility (reversible; non reversible).
- The study was approved by local ethics review committees and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all patients.

Inclusion criteria

- Males or females aged 40–80 years with COPD (American Thoracic Society/European Respiratory Society definition)(2) and current or prior history of $\geq$10 pack-years of cigarette smoking.
- A post-salbutamol FEV_1/forced vital capacity (FVC) ratio $\leq$0.70 and FEV_1 $\geq$35% and $\leq$70% of predicted normal values (The National Health and Nutrition Examination Survey III)(3) at screening (study visit 1).
- Women of child-bearing potential had to be using acceptable methods of contraception.

Exclusion criteria

- COPD caused by alpha 1 antitrypsin deficiency.
- Poorly controlled COPD defined as acute worsening managed by patient with corticosteroids/antibiotics or requiring physician-prescribed treatment, both within 6 weeks of visit 1.
- Hospitalisation for poorly controlled COPD within 12 weeks of visit 1.

- Current diagnosis of asthma, or other lung disease (active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, fibrosis, pulmonary hypertension, interstitial lung disease or other active pulmonary disease) or lung volume reduction surgery within past year. Any clinically significant abnormalities on chest scan not thought due to COPD. Lower respiratory tract infection requiring antibiotics within 6 weeks of visit 1.
- Requirement for long-term or nocturnal oxygen therapy for >12h/day; any clinically significant 12-lead ECG abnormality; patients unable to withhold salbutamol for 6h before spirometry testing; use of medications potentially affecting the study results (Table 1).

Table 1. Medications not permitted during the study and which must not have been taken for the indicated times prior to visit 1.*

Medication	Required period of time prior to screening visit 1
Depot corticosteroids	12 weeks

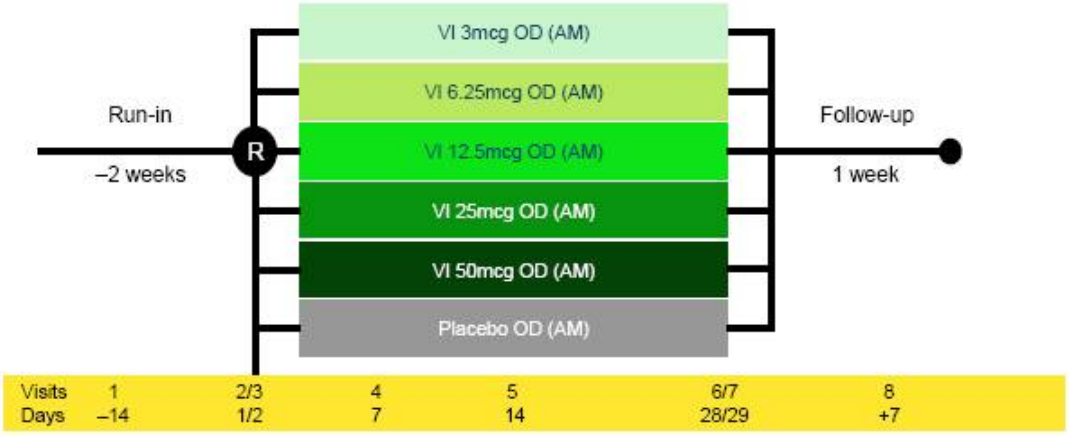
Oral, parenteral and intra-articular corticosteroids	6 weeks
Any other investigational medication	30 days or within five drug half-lives of the investigational drug (whichever is longer)
ICS >1,000mcg/day of fluticasone propionate or equivalent	4 weeks
P-glycoprotein inhibitors (e.g. ritonavir, ketoconazole) or cytochrome P450 3A4 inhibitors (e.g. cimetidine)	4 weeks (grapefruit allowed up to the screening visit)
Tiotropium	1 week
Oral beta$_2$ agonists	48h
LABAs (salmeterol and formoterol)	48h
Corticosteroid/LABA combination products	48h for the LABA component
Theophylline preparations	48h
Zafirlukast, montelukast and zileuton	48h
Cromolyn and nedocromil inhalers	24h
Ipratropium or ipratropium/salbutamol combination products	6h
Inhaled short-acting beta agonists (study salbutamol was provided)	6h

*Note: use of tricyclic antidepressants, monoamine oxidase inhibitors, beta-blockers, anticonvulsants (barbiturates, hydantoins and carbamazepine) and phenothiazines was also prohibited

Methods

- After a 2-week single-blind, placebo run-in period, patients were randomised to one of five VI doses (3, 6.25, 12.5, 25 and 50mcg) or placebo once daily for 28 days (Figure 1).
- All study treatments were administered in a double-blinded manner once daily in the morning using a novel dual-strip dry powder inhalation device.

Figure 1. Study design.



Trough FEV$_1$ at the 23rd and 24th h following dosing on visit 2 and visit 6 was measured at visit 3 and visit 7, respectively, when the patients returned to the clinic the following morning

Safety assessment

- Patients had a chest radiograph at study clinic visit 1 (screening visit), a physical examination at study visits 1 and 7, and an ECG at visits 1, 2 (baseline), 5 and 6. QTc was calculated using Fridericia's Formula (QTcF) and Basset's Formula (QTcB) on Days 1, 14 and 28.

- Patients were assessed for AEs and vital signs were recorded at each clinic visit. They were also asked to record any medical problems using daily diary cards.
- Additionally, samples were obtained for laboratory tests at visits 1, 5 and 6, and for serial potassium and glucose tests at visits 2, 5 and 6.

RESULTS

- Of 851 patients who entered the 2-week run-in period, 602 were randomised and received at least one dose of study treatment (intent-to-treat [ITT] population). Demographics, baseline characteristics and screening pulmonary function were comparable (Table 2). Most patients were white males, mean age was 62 years, approximately 50% still smoked and 76% had a COPD diagnosis <10 years.
- 81% of patients (ITT) used COPD medications during the 12 weeks prior to visit 1, while during the treatment period, ICS was used by similar proportions of patients across the treatment groups.
- Across the treatment groups, mean screening pre- and post-bronchodilator FEV$_1$ values ranged from 1.232 to 1.401L and 1.420 to 1.555L, respectively, and the mean % predicted post-bronchodilator FEV$_1$ from 49.9 to 51.5%. Mean % reversibility ranged from 12.8 to 18.1% and absolute reversibility from 154.1 to 187.5mL.
- Mean treatment compliance was ≥99% in all groups.

Table 2. Patient baseline characteristics and pulmonary function at screening (ITT population).

		VI					
	Placebo (n=101)	**3mcg (n=99)**	**6.25mcg (n=101)**	**12.5mcg (n=101)**	**25mcg (n=101)**	**50mcg (n=99)**	**Total (N=602)**

Demographics							
Male, n (%)	57 (56)	68 (69)	64 (63)	57 (56)	59 (58)	65 (66)	370 (61)
Age, years*	61.6±8.53	61.1±8.57	62.0±7.94	62.6±8.03	62.6±8.88	61.4±8.12	61.9±8.34
BMI,† kg/m²*	28.51±6.03	27.62±7.12	27.23±6.69	27.44±6.83	28.01±6.87	27.27±6.72	27.68±6.71
Race, n (%)							
White	90 (89)	84 (85)	84 (83)	86 (85)	84 (83)	87 (88)	515 (86)
Asian	7 (7)	11 (11)	13 (13)	9 (9)	10 (10)	6 (6)	56 (9)
African American	3 (3)	1 (1)	3 (3)	2 (2)	4 (4)	3 (3)	16 (3)
American Indian or Alaska Native	1 (<1)	3 (3)	1 (<1)	4 (4)	3 (3)	3 (3)	15 (2)
Tobacco history, n (%)							
Current smoker	46 (46)	50 (51)	48 (48)	52 (51)	45 (45)	44 (44)	285 (47)
Former smoker	55 (54)	49 (49)	53 (52)	49 (49)	56 (55)	55 (56)	317 (53)
Smoking pack-years*	47.7±28.25	52.4±32.43	49.6±29.66	49.2±28.66	49.5±29.12	43.1±20.58	48.6±28.38
COPD severity MMRC dyspnoea scale rating, n (%)							
1	9 (9)	7 (7)	7 (7)	8 (8)	8 (8)	12 (12)	51 (8)
2	37 (37)	43 (43)	48 (48)	37 (37)	32 (32)	39 (39)	236 (39)
3	34 (34)	30 (30)	25 (25)	39 (39)	42 (42)	30 (30)	200 (33)
4	17 (17)	18 (18)	14 (14)	13 (13)	19 (19)	18 (18)	99 (16)
5	4 (4)	1 (1)	7 (7)	4 (4)	0	0	16 (3)
Pulmonary function							
% predicted FEV_1*	51.5±10.67	50.3±10.14	49.9±8.57	50.2 ± 9.20	49.9±10.44	51.0±9.64	50.5±9.78
FEV1/FVC (%)*	52.5±8.66	51.4±10.17	49.9±8.33	51.0 ± 9.12	50.1±10.34	52.6±9.58	51.2±9.41
% reversibility in FEV_1*	16.5±15.08	15.1±13.01	12.8±10.86	15.8 ± 14.81	18.1±16.45	13.3±14.78	15.3±14.34
Reversible, n (%)	39 (39)	36 (36)	34 (34)	34 (34)	37 (37)	34 (34)	214 (36)
ICS use at baseline, n (%)	33 (33)	33 (33)	36 (36)	30 (30)	23 (23)	30 (30)	185 (31)

*Values are mean ± SD; †BMI categories: underweight (<18.5kg/m²); normal (18.5kg/m² to <25kg/m²); overweight (25kg/m² to <30kg/m²) and obese (≥30kg/m²); BMI = body mass index; MMRC = Modified Medical Research Council

MMRC dyspnoea scale

1. Not troubled by breathlessness except on strenuous exercise
2. Short of breath when hurrying or walking up a slight hill
3. Walks slower than contemporaries on the level because of breathlessness, or has to stop for breath when walking at own pace
4. Stops for breath after about 100m or after a few minutes on the level
5. Too breathless to leave the house, or breathless when dressing or undressing

Safety data

- Overall incidence of AEs was lower in the VI treatment groups (24–33%) than the placebo group (36%; Table 3).
- Headache was the most common AE, and was highest in the placebo group (10% vs. 3–7% for VI; Table 4). Other common AEs of nausea (1–4%), nasopharyngitis (0–5%), and increased blood potassium (0–3%) were similar across the treatment groups.

Table 3. Overall incidence of AEs (ITT population).

	Number (%) of patients					
		VI				
Type of AE	Placebo (n=101)	3mcg (n=99)	6.25mcg (n=101)	12.5mcg (n=101)	25mcg (n=101)	50mcg (n=99)
Any on-treatment AE	36 (36)	24 (24)	32 (32)	24 (24)	33 (33)	28 (28)
Any drug-related AE	10 (10)	5 (5)	5 (5)	5 (5)	5 (5)	7 (7)
Any post-treatment AE	6 (6)	7 (7)	5 (5)	5 (5)	3 (3)	3 (3)
Any AE leading to withdrawal	3 (3)	3 (3)	4 (4)	2 (2)	0	1 (1)
Any on-treatment SAE	0	1 (1)	1 (<1)	2 (2)	0	0
Any post-treatment SAE	0	1 (1)	1 (<1)	1 (<1)	0	1 (1)

Table 4. Most common (≥3% incidence in any treatment group) AEs during treatment (ITT population).

	Number (%) of patients					
		VI				
Event	Placebo (n=101)	3mcg (n=99)	6.25mcg (n=101)	12.5mcg (n=101)	25mcg (n=101)	50mcg (n=99)
Any AE	36 (36)	24 (24)	32 (32)	24 (24)	33 (33)	28 (28)
Headache	10 (10)	6 (6)	5 (5)	3 (3)	3 (3)	7 (7)
Nausea	4 (4)	1 (1)	3 (3)	2 (2)	2 (2)	1 (1)
Nasopharyngitis	3 (3)	2 (2)	5 (5)	0	1 (<1)	0
Blood potassium increased*	3 (3)	0	1 (<1)	2 (2)	2 (2)	2 (2)
Blood glucose increased	3 (3)	0	1 (<1)	3 (3)	1 (<1)	0
Diarrhoea	1 (<1)	2 (2)	1 (<1)	1 (<1)	3 (3)	0
Ventricular extrasystoles	2 (2)	0	1 (<1)	0	0	3 (3)
Nasal congestion	3 (3)	0	2 (2)	0	0	0
Oropharyngeal pain	0	0	3 (3)	0	0	1 (1)

*Additionally, hyperkalaemia was reported for one patient in the 3mcg group and one patient in the 12.5mcg group

- One patient in the VI 6.25mcg treatment group died from a subdural haematoma during the post-treatment, follow-up period; this event was not considered to be related to study treatment. In total, seven patients in the VI group (1%) experienced non-fatal SAEs during or after treatment: a case of vasovagal syncope and a case of COPD exacerbation in the VI 3mcg group, an aortic aneurysm in the VI 6.25mcg group, cases of atrial fibrillation, COPD exacerbation/pneumonia and hypotension in the VI 12.5mcg group, and a case of hyperkalaemia in the VI 50mcg group
  - of these, only the COPD exacerbation (VI 3mcg group) and hyperkalaemia were considered treatment-related and both were reported post-treatment.
- A total of 13 patients (2%) were withdrawn due to AEs: three (placebo), three (VI 3mcg), four (VI 6.25mcg), two (VI 12.5mcg), zero (VI 25mcg) and one (VI 50mcg).
- Three patients experienced AEs leading to withdrawal that were considered drug-related: headache, nausea, anorexia and dyspnoea in a placebo-treated patient, ventricular extrasystoles (VI 6.25mcg group), and increased blood potassium (VI 50mcg).
- The incidence of AEs considered drug-related was low and similar across the VI groups (5–7%) and highest in the placebo group (10%; Table 5).

Table 5. Drug-related AEs reported in >1 patient (ITT population).

	Number (%) of patients					
		VI				
Event	Placebo (n=101)	3mcg (n=99)	6.25mcg (n=101)	12.5mcg (n=101)	25mcg (n=101)	50mcg (n=99)
Any drug-related AE	10 (10)	5 (5)	5 (5)	5 (5)	5 (5)	7 (7)
Blood potassium increased	2 (2)	0	1 (<1)	1 (<1)	1 (<1)	2 (2)
Blood glucose increased	3 (3)	0	1 (<1)	1 (<1)	1 (<1)	0
Headache	3 (3)	0	0	0	0	0
Palpitations	1 (<1)	0	0	0	1 (<1)	0
Ventricular extrasystoles	0	0	1 (<1)	0	0	1 (1)
Nausea	1 (<1)	1 (1)	0	0	0	0
Hyperkalaemia	0	1 (1)	0	0	0	1 (1)
Pruritus	0	0	0	1 (<1)	1 (<1)	0

- There was a low incidence of AEs potentially indicative of a LABA-class effect (≤3% in any group; Table 6), with no treatment- or dose-related trends in their occurrence.

Table 6. Incidence of LABA class-effect AEs (ITT population).

	Number (%) of patients					
		VI				
Event	Placebo (n=101)	3mcg (n=99)	6.25mcg (n=101)	12.5mcg (n=101)	25mcg (n=101)	50mcg (n=99)
Blood glucose increased	3 (3)	0	1 (<1)	3 (3)	1 (<1)	0
Ventricular extrasystoles	2 (2)	0	1 (<1)	0	0	3 (3)
Hypertension	0	0	0	1 (<1)	2 (2)	1 (1)
Blood pressure increased	1 (<1)	0	0	1 (<1)	0	0
Atrial fibrillation	0	0	0	2 (2)	0	0
Palpitations	1 (<1)	0	1 (<1)	0	0	0
Hypokalaemia	1 (<1)	1 (1)	0	0	0	0
Blood potassium decreased	0	0	0	0	0	1 (1)
Tremor	0	1 (1)	1 (<1)	0	0	0
Sinus tachycardia	0	0	0	0	0	1 (1)
Supraventricular extrasystoles	0	0	1 (<1)	0	0	0
Hyperglycaemia	1 (<1)	0	0	0	0	0

- Mean maximum changes from baseline in 0–4h QTcF intervals were similar (≤8msec on Days 1 and 14, ≤6msec on Day 28) across the VI groups and placebo group (Table 7). QTcB intervals showed similar findings to QTcF intervals.

Table 7. Mean maximum change from baseline in QTcF intervals (0–4h; ITT population).

		VI				
Maximum change from baseline in QTcF interval	Placebo (n=101)	3mcg (n=99)	6.25mcg (n=101)	12.5mcg (n=101)	25mcg (n=101)	50mcg (n=99)
Day 1, n	98	97	100	97	99	96
mean ± SD	6.7±10.83	5.1±9.96	7.5±12.71	6.0±10.24	6.7±10.73	7.3±12.67
Day 14, n	86	90	97	93	95	94
mean ± SD	4.7±12.93	4.2±15.50	7.9±16.85	5.0±14.43	6.3±16.58	6.9±16.42
Day 28, n	82	87	90	89	92	91
mean ± SD	5.6±14.38	4.3±12.82	5.5±18.02	5.2±16.25	5.6±11.92	5.0±17.23

- No treatment- or dose-related increases in vital signs or effects on laboratory parameters were observed, except for a slight increase in eosinophils in the VI groups.
- There were no clinically relevant effects on glucose or potassium levels.

CONCLUSIONS

- Once-daily administration of VI in COPD patients was well tolerated, with a good therapeutic margin over the dose range studied.
- There were no safety signals with increasing dose and the maximal tolerated dose was not demonstrated.

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POSTER P1227 **Dose-related efficacy of vilanterol trifenatate (VI) in chronic obstructive pulmonary disease (COPD)**

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ABSTRACT

Introduction: VI (GW642444M) is an inhaled long-acting beta$_2$ agonist (LABA) with inherent 24h activity under development as once-daily monotherapy for COPD and in combination with a novel inhaled corticosteroid (ICS; fluticasone furoate) for COPD and asthma.

Objective: To evaluate the efficacy of VI administered via a novel single-step activation inhaler in patients with COPD in a dose-ranging study.

Methods: In this multicentre, randomised, placebo-controlled, double-blind, stratified, parallel-group study, 605 patients were randomised to one of six treatments: VI (3, 6.25, 12.5, 25 or 50mcg) or placebo administered once daily for 28 days. The primary efficacy endpoint was the change in trough forced expiratory volume in 1 second (FEV_1) from baseline on Day 29 (23–24h post Day 28 dose). Secondary endpoints included time to increase in $\geq$100mL from baseline FEV_1 on Day 1.

Results: Mean baseline FEV_1 ranged from 1.18–1.33L across treatment groups and the mean (standard deviation [SD]) screening % predicted FEV_1 was 50.5 (9.78). Statistically significant improvements in trough FEV_1 were reported on Day 29 for all doses (3, 6.25, 12.5, 25 and 50mcg) of VI compared with placebo ($p<0.001$) (92, 98, 110, 137 and 165mL, respectively). Time to an increase of $\geq$100mL in FEV_1 on Day 1 was significantly shorter for all VI arms compared with placebo ($p<0.001$) (median time of 6min in the 25 and 50mcg groups).

Conclusion: Once-daily administration of VI in patients with COPD provides clinically relevant 24h improvement in lung function with a rapid onset of effect particularly with the 25 and 50mcg doses.

INTRODUCTION

- VI is a novel, inhaled LABA with inherent 24h activity.(1) VI is in development as a once-daily monotherapy for COPD and, in combination with the ICS, fluticasone furoate, for COPD and asthma.
- This dose-ranging study of VI in COPD patients aimed to determine the optimal dose(s) of VI to be used in further clinical trials. Here we report the efficacy data from the study; safety data are reported separately in poster number P1185.

PATIENTS AND METHODS

Study design

- A phase IIb, randomised, double-blind, placebo-controlled, parallel-group trial conducted at 89 centres from February to October 2008. Patients were stratified by reversibility (reversible; non-reversible).
- The study was approved by local ethics review committees and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all patients.

Inclusion criteria

- Males or females aged 40–80 years with COPD (American Thoracic Society/European Respiratory Society definition)(2) and current or prior history of $\geq$10 pack-years of cigarette smoking.
- A post-salbutamol FEV_1/forced vital capacity (FVC) ratio $\leq$0.70 and FEV_1 $\geq$35% and $\leq$70% of predicted normal values (The National Health and Nutrition Examination Survey III)(3) at screening (study visit 1).
- Women of child-bearing potential had to be using acceptable methods of contraception.

Exclusion criteria

- COPD caused by alpha 1 antitrypsin deficiency.
- Poorly controlled COPD defined as acute worsening managed by patient with corticosteroids/antibiotics or requiring physician-prescribed treatment, both within 6 weeks of visit 1.
- Hospitalisation for poorly controlled COPD within 12 weeks of visit 1.
- Current diagnosis of asthma, or other lung disease (active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, fibrosis, pulmonary hypertension, interstitial lung disease or other active pulmonary disease) or lung volume reduction surgery within past year. Any clinically significant abnormalities on chest scan not thought due to COPD. Lower respiratory tract infection requiring antibiotics within 6 weeks of visit 1.
- Requirement for long-term or nocturnal oxygen therapy for >12h/day; any clinically significant 12-lead electrocardiogram abnormality; patients unable to withhold salbutamol for 6h before spirometry testing; use of medications potentially affecting the study results (Table 1).

Table 1. Medications not permitted during the study and which must not have been taken for the indicated times prior to visit 1.*

Medication	Required period of time prior to screening visit 1
Depot corticosteroids	12 weeks
Oral, parenteral and intra-articular corticosteroids	6 weeks

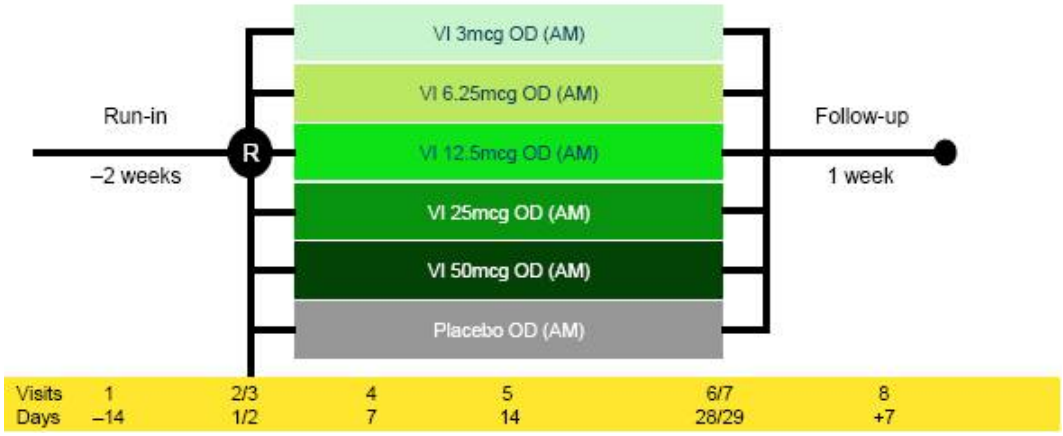
Any other investigational medication	30 days or within five drug half-lives of the investigational drug (whichever is longer)
Inhaled corticosteroids >1,000mcg/day of fluticasone propionate or equivalent	4 weeks
P-glycoprotein inhibitors (e.g. ritonavir and ketoconazole) or cytochrome P450 3A4 inhibitors (e.g. cimetidine)	4 weeks (grapefruit allowed up to the screening visit)
Tiotropium	1 week
Oral beta$_2$ agonists	48h
LABAs (salmeterol and formoterol)	48h
Corticosteroid/LABA combination products	48hrs for the LABA component
Theophylline preparations	48h
Zafirlukast, montelukast and zileuton	48h
Cromolyn and nedocromil inhalers	24h
Ipratropium or ipratropium/salbutamol combination products	6h
Inhaled short-acting beta agonists (study salbutamol was provided)	6h

*Note: use of tricyclic antidepressants, monoamine oxidase inhibitors, beta-blockers, anticonvulsants (barbiturates, hydantoins and carbamazepine) and phenothiazines was also prohibited

Methods

- After a 2-week, single-blind, placebo run-in period, patients were randomised to one of five VI doses (3, 6.25, 12.5, 25 and 50mcg) or placebo once daily for 28 days (Figure 1).
- All study treatments were administered in a double-blinded manner once daily in the morning using a novel dual-strip dry powder inhalation device.
- Spirometry was assessed at visits 1 (screening), 2 (baseline), 3, 5, 6 and 7, peak expiratory flow was assessed twice daily every day, COPD symptoms were recorded using daily diary cards.
- The primary efficacy endpoint was the mean change from baseline (Day 1) in trough (pre-dose, pre-bronchodilator) FEV$_1$ on Day 29 (mean 23 and 24h post Day 28 dose).

Figure 1. Study design.



Trough FEV$_1$ at the 23rd and 24th h following dosing on visit 2 and visit 6 was measured at visit 3 and visit 7, respectively, when the patients returned to the clinic the following morning

RESULTS

- Of 851 patients who entered the 2-week run-in period, 602 were randomised and received at least one dose of study treatment (intent-to-treat [ITT] population). Demographics, baseline characteristics and screening pulmonary function were comparable (Table 2). Most patients were white males, mean age was 62 years, approximately 50% still smoked and 76% had a COPD diagnosis <10 years.

- Across the treatment groups, mean screening pre- and post-bronchodilator FEV$_1$ values ranged from 1.232 to 1.401L and 1.420 to 1.555L, respectively, and the mean % predicted post-bronchodilator FEV$_1$ from 49.9 to 51.5%. Mean % reversibility ranged from 12.8 to 18.1% and absolute reversibility from 154.1 to 187.5mL.

- Mean treatment compliance was ≥99% in all groups.

Table 2. Patient baseline characteristics and pulmonary function at screening (ITT population).

		VI					
	Placebo (n=101)	**3mcg (n=99)**	**6.25mcg (n=101)**	**12.5mcg (n=101)**	**25mcg (n=101)**	**50mcg (n=99)**	**Total (N=602)**
Demographics							
Male, n (%)	57 (56)	68 (69)	64 (63)	57 (56)	59 (58)	65 (66)	370 (61)
Age, years*	61.6±8.53	61.1±8.57	62.0±7.94	62.6±8.03	62.6±8.88	61.4±8.12	61.9±8.34
BMI,† kg/m^2*	28.51±6.03	27.62±7.12	27.23±6.69	27.44±6.83	28.01±6.87	27.27±6.72	27.68±6.71
Race, n (%)							
White	90 (89)	84 (85)	84 (83)	86 (85)	84 (83)	87 (88)	515 (86)

Asian	7 (7)	11 (11)	13 (13)	9 (9)	10 (10)	6 (6)	56 (9)
African-American	3 (3)	1 (1)	3 (3)	2 (2)	4 (4)	3 (3)	16 (3)
American Indian or Alaska Native	1 (<1)	3 (3)	1 (<1)	4 (4)	3 (3)	3 (3)	15 (2)
Tobacco history, n (%)							
Current smoker	46 (46)	50 (51)	48 (48)	52 (51)	45 (45)	44 (44)	285 (47)
Former smoker	55 (54)	49 (49)	53 (52)	49 (49)	56 (55)	55 (56)	317 (53)
Smoking pack-years*	47.7±28.25	52.4±32.43	49.6±29.66	49.2±28.66	49.5±29.12	43.1±20.58	48.6±28.38
COPD severity MMRC dyspnoea scale rating, n (%)							
1	9 (9)	7 (7)	7 (7)	8 (8)	8 (8)	12 (12)	51 (8)
2	37 (37)	43 (43)	48 (48)	37 (37)	32 (32)	39 (39)	236 (39)
3	34 (34)	30 (30)	25 (25)	39 (39)	42 (42)	30 (30)	200 (33)
4	17 (17)	18 (18)	14 (14)	13 (13)	19 (19)	18 (18)	99 (16)
5	4 (4)	1 (1)	7 (7)	4 (4)	0	0	16 (3)
Pulmonary function							
% predicted FEV1*	51.5±10.67	50.3±10.14	49.9±8.57	50.2±9.20	49.9±10.44	51.0±9.64	50.5±9.78
FEV1/FVC (%)*	52.5±8.66	51.4±10.17	49.9±8.33	51.0±9.12	50.1±10.34	52.6±9.58	51.2±9.41
% reversibility in FEV1*	16.5±15.08	15.1±13.01	12.8±10.86	15.8±14.81	18.1±16.45	13.3±14.78	15.3±14.34
Reversible, n (%)	39 (39)	36 (36)	34 (34)	34 (34)	37 (37)	34 (34)	214 (36)
ICS use at baseline, n (%)	33 (33)	33 (33)	36 (36)	30 (30)	23 (23)	30 (30)	185 (31)

*Values are mean ± SD; †BMI categories: underweight (<18.5kg/m^2); normal (18.5kg/m^2 to <25kg/m^2); overweight (25kg/m^2 to <30kg/m^2) and obese (≥30kg/m^2); BMI = body mass index; MMRC = Modified Medical Research Council

MMRC dyspnoea scale

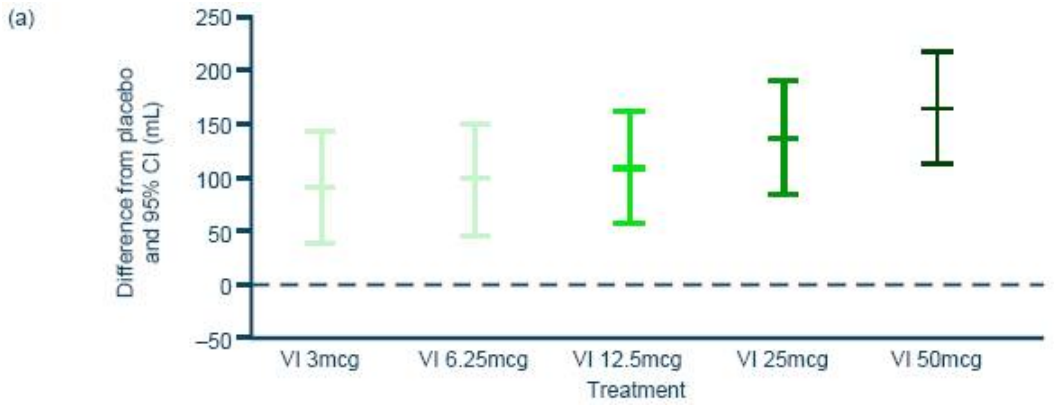
1. Not troubled by breathlessness except on strenuous exercise
2. Short of breath when hurrying or walking up a slight hill
3. Walks slower than contemporaries on the level because of breathlessness, or has to stop for breath when walking at own pace
4. Stops for breath after about 100m or after a few minutes on the level
5. Too breathless to leave the house, or breathless when dressing or undressing

Primary endpoint

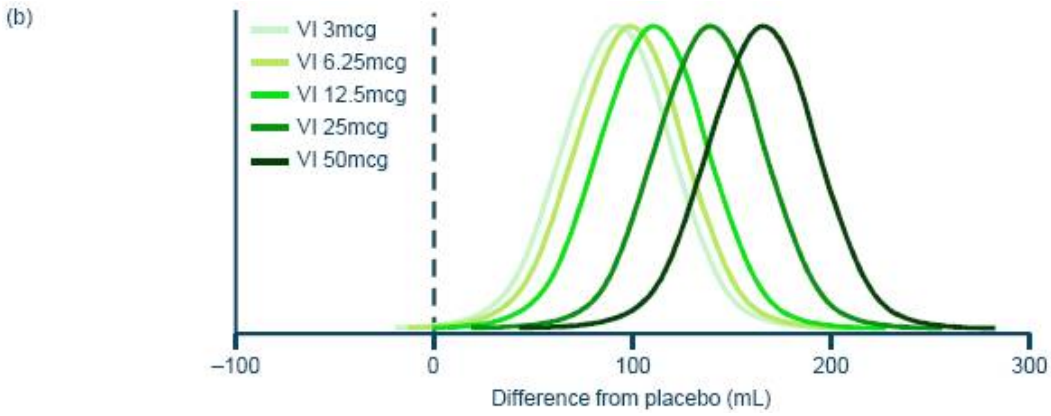
· Improvements in trough FEV_1 versus placebo on Day 29 were statistically significant ($p<0.001$) with all doses of VI (92, 98, 110, 137 and 165mL, for the 3, 6.25, 12.5, 25, 50mcg doses, respectively) (Figure 2a).

· Posterior probabilities for a true >100mL increase were >90% with both the 25mcg (92%) and 50mcg (99%) VI doses, but were lower for the 3mcg (37%), 6.25mcg (47%) and 12.5mcg (64%) doses; probabilities for a true >130mL increase were 90%, 61%, 22%, 11% and 7% with the 50, 25, 12.5, 6.25 and 3mcg doses, respectively (Figure 2b).

Figure 2. Adjusted mean change from placebo in trough FEV_1 at Day 29 (a) and posterior probability distribution of the treatment difference in change from baseline in trough FEV_1 on Day 29 (b).Error bars are 95% confidence intervals (CIs); ITT population.



Analyses were performed using analysis of covariance with covariates of baseline, sex, age, smoking status at screening, reversibility stratum and treatment



Bayesian analysis with non-informative prior distribution; Analyses were adjusted for baseline (pre-dose on Day 1), sex, age, smoking status at screening, reversibility stratum and treatment

Secondary endpoints

- On Days 1 and 28, there were significant ($p \leq 0.003$) dose-related increases from baseline in 0–24h weighted mean FEV_1 values for all VI doses versus placebo (Table 3)
  - clinically relevant differences of ≥100mL were observed on both days at all dose levels except for 3mcg on Day 1
  - differences of ≥130mL were observed on both days with the 25 and 50mcg doses, and on Day 28 with the 12.5mcg dose.

Table 3. Change from baseline 0–24h weighted mean FEV_1 on Days 1 and 28 (ITT population).

0-24h weighted mean FEV_1 (mL)	Placebo (n=101)	VI 3mcg (n=99)	VI 6.25mcg (n=101)	VI 12.5mcg (n=101)	VI 25mcg (n=101)	VI 50mcg (n=99)
Day 1						
n*	101	99	100	99	99	99
n†	100	97	100	99	99	97
LSM	1.283	1.340	1.387	1.404	1.434	1.458
LSM change±SE‡	0.028±0.0135	0.085±0.0137	0.132±0.0135	0.149±0.0136	0.178±0.0136	0.202±0.0137
Difference vs placebo	—	0.057	0.104	0.120	0.150	0.174
95% CI	—	0.019–0.095	0.066–0.141	0.083–0.158	0.112–0.188	0.136–0.212
p value	—	0.003	<0.001	<0.001	<0.001	<0.001
Day 28						
n*	101	99	100	99	99	99
n†	84	88	91	92	92	91
LSM	1.265	1.369	1.390	1.407	1.423	1.441
LSM change±SE‡	0.010±0.0189	0.114±0.0187	0.135±0.0185	0.152±0.0185	0.168±0.0185	0.186±0.0186
Difference vs placebo	—	0.105	0.125	0.142	0.158	0.177
95% CI	—	0.052–0.157	0.073–0.177	0.090–0.194	0.106–0.210	0.125–0.229
p value	—	<0.001	<0.001	<0.001	<0.001	<0.001

*Number of patients with analysable data on one or more days; †Number of patients with analysable data on the given day ‡SE for both LSM and LSM change; Note: analysis performed using repeated measures with covariates of baseline, sex, age, smoking status (at screening), reversibility stratum, Day (nominal), treatment and Day by treatment and Day by baseline interactions; LSM = least square mean; SE = standard error

- Time to achieve a ≥100mL increase in FEV_1 over the first 4h post-dose on Day 1 for each VI dose group was significantly ($p<0.001$) shorter than for placebo, and shortest in the 25 and 50mcg dose groups (median time 6min) (Table 4)
  - the time to achieve a ≥12% increase in FEV_1 over the first 4h post-dose on Day 1 for each VI dose group was also shorter versus placebo, supporting the time to achieve a ≥100mL increase findings.

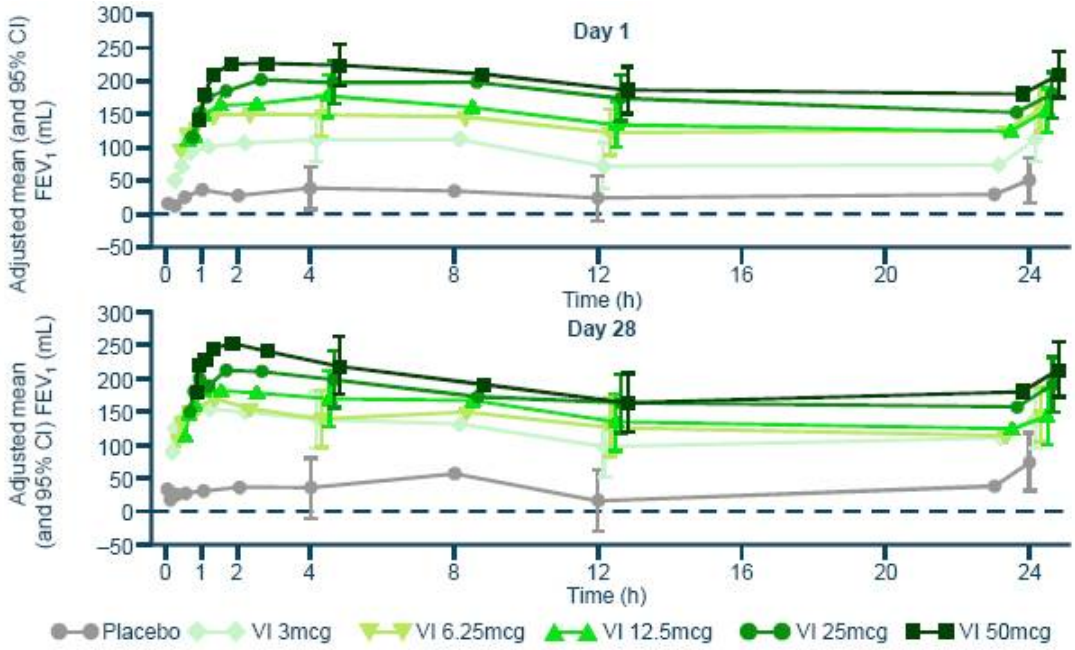
Table 4. Log-rank analyses of times for patients to achieve ≥100mL increase from baseline in FEV_1 (0–4h post-dose) (ITT population).*

Day 1 (0–4h post-dose)	Placebo (n=101)	VI 3mcg (n=99)	VI 6.25mcg (n=101)	VI 12.5mcg (n=101)	VI 25mcg (n=101)	VI 50mcg (n=99)
n	101	99	101	100	100	99
No. events	42 (42)	73 (74)	80 (79)	83 (83)	89 (89)	91 (92)
No. censored	59 (58)	26 (26)	21 (21)	17 (17)	11 (11)	8 (8)
Median time (min)	NA†	32	16	16	6	6
p value	—	<0.001	<0.001	<0.001	<0.001	<0.001

*Stratified by reversibility (reversible, non-reversible); †If >50% of patients were censored then median time to a 100mL increase in FEV_1 was not defined

- For serial FEV_1 measurements, adjusted mean changes from baseline FEV_1 over time on Days 1 and 28 show a dose-response effect, with a sustained duration of action over the 24h period (all doses of VI versus placebo; Figure 3).

Figure 3. Adjusted treatment differences from baseline in serial FEV_1 on Day 1 and Day 28; ITT population.



Analyses were performed using repeated measures with covariates of baseline, sex, age, smoking status at screening, reversibility stratum, time (nominal), treatment, time by treatment and time by baseline interactions. Note: FEV_1 is plotted at 5, 15 and 30min and 1, 2, 4, 8, 12, 23 and 24h post-dose. At each timepoint treatments are offset

CONCLUSION

- Once-daily administration of VI in patients with COPD provides clinically relevant 24h improvement in lung function with a rapid onset of effect, particularly with the 25mcg and 50mcg doses.

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