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 3, 2012**

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 3, 2012 at the European Respiratory Society (ERS) Annual Congress 2012 in Vienna, Austria, GlaxoSmithKline (GSK) presented posters containing information from Phase 2 and Phase 3 studies of the combination treatment fluticasone furoate/vilanterol (FF/VI) and its component, FF, and from the Phase 2b study of umeclidinium bromide (UMEC). FF/VI, with proposed brand names of Relvar™ and Breo™, is an investigational once-daily inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA) combination treatment for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD) and patients with asthma. UMEC, a long-acting muscarinic antagonist (LAMA), combined with VI, a LABA, is a once-daily investigational medicine for the maintenance treatment of patients with COPD. FF/VI and UMEC/VI are in development under the LABA collaboration agreement between GSK and the Theravance, Inc. (the "Company"). The Company also presented a poster containing information on a Phase 2a study of TD-4208, its internally-discovered investigational LAMA for the treatment of COPD. The posters are filed as Exhibits 99.1 to 99.16 to this report and are incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit	**Description**
Exhibit 99.1	Efficacy of the novel inhaled corticosteroid, fluticasone furoate (FF)/long-acting beta$_2$-agonist vilanterol (VI) combination in reducing COPD exacerbations

Exhibit 99.2	Safety of fluticasone furoate (FF), an inhaled corticosteroid in combination with vilanterol (VI), a long-acting beta agonist in management of COPD exacerbations
Exhibit 99.3	Lung function effects and safety of fluticasone furoate (FF)/vilanterol (VI) in patients with COPD: mid-high dose assessment
Exhibit 99.4	Efficacy of combination fluticasone furoate/vilanterol (FF/VI) and salmeterol/fluticasone propionate (SFC) over 12 weeks in patients with COPD
Exhibit 99.5	Effect of fluticasone furoate (FF)/vilanterol (VI) once daily on risk of severe exacerbations in asthma
Exhibit 99.6	Efficacy and safety of fluticasone furoate/vilanterol (FF/VI) once-daily for 24 weeks in persistent asthma
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Exhibit 99.9	Safety and tolerability of the novel inhaled corticosteroid (ICS) fluticasone furoate (FF) in combination with the long-acting $beta_2$ agonist (LABA) vilanterol (VI) administered once daily in patients with asthma
Exhibit 99.10	Efficacy and safety of once-daily fluticasone furoate (FF) in patients with persistent asthma: a 24-week randomised trial
Exhibit 99.11	The pharmacokinetics (PK) and pharmacodynamics (PD) of the fluticasone furoate (FF) and vilanterol (VI) combination in subjects with severe renal impairment
Exhibit 99.12	The pharmacokinetics (PK) and pharmacodynamics (PD) of the fluticasone furoate (FF) and vilanterol (VI) combination in subjects with hepatic impairment
Exhibit 99.13	The efficacy of inhaled fluticasone furoate (FF) and vilanterol (VI) administered in combination in asthma is comparable when administered in the morning or evening
Exhibit 99.14	Efficacy of fluticasone furoate (FF) and vilanterol (VI), separately and in combination (FF/VI), in an allergen challenge model
Exhibit 99.15	Umeclidinium (GSK573719) dose response and dosing interval in COPD
Exhibit 99.16	A Randomized, Crossover Study to Examine the Pharmacodynamics and Safety of a New Antimuscarinic TD-4208 in Patients with 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 4, 2012

By: /s/ **Michael W. Aguiar**

Michael W. Aguiar
Chief Financial Officer

EXHIBIT INDEX

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POSTER P2888

Efficacy of the novel inhaled corticosteroid, fluticasone furoate (FF)/long-acting beta$_2$-agonist vilanterol (VI) combination in reducing COPD exacerbations

Dransfield MT(1), Calverley PMA(2), Bourbeau J(3), Jones P(4), Hanania NA(5), Mahler DA(6), Vestbo J(7), Wachtel A(8), Martinez F(9), Barnhart F(10), Sanford L(11), Lettis S(11), Crim C(10)

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INTRODUCTION

- The combination of an inhaled corticosteroid (ICS) with a long-acting beta$_2$ agonist (LABA) is an established treatment option for COPD patients experiencing acute exacerbations.(1)
- Exacerbation frequency is a key target for preventive treatment in COPD. Exacerbations are associated with accelerated deterioration and are a stronger predictor of adverse outcomes than percent predicted lung function.(1)
- FF and VI are, respectively, a novel ICS and LABA in development as a once-daily combination therapy (FF/VI) for COPD and asthma.

OBJECTIVES

- To assess the impact of addition of FF to VI on COPD exacerbations over one year, in patients with moderate-to-severe COPD. Safety endpoints are described separately (poster no. P2113).

METHODS

- Two phase III, multi-centre, randomised, double-blind, parallel-group studies (HZC871 and HZC970) identical in design, conduct and analysis.
- Patients (post-bronchodilator FEV_1 $\leq$70%; FEV_1/FVC ratio $\leq$70%; smoking history $\geq$10 pack years, having had $\geq$1 documented COPD exacerbation in the year prior to screening) completed a 4-week run-in period during which they received fluticasone propionate (FP)/salmeterol 250/50mcg twice-daily via DISKUS®/ ACCUHALER™ to determine adherence.
- Patients were randomised to receive FF/VI (50/25, 100/25, 200/25mcg) or VI (25mcg) once daily in the morning via a novel dry powder inhaler for 52 weeks.

RESULTS

Study population and demographics

- Pooled patient demographics and baseline characteristics are provided in Table 1.
- 3255 patients were randomised and received at least one dose of study medication (ITT population); 2406 completed the studies.
- On-treatment withdrawal rates (FF/VI 50/25, 100/25, 200/25mcg, VI 25mcg) were, respectively: 25%, 25%, 25%, 29%.
- More patients in the VI group withdrew due to lack of efficacy, including exacerbations (VI 7% vs. FF/VI 3–4%).

Table 1. Patient demographics and baseline characteristics (pooled HZC871 & HZC970, ITT population)

	FF/VI 50/25mcg (N=820)	FF/VI 100/25mcg (N=806)	FF/VI 200/25mcg (N=811)	VI 25mcg (N=818)
Age, years	63.6 (9.31)	63.8 (9.17)	63.6 (9.07)	63.6 (9.36)
Female, n (%)	344 (42)	353 (44)	344 (42)	344 (42)
Post-bronchodilator FEV_1, L	1.29 (0.48)	1.30 (0.48)	1.27 (0.45)	1.28 (0.46)
% predicted post-bronchodilator FEV_1	45.4 (13.6)	46.0 (13.4)	45.2 (13.4)	45.2 (13.0)
% reversibility FEV_1	14.4 (15.4)	14.7 (15.5)	14.6 (18.5)	14.5 (16.6)
Exacerbation History (1yr prior to screening)				
$\geq$1 exacerbation requiring oral/systemic corticosteroids and/or antibiotics, n (%)	764 (93.2)	744 (92.3)	742 (91.5)	755 (92.3)
$\geq$1 exacerbation requiring hospitalisation, n (%)	173 (21.1)	169 (21.0)	174 (21.5)	146 (17.8)

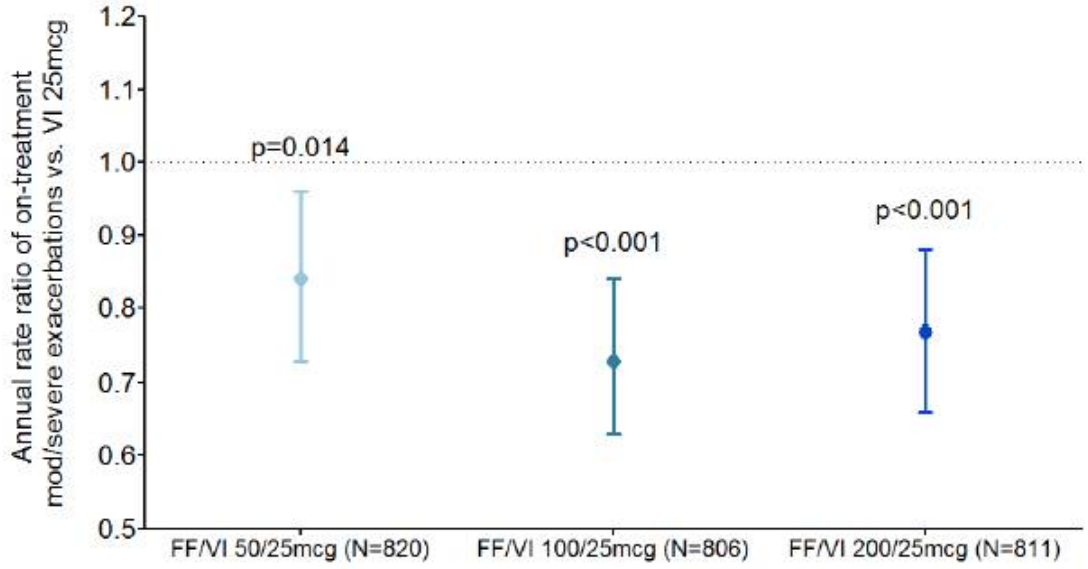
Values are mean (SD) unless otherwise stated; ITT=intent-to-treat

Efficacy

- Relative to VI 25mcg, significant reductions in annual rate of on-treatment moderate/severe exacerbations* (primary endpoint) were seen with all strengths of FF/VI (Fig. 1)
    - mean (95% CI) rate reductions were: 16% (4, 27), 27% (16, 37) and 23% (12, 34) for FF/VI 50/25, 100/25, 200/25mcg, respectively.
- FF/VI 100/25mcg and 200/25mcg significantly reduced the risk (hazard ratio [HR] 0.75–0.76, p<0.001) for time to first on-treatment moderate/severe exacerbation (secondary endpoint) relative to VI 25mcg, however FF/VI 50/25mcg did not (HR 0.89, p=0.114) (Fig. 2).
- Significant reductions relative to VI were observed in the annual rate of on-treatment exacerbations requiring systemic or oral corticosteroids (secondary endpoint): 17% (1, 29), p=0.033; 30% (17, 41), p<0.001; 27% (14, 38), p<0.001 for FF/VI 50/25, 100/25, 200/25mcg, respectively.

*Moderate exacerbation: worsening of COPD symptoms requiring treatment with oral corticosteroids or antibiotics; severe exacerbation: worsening of COPD symptoms requiring hospitalisation

Figure 1. Annual rate ratios of on-treatment moderate/severe COPD exacerbations (pooled HZC871 & HZC970, ITT population)



Data comparisons vs. VI 25mcg; ratios calculated against moderate/severe exacerbation rates observed with VI in pooled analysis

- Trough (pre-dose) FEV_1 at 52 weeks was significantly improved from baseline (secondary endpoint) relative to VI 25mcg: 38mL, 42mL, 46mL (p<0.001 for all comparisons) with FF/VI 50/25, 100/25, 200/25mcg, respectively (Fig. 3).

Figure 2. Kaplan-Meier plot of time to first on-treatment moderate/severe COPD exacerbation (pooled HZC871 & HZC970, ITT population)

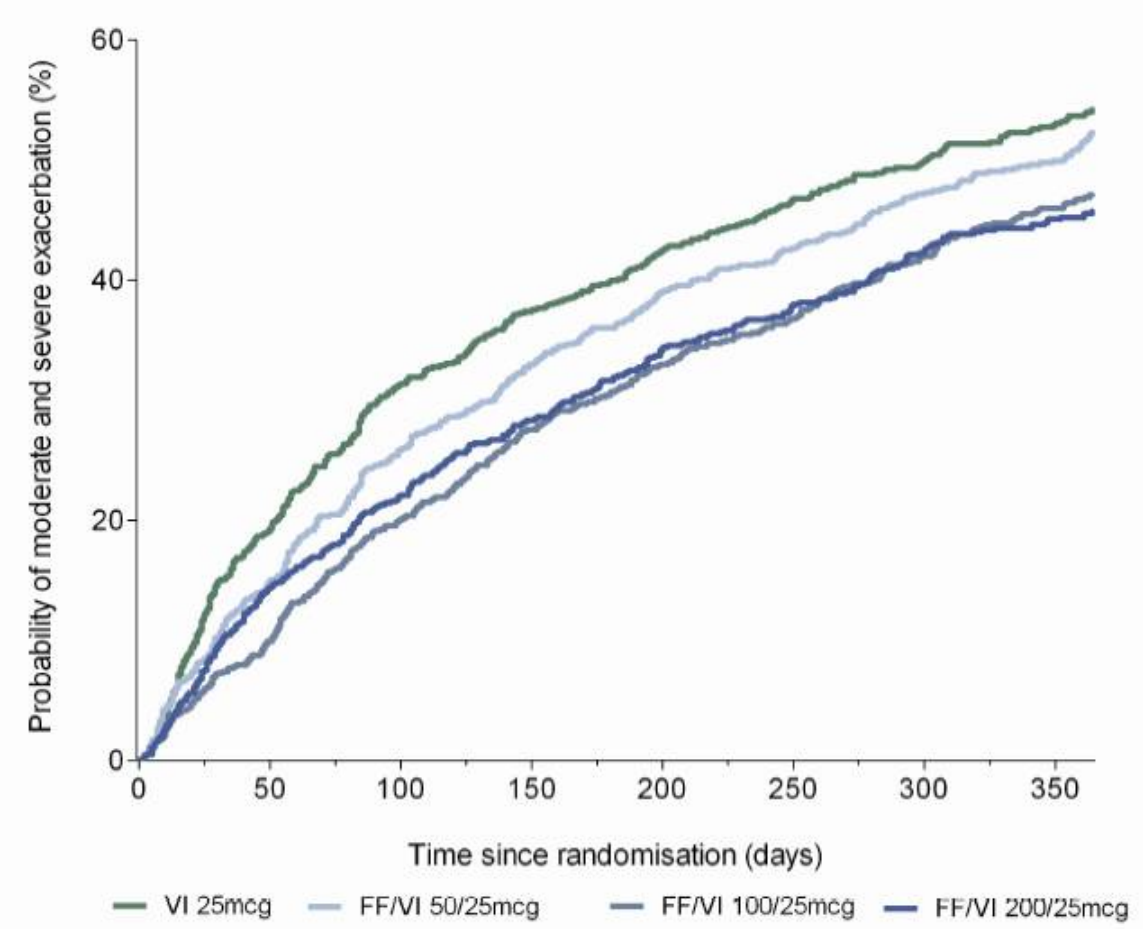
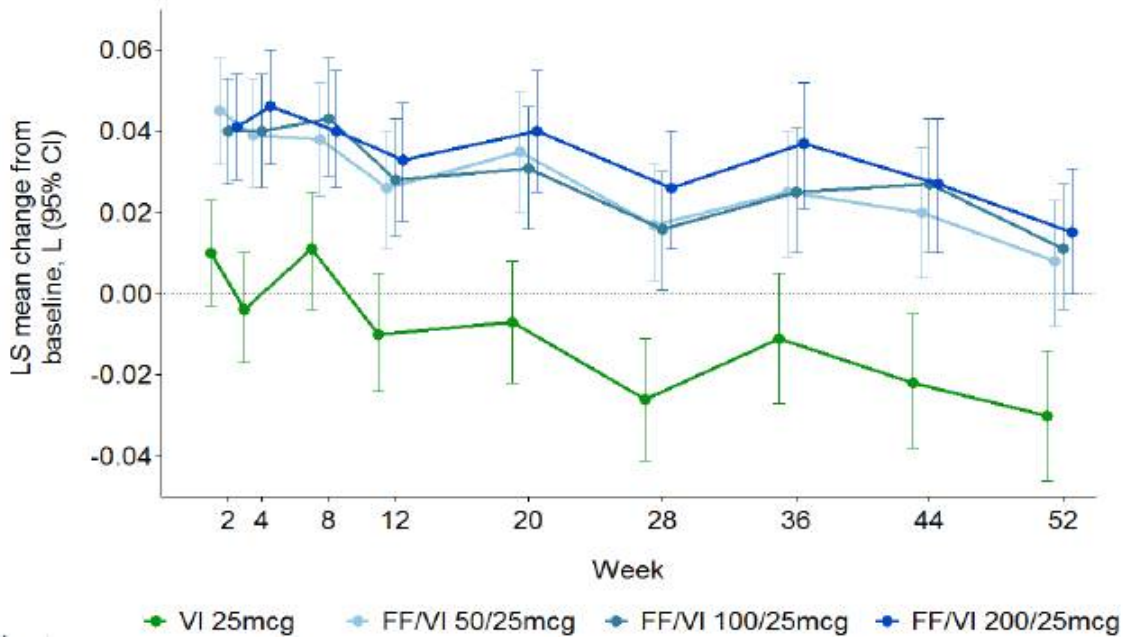


Figure 3. Least squares mean (95% CI) change from baseline in trough FEV_1 (pooled HZC871 & HZC970, ITT population)



LS=least squares; CI=confidence interval

CONCLUSIONS

- Addition of FF to VI significantly reduced the annual rate of moderate/severe exacerbations, annual rate of exacerbations requiring systemic/oral corticosteroids and, for the two higher strengths of FF/VI, the time to onset of first moderate/severe exacerbation. Additionally, a significant improvement in lung function was seen with FF/VI relative to VI.
- The 100/25mcg and 200/25mcg strengths of FF/VI conferred a consistent benefit over the study endpoints, whereas the 50/25mcg strength was not found to significantly delay time to first moderate/severe exacerbation.
- FF/VI has the potential to provide a once-daily preventive ICS/LABA option for COPD patients with a history of exacerbation.

REFERENCE

1. GOLD 2011. Available at: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011_ Feb21.pdf [Last accessed 13 July 2012].

ACKNOWLEDGEMENTS

· The presenting author, M Dransfield, declares the following real or perceived conflicts of interest during the last 3 years in relation to this presentation: grant support from the National Heart, Lung, and Blood Institute; industry sponsored contracts from Boehringer Ingelheim, Boston Scientific, GlaxoSmithKline and Otsuka; consultancy for GlaxoSmithKline.

· These studies were funded by GlaxoSmithKline; GSK Study Codes HZC102871 & HZC102970, Clinicaltrials.gov NCT01009463 & NCT01017952.

· Editorial support (in the form of writing assistance, assembling tables and figures, collating author comments, grammatical editing and referencing, was provided by Ian Grieve at Gardiner-Caldwell Communications; this support was funded by GlaxoSmithKline.

Presented at the European Respiratory Society Annual Congress 2012 Vienna, Austria, 1–5 September, 2012

POSTER P2113

Safety of fluticasone furoate (FF), an inhaled corticosteroid in combination with vilanterol (VI), a long-acting beta agonist in management of COPD exacerbations

Calverley PMA(1), Dransfield MT(2), Bourbeau J(3), Jones P(4), Hanania NA(5), Mahler DA(6), Vestbo J(7), Wachtel A(8), Martinez F(9), Barnhart F(10), Sanford L(11), Lettis S(11), Crim C(10)

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INTRODUCTION

- The combination of inhaled corticosteroids (ICS) with a long-acting $beta_2$ agonist (LABA) is an established treatment option for COPD patients who experience acute exacerbations.(1)
- FF and VI are, respectively, a novel ICS and LABA in development as a once-daily combination therapy (FF/VI) for COPD and asthma.
- Although the benefits of ICS in COPD are established, an association of ICS use with an increased risk of pneumonia(2) and bone disorders(3) has been reported.

OBJECTIVES

- To assess the safety and tolerability of three once-daily dosing regimens of FF/VI and one of VI in patients ≥40 years of age with moderate-to-severe COPD. Efficacy endpoints are described separately (poster no. P2888).

METHODS

- Two phase III, multi-centre, randomised, double-blind, parallel-group studies (HZC871 and HZC970) identical in design, conduct and analysis. Data from these studies were pooled.
- Patients (post-bronchodilator FEV_1 ≤70%; FEV_1/FVC ratio ≤70%; smoking history ≥10 pack years; having had ≥1 documented COPD exacerbation in the year prior to screening) completed a 4-week run-in period during which they received fluticasone propionate/salmeterol 250/50mcg twice daily via DISKUS™/ACCUHALER™ to determine adherence.
- Patients were randomised to receive one of the following, once daily in the morning via a novel dry powder inhaler for 52 weeks
  - FF/VI 50/25mcg
  - FF/VI 100/25mcg
  - FF/VI 200/25mcg
  - VI 25mcg.

RESULTS

Study population and demographics

- Pooled patient demographics and baseline characteristics are provided in Table 1.
- 3255 patients were randomised and received at least one dose of study medication (ITT population); 2406 completed the studies.

Table 1. Patient demographics and baseline characteristics (pooled HZC871 & HZC970, ITT population)

	FF/VI 50/25mcg (N=820)	FF/VI 100/25mcg (N=806)	FF/VI 200/25mcg (N=811)	VI 25mcg (N=818)
Age, years	63.6 (9.31)	63.8 (9.17)	63.6 (9.07)	63.6 (9.36)
Female, n (%)	344 (42)	353 (44)	344 (42)	344 (42)
Post-bronchodilator FEV_1 , L	1.29 (0.48)	1.30 (0.48)	1.27 (0.45)	1.28 (0.46)
% predicted post-bronchodilator FEV_1	45.4 (13.6)	46.0 (13.4)	45.2 (13.4)	45.2 (13.0)
% reversibility FEV_1	14.4 (15.4)	14.7 (15.5)	14.6 (18.5)	14.5 (16.6)
Exacerbation history (1yr prior to screening)				
≥1 exacerbation requiring oral/systemic corticosteroids and/or antibiotics, n (%)	764 (93.2)	744 (92.3)	742 (91.5)	755 (92.3)
≥1 exacerbation requiring hospitalisation, n (%)	173 (21.1)	169 (21.0)	174 (21.5)	146 (17.8)

Values are mean (SD) unless otherwise stated; ITT = intent-to-treat

- On-treatment withdrawal rates (FF/VI 50/25, 100/25, 200/25mcg, VI 25mcg) were, respectively: 25%, 25%, 25%, 29%. The incidence of withdrawal due to adverse events (AEs) was 7–8% in the FF/VI groups and 6% in the VI group.

Safety

- The most common on-treatment AEs were nasopharyngitis (14–19%), candidiasis (7–13%) and upper respiratory tract infection (9–11%) (Table 2).
- More patients receiving FF/VI (17–21%) than VI (14%) experienced AEs that were deemed treatment related by the investigator.
- Percent of patients with events in the Cardiac disorders system order class: VI 6%, FF/VI arms 4–5%.
- No fatal AEs were considered by the investigator to be treatment related.
- The incidence of local steroid effects and bone disorders, including fractures, was higher in patients receiving FF/VI than VI (Table 3). Bone fractures were the majority of events in the bone disorders category. The incidence of bone fractures overall was low in all treatment groups, with a higher incidence in all FF/VI groups (2%) compared with the VI 25mcg group (<1%)
    - the proportion of traumatic fractures was 75%, 73%, 68% and 38%, respectively for VI 25mcg, FF/VI 50/25, 100/25 and 200/25mcg. Fractures customarily associated with corticosteroid use (e.g. spinal compression/thoracolumbar vertebral fractures, hip and acetabular fractures) occurred in <1% across all treatment arms.

Table 2. Summary of AEs (pooled HZC871 & HZC970, ITT population)

	FF/VI 50/25mcg (N=820)	FF/VI 100/25mcg (N=806)	FF/VI 200/25mcg (N=811)	VI 25mcg (N=818)
AE overview				
On-treatment AEs	620 (76)	621 (77)	622 (77)	575 (70)
Treatment-related	169 (21)	134 (17)	140 (17)	113 (14)
On-treatment serious AEs	136 (17)	123 (15)	124 (15)	126 (15)
Any fatal AEs(a)	16 (2)	10 (1)	14 (2)	13 (2)
On-treatment	14 (2)	8 (<1)	13 (2)	8 (<1)
Post-treatment	3 (<1)	3 (<1)	2 (<1)	5 (<1)
On-treatment AEs occurring in ≥5% patients/treatment group				
Nasopharyngitis	112 (14)	128 (16)	158 (19)	112 (14)
Candidiasis(b)	110 (13)	87 (11)	88 (11)	55 (7)
Upper respiratory tract infection	84 (10)	90 (11)	75 (9)	78 (10)
Headache	61 (7)	57 (7)	67 (8)	60 (7)
COPD	53 (6)	56 (7)	53 (7)	53 (6)
Back pain	40 (5)	54 (7)	37 (5)	53 (6)
Pneumonia (preferred term)	46 (6)	49 (6)	45 (6)	23 (3)
Bronchitis	41 (5)	38 (5)	47 (6)	42 (5)
Sinusitis	47 (6)	42 (5)	40 (5)	36 (4)
Oropharyngeal pain	30 (4)	31 (4)	39 (5)	31 (4)

Values are n (%) unless otherwise stated;

(a)3 patients had an event whilst on-treatment and an event post-treatment, both of which were recorded as leading to death; (b)candidiasis, oral candidiasis, oropharyngeal candidiasis and oesophageal candidiasis

Table 3. AE groupings of pre-defined special interest (pooled HZC871 & HZC970, ITT population)

	FF/VI 50/25mcg (N=820)	FF/VI 100/25mcg (N=806)	FF/VI 200/25mcg (N=811)	VI 25mcg (N=818)
Local steroid effects	142 (17)	121 (15)	140 (17)	96 (12)
Lower respiratory tract infections excl. pneumonia	57 (7)	60 (7)	63 (8)	64 (8)
Pneumonia, all recorded	48 (6)	51 (6)	55 (7)	27 (3)
Hazard ratio (95% CI) for time to 1st pneumonia vs. VI(a)	0.58 (0.36, 0.93)	0.54 (0.34, 0.85)	0.50 (0.31, 0.79)	—
Fatal pneumonia	0	1 (<1)	6 (<1)	0
Hypersensitivity	38 (5)	37 (5)	29 (4)	26 (3)
Bone disorders	24 (3)	27 (3)	21 (3)	9 (1)
Effects on glucose	18 (2)	15 (2)	22 (3)	14 (2)

(a) A hazard ratio less than unity favours VI

Safety (continued)

- Pneumonia occurred approximately twice as often in the FF/VI groups than in the VI group (Table 3).

- There were six cases of fatal pneumonia and one case of fatal COPD exacerbation with concurrent pneumonia in the FF/VI 200/25mcg group, all of which occurred in the HZC871 study and the majority of these cases were reported from one site; one case of fatal pneumonia occurred in the FF/VI 100/25 group of the HZC970 study

    - the number of fatal cases was too small to allow investigation of risk factors for fatal pneumonia.

- No clinically relevant changes in clinical chemistry or haematology values, or in ECG-measured heart rate or QTcF, were observed.

CONCLUSIONS

- The use of FF/VI was associated with the expected increase in known steroid-associated AEs and bone disorders; correspondingly, the incidence of AEs and treatment-related AEs was higher in patients receiving FF/VI than VI.

- Overall rates of serious and fatal AEs were similar across the four treatment groups.

- The increase in risk of pneumonia with FF is consistent with the findings of previous studies of ICS in COPD.(2)

REFERENCES

(1) GOLD 2011. Available at: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011_ Feb21.pdf [Last accessed 26 June 2012].
(2) Crim, C et al. *Eur Respir J* 2009;34:641–647.
(3) Loke YC, et al. *Thorax* 2011;66:699-708

ACKNOWLEDGEMENTS

- The presenting author, PMA Calverley, declares the following real or perceived conflicts of interest during the last 3 years in relation to this presentation: received funds for advising the sponsors of this study on its conduct and analysis; performed similar functions with other pharmaceutical companies including AstraZeneca, Boehringer Ingelheim, Novartis, Nycomed and Takeda.

- These studies were funded by GlaxoSmithKline; GSK Study Codes HZC102871 & HZC102970, Clinicaltrials.gov NCT01009463 & NCT01017952.

- Editorial support (in the form of writing assistance, assembling tables and figures, collating author comments, grammatical editing and referencing) was provided by Ian Grieve at Gardiner-Caldwell Communications and was funded by GlaxoSmithKline.

Presented at the European Respiratory Society Annual Congress 2012 Vienna, Austria, 1–5 September, 2012

POSTER P2887

Lung function effects and safety of fluticasone furoate (FF)/vilanterol (VI) in patients with COPD: mid-high dose assessment

Martinez F(1), Boscia J(2), Feldman G(3), Scott-Wilson C(4), Kilbride S(5), Fabbri L(6), Calverley PMA(7), Crim C(4)

(1)University of Michigan, Ann Arbor, MI, USA; (2)CU Pharmaceutical Research, Union, SC, USA; (3)S. Carolina Pharmaceutical Research, Spartanburg, SC, USA; (4)GlaxoSmithKline, Research Triangle Park, NC, USA; (5)GlaxoSmithKline, London, UK; (6)University of Modena and Reggio Emilia Modena, Modena, Italy; (7)University of Liverpool, Liverpool, UK

INTRODUCTION

- There is increasing interest in once-daily dosing for respiratory medications; current inhaled corticosteroid (ICS)/long-acting beta$_2$ agonist (LABA) combinations require twice-daily dosing, which may result in lower adherence and greater COPD costs.(1)
- FF/VI is a novel combination ICS/LABA that has been assessed in COPD at various strengths in small-scale studies.(2),(3)

OBJECTIVES

- To compare the efficacy and safety of two mid-to-high strengths of FF/VI with its constituent components, FF and VI, and placebo in patients with moderate-to-severe COPD.

METHODS

- Multi-centre, randomised, stratified (smoking status), placebo-controlled, double-blind, parallel-group study.
- Patients: age ≥40 years; history of moderate-to-severe COPD; smoking history ≥10 pack-years; post-bronchodilator (postBD) forced expiratory volume in 1s (FEV_1)/forced vital capacity (FVC) ratio ≤0.70; postBD FEV_1 ≤0.70 predicted; score of ≥2 on the Modified Medical Research Council Dyspnoea Scale (mMRC).
- Following a 2-week single-blind placebo run-in, patients were randomised in a 1:1:1:1:1:1 ratio to receive one of six treatments taken once daily in the morning via novel dry powder inhaler for 24 weeks: FF 100mcg, FF 200mcg, VI 25mcg, FF/VI 100/25mcg, FF/VI 200/25mcg, or placebo
- Salbutamol (as needed) and ipratropium bromide alone (stable dose) were permitted for symptom relief during run-in and treatment periods.

RESULTS

Study population and demographics

- Of 1909 patients screened, 1224 formed the intent-to-treat (ITT) population, 924 of whom completed the study.
- Patient characteristics at baseline are outlined in Table 1.
- Patient-reported medication use prior to screening: short-acting beta$_2$-agonists 62%, short-acting anticholinergics 34%, LABA 35%, ICS 24%.

Table 1. Descriptive characteristics of the study group (ITT population)

	Placebo N=205	FF 100mcg N=204	FF 200mcg N=203	VI 25mcg N=203	FF/VI 100/25mcg N=204	FF/VI 200/25mcg N=205
Demographics						
Age, yr	61.9 (8.14)	61.8 (8.28)	61.8 (9.02)	61.2 (8.62)	61.9 (8.79)	61.1 (8.67)
Male, %	74	74	74	74	71	67
BMI, kg/m(2)	26.9 (5.36)	27.1 (5.71)	26.7 (6.35)	26.2 (5.21)	26.2 (5.12)	25.9 (4.86)
Current/former smoker, %	53/47	56/44	55/45	55/45	53/47	55/45
Physiology						
FEV_1 (L; preBD)	1.35 (0.45)	1.41 (0.48)	1.30 (0.49)	1.37 (0.48)	1.36 (0.52)	1.33 (0.50)
FEV_1 (% pred; preBD)	43.5 (13.0)	44.6 (13.0)	42.7 (12.7)	43.7 (12.9)	43.8 (13.8)	43.0 (13.0)
FEV_1 (L; postBD)	1.50 (0.47)	1.53 (0.48)	1.44 (0.47)	1.52 (0.47)	1.49 (0.51)	1.46 (0.51)
FEV_1 (% pred; postBD)	48.3 (12.7)	48.4 (12.2)	47.1 (12.0)	48.5 (12.9)	48.1 (12.9)	47.1 (12.8)
FEV_1/FVC (%; postBD)	46.1 (11.3)	47.2 (11.3)	46.6 (10.7)	47.7 (11.1)	47.4 (11.3)	45.9 (11.5)
FEV_1 reversibility (%)	12.9 (13.3)	11.3 (15.5)	12.4 (14.2)	12.7 (16.0)	12.5 (16.2)	10.3 (13.8)
mMRC: Score	2.4 (0.6)	2.4 (0.5)	2.4 (0.5)	2.4 (0.5)	2.4 (0.5)	2.4 (0.5)

Values are mean (SD) unless otherwise stated
SD=standard deviation; BMI=body mass index; preBD=pre-bronchodilator; pred=predicted; postBD=post-bronchodilator; mMRC=Modified Medical Research Council Dyspnoea Scale

Efficacy: Co-Primary

- Weighted mean (wm; 0–4h post-dose, Day 168) and change from baseline in trough (23–24h post-dose, Day 169) FEV_1 improved with all active therapies (Fig. 1a and b)
    - wm and trough FEV_1 significantly improved for VI 25mcg and FF/VI 200/25mcg vs. placebo; wm FEV_1 significantly improved for FF/VI 200/25mcg vs. FF 200mcg; trough FEV_1 was not significantly different for FF/VI 200/25mcg vs. VI 25mcg (Table 2)
    - Significance for other comparisons could not be inferred due to the hierarchy employed in the statistical analysis.

Table 2. Primary and secondary study endpoint comparisons(a) (ITT population)

Comparisons	wmFEV_1 (0–4h) Day 168	Trough FEV_1 Day 169	CRQ-SAS Dyspnea Day 168(b)	Peak FEV_1 Day 1
VI vs. PBO	**0.185***	**0.100***	0.07	0.147
	(0.133, 0.237)	**(0.048, 0.151)**	(-0.14, 0.28)	(0.117, 0.177)
FF/VI 200/25 vs. PBO	**0.209***	**0.131***	0.1	0.141
	(0.157, 0.261)	**(0.080, 0.183)**	(-0.12, 0.31)	(0.111, 0.171)
FF/VI 200/25 vs. VI 25	0.024	0.032	0.03	-0.006
	(-0.027, 0.075)	(-0.019, 0.083)	(-0.18, 0.23)	(-0.036, 0.024)
FF 200/25 vs. FF 200	**0.168***	0.123	0.1	0.134
	(0.117, 0.219)	(0.072, 0.174)	(-0.11, 0.31)	(0.104, 0.164)
FF 200 vs. PBO	0.041	0.008	-0.01	0.007
	(-0.011, 0.093)	(-0.044, 0.060)	(-0.22, 0.21)	(-0.023, 0.037)
FF/VI 100/25 vs. PBO	0.214	0.144	0.24	0.152
	(0.161, 0.266)	(0.091, 0.197)	(0.02, 0.46)	(0.122, 0.182)
FF/VI 100/25 vs. VI 25	0.029	0.045	0.17	0.005
	(-0.023, 0.081)	(-0.008, 0.097)	(-0.04, 0.38)	(-0.025, 0.036)
FF 100/25 vs. FF 100	0.168	0.100	0.36	0.128
	(0.116, 0.220)	(0.047, 0.152)	(0.14, 0.57)	(0.098, 0.158)
FF 100 vs. PBO	0.046	0.044	-0.12	0.024
	(-0.006, 0.098)	(-0.008, 0.097)	(-0.33, 0.10)	(-0.006, 0.055)

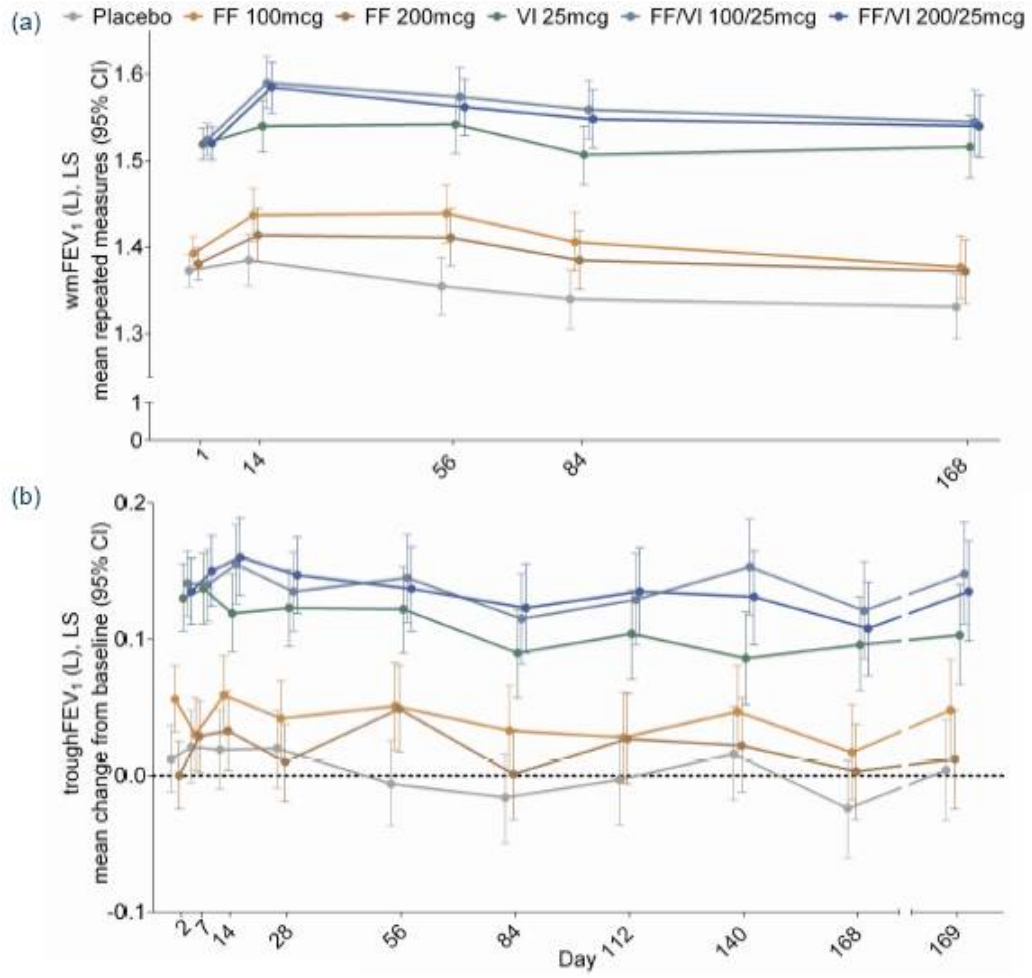
Values are differences in least square mean (95% CI);

*significant difference ($p<0.001$). (a)Log rank analysis was used to analyse the secondary endpoint of time to 100mL improvement on Day 1. Inference from the associated p-values could not be drawn due to the testing hierarchy employed; b = for regulatory purposes in the USA, CRQ-SAS is considered an 'other' endpoint.

Efficacy: Secondary

- Chronic Respiratory Questionnaire Self-Administered Standardized (CRQ-SAS) dyspnoea domain scores improved numerically for all comparisons except FF (either strength) vs. placebo; no comparisons achieved minimally clinically important difference (Table 2).
- Peak FEV_1 (0–4h) on Day 1 numerically improved for all comparisons except FF/VI 200/25 vs. VI 25 (Table 2).
- Median (actual) time to onset (increase of 100mL above baseline in FEV_1) on Day 1 was 16–17 min in the FF/VI and VI treatment groups, 231 and 242 min in the FF 200 and 100 groups, respectively and not determinable in the placebo group.

Figure 1. Lung function data over time for wmFEV_1 (a) and trough FEV_1 (b) (ITT population)



LS=least squares; CI=confidence interval

Safety

- Incidence of adverse events AEs and serious AEs (SAEs), were similar with active therapy vs. placebo (Table 3).
- Pneumonia events were low, ≤2% of subjects in FF-containing arms, <1% with VI 25 and 0 with placebo. No events were fatal.

- 6 deaths were reported during the study; 5 on-treatment (1 each in the placebo, FF/VI 100/25 and 200/25 groups and 2 in the VI 25 group. None were considered treatment-related.
- Exacerbations occurred more frequently in the placebo arm (10%) vs. treatment arms (2–9%), and for VI (9%) vs. FF (2–5%).
- There were no clinically relevant abnormalities in clinical chemistry/haematology parameters, vital signs, 12-lead ECG and 24 h Holter monitoring.
- Assessment of 24 h urinary cortisol showed no clinically relevant or statistically significant effect of any treatment.

Table 3. Overview of AEs and SAEs (ITT population)

n (%)	Placebo N=205	FF 100mcg N=204	FF 200mcg N=203	VI 25mcg N=203	FF/VI 100/25mcg N=204	FF/VI 200/25mcg N=205
Any on-treatment AEs	96 (47)	78 (38)	96 (47)	85 (42)	92 (45)	93 (45)
Nasopharyngitis	17 (8)	14 (7)	20 (10)	19 (9)	13 (6)	13 (6)
Headache	15 (7)	13 (6)	11 (5)	20 (10)	11 (5)	15 (7)
Any on-treatment treatment-related AEs	20 (10)	13 (6)	27 (13)	13 (6)	21 (10)	18 (9)
Infections and infestations (SOC)	6 (3)	7 (3)	14 (7)	3 (1)	13 (6)	10 (5)
Oral candidiasis*	2 (<1)	5 (2)	4 (2)	2 (<1)	8 (4)	3 (1)
Oropharyngeal candidiasis*	3 (1)	0	5 (2)	1 (<1)	2 (<1)	3 (1)
AEs leading to permanent discontinuation or withdrawal	23 (11)	14 (7)	15 (7)	14 (7)	20 (10)	23 (11)
Any on-treatment SAEs	10 (5)	6 (3)	10 (5)	16 (8)	12 (6)	15 (7)

On-treatment and drug-related AEs occurring in ≥5% of patients in any treatment group are presented.
SOC=System Organ Class;* mutually exclusive coding

CONCLUSIONS

- The addition of the LABA VI to FF resulted in a rapid and sustained improvement in FEV_1 in COPD patients with moderate-to-severe airflow obstruction.

- Once-daily FF/VI exhibited a tolerability profile that did not differ markedly from its individual components.

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POSTER P2889

Efficacy of combination fluticasone furoate/vilanterol (FF/VI) and salmeterol/fluticasone propionate (SFC) over 12 weeks in patients with COPD

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INTRODUCTION

- Currently available inhaled corticosteroid (ICS)/long-acting beta$_2$ agonist (LABA) combinations require twice-daily dosing.
- Fluticasone furoate/vilanterol (FF/VI) is a new once-daily ICS/LABA.
- This is the first study to compare FF/VI with an established twice-daily ICS/LABA, fluticasone propionate (FP) and salmeterol (SAL) combination (SFC) in COPD.

OBJECTIVES

- To compare the efficacy and safety profiles of once-daily FF/VI and twice-daily SFC in patients with moderate-to-severe COPD.

METHODS

- Randomised, multi-centre, double-blind, double-dummy, parallel-group, comparative efficacy study.
- Patients: ≥40 years of age with a clinical history compatible with COPD; diagnostic confirmation by post-bronchodilator FEV_1/FVC ratio of ≤0.70; FEV_1 ≤70% predicted; smoking history of ≥10 pack-years; moderate and/or severe COPD exacerbation within the last 3 years.
- A sample size of 212 patients per group provided 90% power to detect a 60 mL difference between FF/VI and SFC in 24 h weighted mean (wm) FEV_1 on Day 85 (primary endpoint)
  - median time-to-onset, defined as 100 mL FEV_1 improvement over baseline on Day 1 and change from baseline in trough (pre-dose) FEV_1 on Day 85 were secondary endpoints
  - the COPD-specific St George's Respiratory Questionnaire (SGRQ Total) score and rescue-free 24 h periods were other endpoints.
- Following a 2-week single blind placebo run-in, patients were randomised in a 1:1 ratio to receive the following study medication for 12 weeks
  - FF/VI 100/25mcg once daily in the morning via novel dry powder inhaler (nDPI) plus placebo twice daily (AM/PM) via DISKUS™/ACCUHALER™
  - SFC 50/500mcg twice daily (morning/evening) via DISKUS™/ACCUHALER™ plus placebo once daily in the evening via nDPI.
- Salbutamol was supplied to patients for symptomatic relief during run-in and treatment periods.

RESULTS

Study population and demographics

- Baseline characteristics of study participants are outlined in Table 1.
- Of 528 patients randomised (intent-to-treat [ITT] population), 489 completed the study.
- Withdrawal rates were higher for FF/VI (9%) than for SFC (6%)
  - most frequent reasons were protocol deviations (FF/VI 3%, SFC 2%) and adverse events (AEs; FF/VI 2%, SFC 1%).

Table 1. Patient demographics and baseline characteristics (ITT population)

	FF/VI 100/25mcg OD N=266	SFC 50/500mcg BD N=262
Demographics		
Age, years	63.0 (8.10)	62.9 (9.07)
Male, n (%)	212 (80)	221 (84)
Race, n (%)		
White	218 (82)	208 (79)
Asian	48 (18)	53 (20)
BMI, kg/m(2)	26.2 (5.67)	25.6 (4.94)

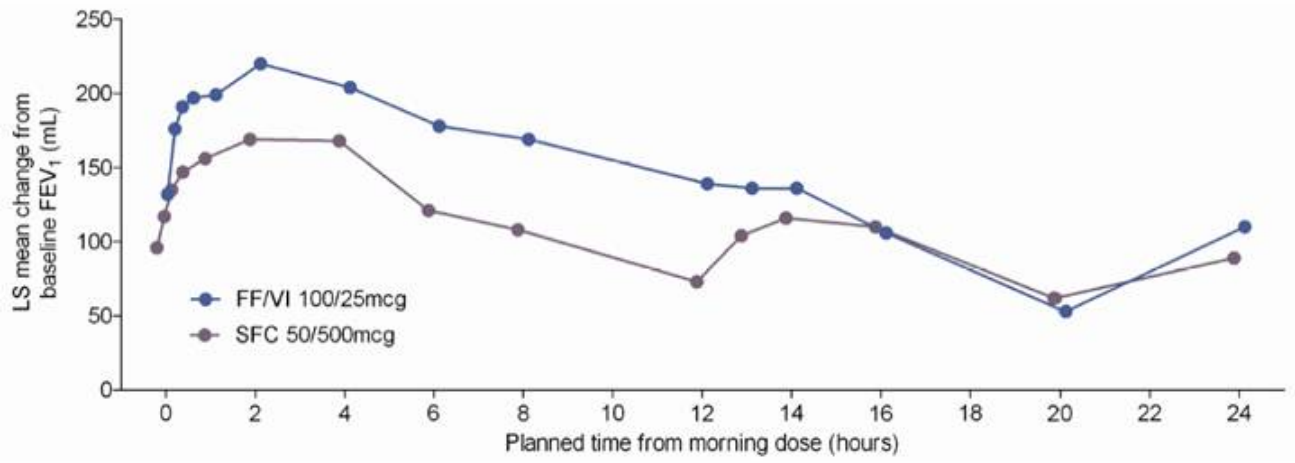
Baseline lung function		
Post-BD FEV_1, L	1.28 (0.427)	1.30 (0.447)
Percent predicted FEV_1, %	43 (11.9)	43 (12.4)

Values are mean (SD) unless otherwise stated; OD=once daily; BD=twice daily

Efficacy

- There was a non-significant trend favouring FF/VI (130mL) vs. SFC (108mL) for weighted mean FEV_1 after 12 weeks (D22mL [95% CI: –18, 63], p=0.282); the 24 h time course is illustrated in Fig. 1.
- Median time to 100mL improvement from baseline was 16 min for FF/VI and 28 min for SFC (p=0.280).
- Mean change from baseline in trough FEV_1 on Day 85 was 111mL for FF/VI and 88mL for SFC (D23mL [95% CI: –20, 66], p=0.294).
- A clinically meaningful improvement in SGRQ Total score was seen with FF/VI, but did not differ significantly from SFC (mean change –4.31 vs. –2.96, p=0.215).
- Rescue-free 24 h periods were similar during Week 1 (FF/VI 61.6%, SFC 58.5%) and across Weeks 1–12 (FF/VI 62.5%, SFC 59.8%).

Figure 1. 0–24h LS mean change from baseline (mL) on day 84 (ITT population)



FEV_1 measurements were collected at 5, 15, 30 and 60 min, and 2, 4, 6, 8, 12, 13, 14, 16, 20 and 24 h on Day 84; LS=least squares

Safety

- On-treatment AEs are summarised in Table 2.
- On-treatment AEs, treatment-related AEs and serious AEs (SAEs) were similar for FF/VI and SFC
  - no SAEs were considered treatment related by the investigator
  - there were no fatal on-treatment AEs; one fatal event during the post-treatment period (congestive heart failure) was not considered treatment related.
- Cardiovascular AEs were more frequent in the FF/VI group; local steroid effects were more frequent in the SFC group.

Table 2. Summary of on-treatment AEs by treatment group (ITT population)

n (%)	FF/VI 100/25mcg OD N=266	SFC 50/500mcg BD N=262
On-treatment AEs (≥5%)		
Any AE	73 (27)	68 (26)
Headache	20 (8)	18 (7)
Nasopharyngitis	8 (3)	12 (5)

- Exacerbation frequency: FF/VI 2%, SFC 3%; all exacerbations resolved during the study period.
- There were few reports of pneumonia in both treatment groups (FF/VI: 1 patient, SFC: 2 patients).
- There were no apparent treatment-related changes in clinical laboratory parameters, ECGs or vital signs.

CONCLUSION

- Once-daily FF/VI and twice-daily SFC improved lung function and health status similarly in patients with moderate-to-severe COPD without substantial safety concerns.

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POSTER P1788

Effect of fluticasone furoate (FF)/vilanterol (VI) once daily on risk of severe exacerbations in asthma

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INTRODUCTION

- The addition of LABA to ICS in twice-daily combination regimens has been shown to significantly improve pulmonary function and reduce the risk of exacerbations relative to ICS alone.(1),(2)
- FF and VI are, respectively, a novel ICS and LABA in development for once-daily combination therapy in asthma and COPD.

OBJECTIVES

- To assess the risk of severe asthma exacerbations with once-daily FF/VI 100/25mcg compared with once-daily FF 100mcg in patients ≥12 years of age with asthma uncontrolled on ICS.

METHODS

- Phase III, randomised, multi-centre, double-blind, parallel-group study of variable duration (≥24–76 weeks).
- End of study was when 330 patients experienced an on-treatment severe asthma exacerbation
  - a deterioration of asthma requiring use of systemic corticosteroids for ≥3 days or inpatient hospitalisation or emergency room visit due to asthma, with use of systemic corticosteroids.(3)
- Eligible patients had history of asthma for ≥1yr prior to screening and ≥1 asthma exacerbation requiring systemic corticosteroids and/or hospital/emergency room visit in the previous year.
- Patients received one of the following treatments for a minimum of 24 weeks up to 76 weeks after a 2-week run-in period
  - FF/VI 100/25mcg once daily in the evening via novel dry powder inhaler (nDPI)
  - FF 100mcg once-daily in the evening via nDPI.
- An interim analysis for safety and efficacy was carried out by an independent data monitoring committee, after around half of the designated number of patients experienced an on-treatment severe asthma exacerbation.

RESULTS

Study population and demographics (Table 1)

- Of 2668 patients screened, 2020 were randomised, 2019 received at least one dose of study medication (intent-to-treat [ITT] population) and 1748 completed the study (FF/VI: 88%; FF: 85%).

Table 1. Patient demographics and baseline characteristics (ITT population)

	FF/VI 100/25mcg (N=1009)	FF 100mcg (N=1010)	Total (N=2019)
Age, years	41.1 (17.10)	42.3 (16.82)	41.7 (16.96)
Female sex, n (%)	661 (66)	689 (68)	1350 (67)
Screening pre-bronchodilator FEV_1, L	2.144 (0.6091)	2.101 (0.6090)	2.108 (0.6090)
Screening % predicted FEV_1	68.8 (10.62)	69.0 (10.41)	68.9 (10.52)
Screening % reversibility FEV_1	24.4 (12.71)	24.3 (12.10)	24.4 (12.41)

Values are mean (SD) unless otherwise stated

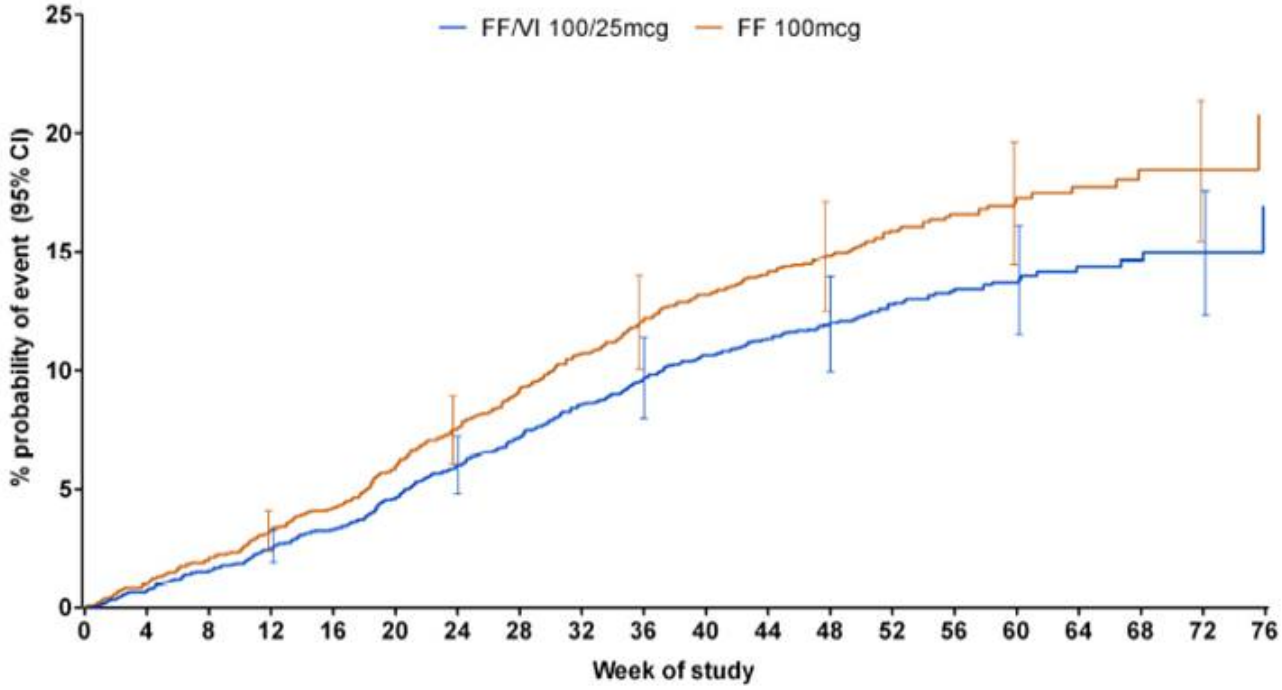
- 583 (58%) of patients in the FF/VI group and 567 (56%) in the FF group received study treatment for ≥52 weeks.

Efficacy

- The time to first severe asthma exacerbation (primary endpoint) was significantly delayed with FF/VI vs. FF (hazard ratio [HR] 0.795 [95% CI: 0.642, 0.985]; interim adjusted p=0.036); a 20% risk reduction (Fig. 1).

- Annualised rate of severe asthma exacerbations (secondary endpoint) was significantly lower with FF/VI (0.14/yr) vs. FF (0.19/yr) (p=0.014); a 25% (95% CI: 5, 40) rate reduction.

Figure 1. Time to first severe asthma exacerbation, cumulative incidence (ITT population)



CI = confidence interval

Note: Cox Proportional Hazards Model with covariates of baseline disease severity (baseline FEV_1), sex, age, region, and treatment

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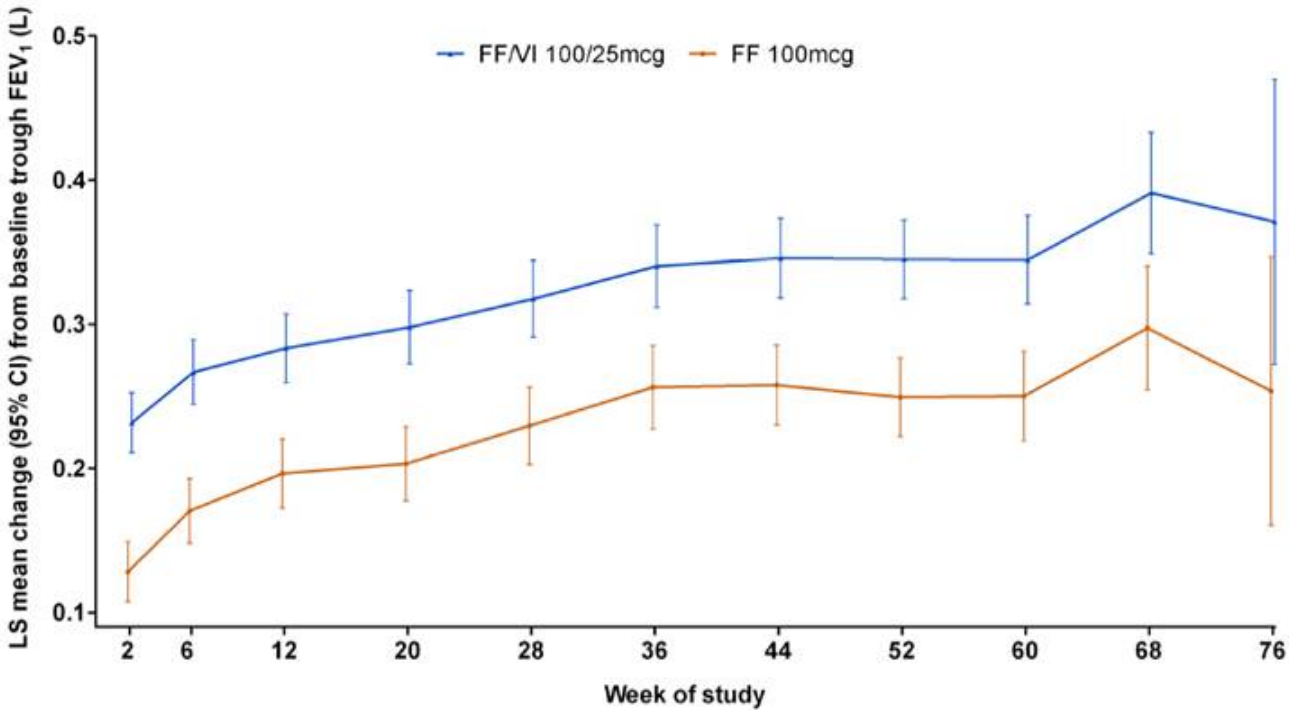
- 186 (18%) of patients receiving FF experienced ≥1 severe asthma exacerbation during the treatment period compared with 154 (15%) receiving FF/VI. Total exacerbations: FF/VI 200, FF 271.

- Mean change from baseline in trough FEV_1 (secondary endpoint) was significantly greater with FF/VI (ANCOVA p<0.001). Output of a repeated measures analysis of change from baseline in trough FEV_1 is shown in Fig. 2.

Figure 2. Repeated measures analysis of change from baseline in trough FEV_1 (ITT population)



LS = least squares; CI = confidence interval

Note: Each patient's final FEV_1 measurement (taken at the Week 76/end of study visit) was re-labelled according to that patient's duration on treatment

Safety

- Incidence of AEs was similar between treatment groups (Table 2).
- AEs deemed treatment related: 7% both groups.
- Withdrawal due to AEs: 2% both groups.
- Incidence of serious AEs: FF/VI 4%, FF 3%. One SAE (tachyarrhythmia) in the FF/VI group and three (pleurisy, asthma, non-cardiac chest pain) in the FF group were deemed potentially treatment-related by the investigator.
- Three fatal AEs occurred: pneumonia, on-treatment (FF group), road traffic accident, on-treatment (FF/VI group), and metastatic lung cancer, post-treatment (FF group); none were deemed to be related to treatment or asthma.
- The proportion of patients hospitalised due to severe asthma exacerbations was low in both treatment groups (<1%).

Table 2. On-treatment AEs occurring in ≥5% of patients in either treatment group (ITT population)

	Number (%) of patients	
AE (preferred term)	FF/VI 100/25mcg (N=1009)	FF 100 mcg (N=1010)
Any AE	636 (63)	652 (65)
Headache	188 (19)	179 (18)
Nasopharyngitis	155 (15)	131 (13)
Upper respiratory tract infection	73 (7)	93 (9)
Bronchitis	59 (6)	74 (7)
Cough	55 (5)	64 (6)
Oropharyngeal pain	41 (4)	55 (5)
Influenza	50 (5)	38 (4)

CONCLUSIONS

- The addition of VI to FF significantly reduced the risk of severe asthma exacerbations in a population uncontrolled on ICS and with a recent history of ≥1 exacerbations.
- The overall frequency of severe asthma exacerbations in both treatment groups was low compared with those seen in other studies of ICS with or without LABA.
- FF/VI improved lung function, as measured by trough FEV_1, relative to FF and had a similar safety profile with no increased risk of serious asthma-related events.

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POSTER P1794

Efficacy and safety of fluticasone furoate/vilanterol (FF/VI) once-daily for 24 weeks in persistent asthma

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INTRODUCTION

- Inhaled corticosteroids (ICS) are considered the most effective anti-inflammatory treatments for all severities of persistent asthma.(1)
- Adding a long-acting beta$_2$ agonist (LABA) to an ICS improves asthma control and reduces exacerbation frequency.(2)
- FF and VI are, respectively, a novel ICS and LABA in development as a combined (FF/VI) once-daily therapy for asthma and COPD.

OBJECTIVES

- To compare the efficacy and safety of once-daily FF/VI with once-daily FF and twice-daily fluticasone propionate (FP) in patients ≥12 years of age with moderate-to-severe persistent asthma.
- To demonstrate non-inferiority of once-daily FF 200mcg vs. twice-daily FP 500mcg in trough FEV$_1$, using a non-inferiority margin of 125mL.

METHODS

- Phase III, randomised, multi-centre, double-blind, double-dummy, parallel-group study.
- Patients: asthma for ≥12 weeks; documented use of ICS (with/without LABA) for ≥12 weeks with stable ICS dose (FP 500mcg twice daily (or equivalent) or mid-dose ICS/LABA) for ≥4 weeks; pre-bronchodilator FEV$_1$ 40–90% predicted.
- Following a 4-week run-in, patients were randomised (1:1:1) to receive one of the following for 24 weeks
  - FF/VI 200/25mcg once daily (evening dosing) via novel dry powder inhaler (nDPI)
  - FF 200mcg once daily (evening dosing) via nDPI
  - FP 500mcg twice daily (morning/evening dosing) via DISKUS™/ACCUHALER™.

RESULTS

Study population and demographics (Table 1)

- Of 1206 patients screened, 586 were randomised and dosed (intent-to-treat [ITT] population) and 476 completed the study.

Table 1. Patient demographics and baseline characteristics (ITT population)

	FF/VI 200/25mcg OD (N=197)	FF 200mcg OD (N=194)	FP 500mcg BD (N=195)	Total (N=586)
Age, years	46.6 (15.05)	44.6 (14.33)	47.3 (14.06)	46.2 (14.51)
Female gender, n (%)	116 (59)	113 (58)	116 (59)	345 (59)
Screening pre-bronchodilator FEV$_1$, L	2.017 (0.6226)	2.072 (0.6432)	2.017 (0.6659)	2.035 (0.6435)
Screening % predicted FEV$_1$	62.99 (12.335)	63.27 (12.575)	63.59 (12.412)	63.28 (12.421)
Screening % reversibility FEV$_1$	29.58 (19.828)	29.17 (17.035)	29.56 (16.375)	29.44 (17.790)

Values are mean (SD) unless otherwise stated

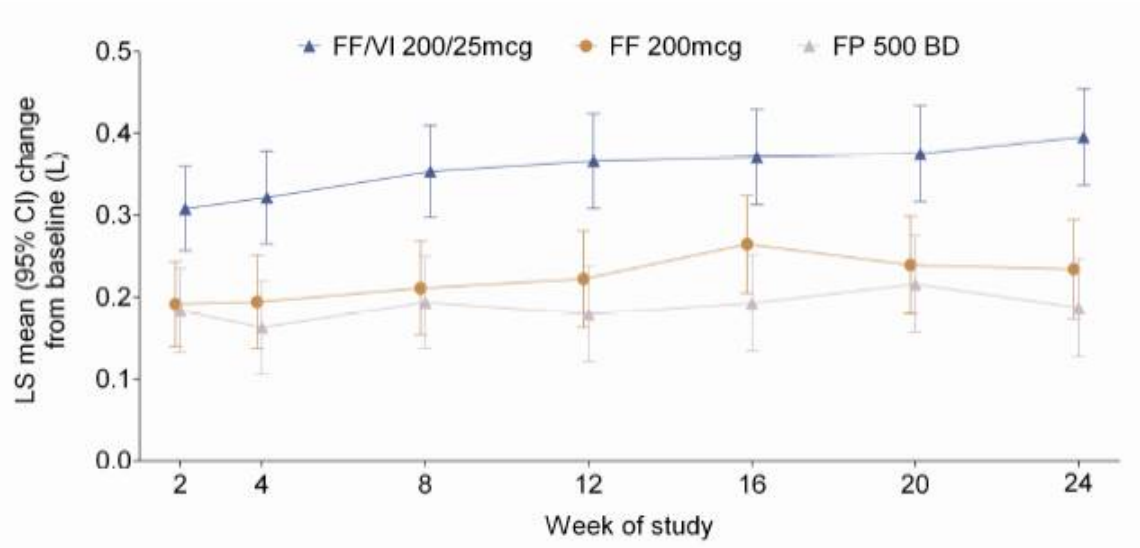
Efficacy

- FF/VI demonstrated benefit over FF and FP in mean change from baseline in trough (pre-bronchodilator, pre-dose) FEV$_1$ at Week 24 (co-primary endpoint; ANCOVA analysis; last observation carried forward): 394mL FF/VI; 201mL FF; 183mL FP
  - treatment differences (95% CI): FF/VI vs. FF 193mL (108, 277); FF/VI vs. FP 210mL (127, 294) (both p<0.001)

- FF 200mcg was non-inferior to FP 500mcg: treatment difference 18mL (–66mL, 102mL)
- repeated measures analysis was consistent (Fig. 1).

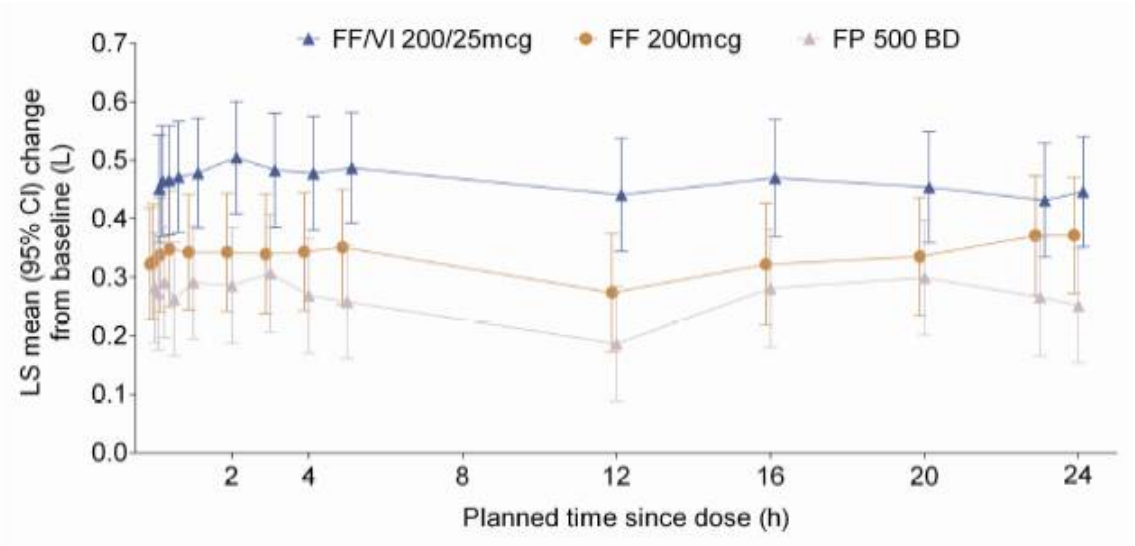
- FF/VI demonstrated benefit over FF and FP in weighted mean 0–24h post-dose serial FEV_1 after 24 weeks (co-primary endpoint; ANCOVA analysis): 2.668L FF/VI; 2.532L FF; 2.462L FP
  - treatment differences (95% CI): FF/VI vs. FF 136mL (1, 270; p=0.048); FF/VI vs. FP 206mL (73, 339; p=0.003)
  - individual serial FEV_1 assessments are shown in Fig. 2.
- There were significantly more % rescue-free 24-h periods (powered secondary endpoint) (11.7 [p<0.001], equivalent to 0.8 per week) and % symptom-free 24-h periods (secondary endpoint) (8.4 [p=0.01], 0.6 per week) compared with baseline for FF/VI vs. FF.
- No statistical difference between FF/VI and FF in Total Asthma Quality of Life Questionnaire score at either Weeks 12 or 24 (secondary endpoint).

Figure 1. Repeated measures analysis of change from baseline in trough FEV_1 over 24 weeks (ITT population)



LS = least squares; CI = confidence interval

Figure 2. Adjusted mean change from baseline of individual serial FEV_1 assessments at Week 24 (ITT population)



LS = least squares; CI = confidence interval

Safety

- Incidences of on-treatment adverse events (AEs) and treatment-related AEs are summarised in Table 2.
- Incidence of serious AEs (SAEs): FF/VI 3%, FF <1%, FP 1%
  - two SAEs were considered treatment related (atrial fibrillation in FF/VI group, haemoptysis in FP group); both resolved.

- Ratio to baseline for 24-h urinary cortisol excretion at Week 24: 0.84 FP, 0.91 FF, 0.98 FF/VI.

- There were no clinically meaningful differences in systolic and diastolic blood pressure, pulse rate or ECG at Week 24 across treatment groups.

Table 2. Summary of AEs by treatment group (ITT population)

n (%)	FF/VI 200/25mcg OD (N=197)	FF 200mcg OD (N=194)	FP 500mcg BD (N=195)
On-treatment AEs	92 (47)	90 (46)	97 (50)
Treatment-related AEs	17 (9)	8 (4)	16 (8)
AEs leading to discontinuation of study drug or withdrawal from study	7 (4)	3 (2)	2 (1)
Most frequent on-treatment AEs			
Nasopharyngitis	25 (13)	27 (14)	39 (20)
Headache	11 (6)	13 (7)	15 (8)
Cough	3 (2)	6 (3)	13 (7)

AEs occurring in ≥5% of patients in any treatment group are presented

CONCLUSIONS

- Treatment with once-daily FF/VI 200/25mcg over 24 weeks was associated with significantly greater improvements in lung function and asthma stability versus once-daily FF 200mcg and was generally well tolerated in this asthma population.

- Once-daily FF 200mcg was not inferior to twice-daily FP 500mcg, as assessed by trough FEV_1.

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POSTER P1795

Efficacy and safety of fluticasone furoate (FF)/vilanterol (VI) compared with fluticasone propionate/salmeterol combination (FP/SAL) in adults and adolescents with persistent asthma

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INTRODUCTION

- For asthma patients symptomatic despite ICS therapy, a long-acting beta$_2$ agonist (LABA) may be added.(1),(2)
- Current ICS/LABA combinations for asthma such as FP/SAL are administered twice daily; once-daily dosing of ICS/LABA may improve symptom control by improving patient adherence.
- The combination of FF (an ICS) and VI (a LABA) is in development as a once-daily therapy for asthma.

OBJECTIVES

- To compare the efficacy of FF/VI 100/25mcg administered once daily in the evening with FP/SAL 250/50mcg administered twice daily (morning and evening) over a 24-week treatment period in patients ≥12 years of age with persistent asthma.

METHODS

- Phase III, multi-centre, randomised, double-blind, double-dummy, parallel group study.
- Eligible patients: aged ≥12 years; ≥12% and ≥200mL reversibility of FEV$_1$ with salbutamol; evening pre-bronchodilator FEV$_1$ 40–85% pred; documented use of ICS for ≥12 weeks with stable ICS dose (FP 250mcg twice daily or equivalent) for ≥4 weeks.
- After 4-week run-in on FP 250mcg twice daily, patients were randomised to 24 weeks' treatment with
  - FF/VI 100/25mcg once daily (evening dosing) via novel dry power inhaler
  - FP/SAL 250/50mcg twice daily via DISKUS™/ACCUHALER™.

RESULTS

Study population and demographics (Table 1)

- Of 1564 patients screened, 806 were randomised (intent-to-treat [ITT] population) and 715 completed the study.

Efficacy

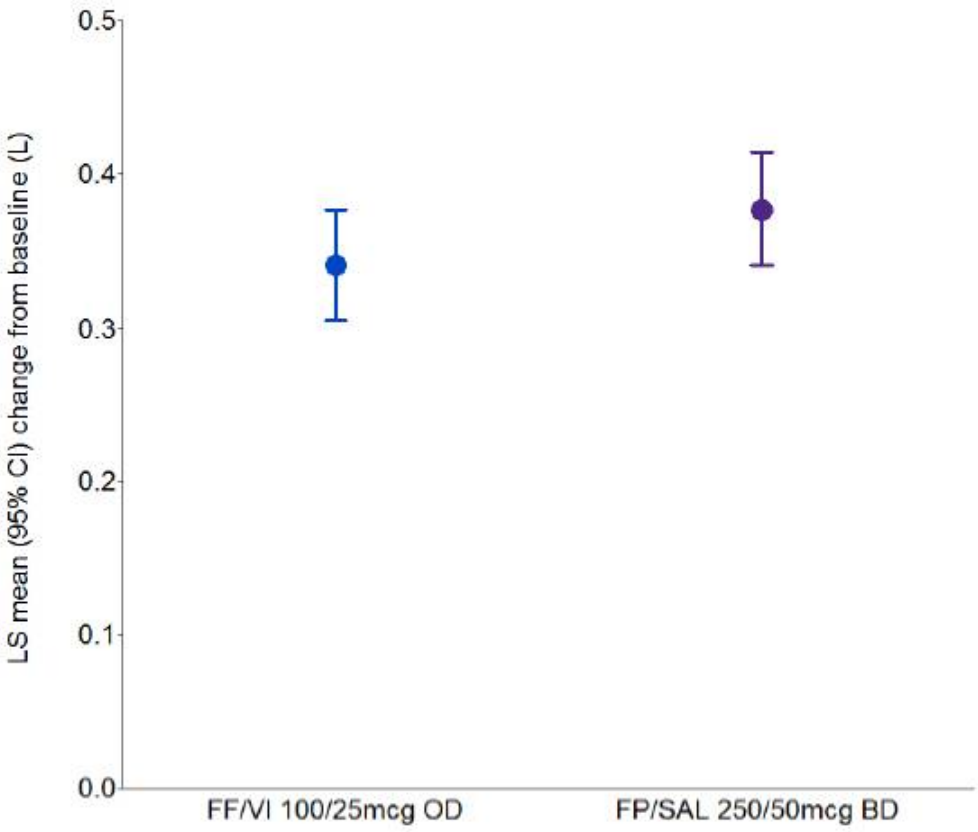
- Clinically important improvements from baseline in 0–24h serial weighted mean (wm) FEV$_1$ after 24 weeks (primary endpoint) were seen with both FF/VI (341mL) and FP/SAL (377mL)
  - the adjusted mean treatment difference was not statistically significant (–37mL [95% CI: –88, 15], p=0.162; Fig. 1).

Table 1. Patient demographics and baseline lung function (ITT population)

	FF/VI 100/25mcg once daily (N=403)	FP/SAL 250/50mcg twice daily (N=403)
Mean age, years (range)	43.8 (12–79)	41.9 (12–80)
Female, n (%)	244 (61)	245 (61)
Race, n (%)		
White	242 (60)	232 (58)
Asian	124 (31)	125 (31)
African American/African heritage	36 (9)	43 (11)
Other(a)	1 (<1)	3 (<1)
%reversibility of FEV$_1$(b), L, mean (SD)	26.4 (14.44)	29.0 (18.04)
Pre-dose FEV$_1$ (L), mean (SD)	2.011 (0.6389)	2.048 (0.6246)
%predicted FEV$_1$, mean (SD)	68.0 (11.68)	68.8 (11.01)

(a)Native Hawaiian or other Pacific islander (n=1 [<1%] FF/VI; n=1 [<1%] FP/SAL); African American/African heritage and White (n=0 FF/VI; n= 2 [<1%] FP/SAL)
(b)Screening values

Figure 1. Adjusted means for 0–24h wmFEV$_1$ at Week 24 (ITT population)



LS=least squares; CI=confidence interval

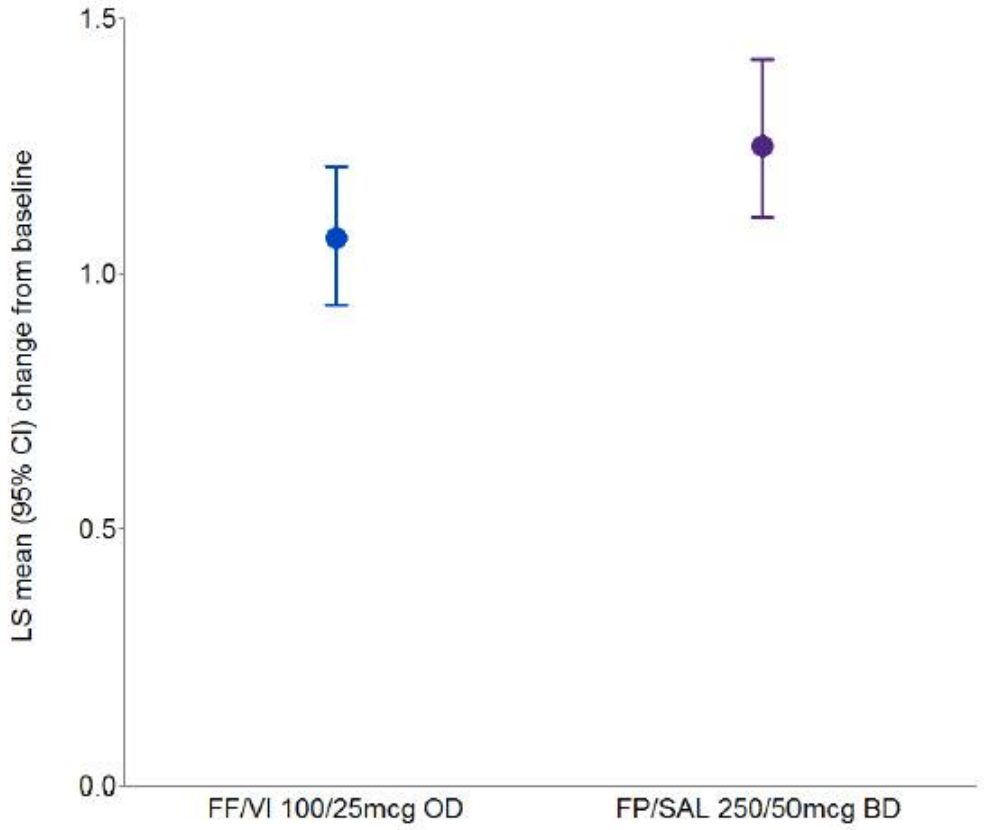
- No statistically significant differences were reported between FF/VI and FP/SAL for serial wmFEV$_1$ (0–4h) and clinic visit trough FEV$_1$ (secondary endpoints).

- A greater number of patients receiving FF/VI vs. FP/SAL had an improvement of ≥0.5 points (minimally important difference)(3) from baseline in their Total Asthma Quality of Life Questionnaire (+12) score (‘other’ endpoint; post-hoc analysis) at Week 24 (46% vs. 38%).

Safety

- Incidences of on-treatment adverse events (AEs), treatment-related AEs and serious AEs (SAEs) were similar between treatments (Table 2)
  - no SAEs were considered treatment-related
  - no deaths were reported during the study.
- No clinically relevant differences between FF/VI and FP/SAL were reported for 24-h urinary cortisol (UC) excretion (adjusted treatment ratio 0.85 [95% CI: 0.72, 1.02], p=0.075) (Fig. 2) or vital signs.

Figure 2. Adjusted ratios to baseline for 24-h UC excretion at Week 24 (UC population)



LS=least squares; CI=confidence interval

Table 2. Summary of AEs and SAEs (ITT population)

n (%)	FF/VI 100/25mcg once daily (N=403)	FP/SAL 250/50mcg twice daily (N=403)
On-treatment AEs	**213 (53)**	**198 (49)**
Nasopharyngitis	46 (11)	46 (11)
Headache	34 (8)	41 (10)
Upper respiratory tract infection	26 (6)	16 (4)
Treatment-related AEs	19 (5)	15 (4)
SAEs	4 (<1)	5 (1)

AEs occurring in ≥5% of patients in any treatment group are presented

CONCLUSIONS

- There was no difference between once-daily FF/VI and twice-daily FP/SAL in improving lung function in patients with persistent asthma.
- FF/VI improved quality of life (post-hoc analysis) compared with FP/SAL.
- No safety issues were identified with either treatment.

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POSTER P2091

Efficacy of fluticasone furoate (FF) as a monotherapy and in combination with vilanterol (VI) over 12 weeks in patients with persistent asthma

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INTRODUCTION

- It is recommended that for patients with asthma who remain symptomatic on inhaled corticosteroids (ICS)-only therapy, a long-acting beta$_2$ agonist (LABA) is added.(1),(2)
- Combination ICS/LABA therapy can improve symptoms and achieve better asthma control, and in more patients, than ICS alone.(2)
- FF is a novel ICS in development as a once-daily treatment in combination with VI, a LABA with inherent 24-h activity, for asthma.

OBJECTIVES

- To compare the efficacy and safety of FF/VI 100/25mcg with FF 100mcg administered once daily in the evening for 12 weeks in patients ≥12 years with persistent asthma.

METHODS

- Phase III, multi-centre, randomised, double-blind, placebo-controlled, parallel group study.
- Patients: ≥12 years of age; asthma for ≥12 weeks prior to screening; maintained on stable low-mid dose ICS or low-dose ICS/LABA.
- Following 4-week run-in, patients were randomised (1:1:1) to receive one of the following for 12 weeks
  - FF/VI 100/25mcg, FF 100mcg or placebo administered once daily in the evening via novel dry powder inhaler.

RESULTS

Study population and demographics (Table 1)

- Of 1110 patients screened, 610 were randomised and 609 received at least one dose of study medication (intent-to-treat [ITT] population) and 515 completed the study.

Trough FEV$_1$ and serial (0–24h) wmFEV$_1$ (Fig. 1)

- For trough FEV$_1$ (pre-bronchodilator and pre-dose) at Week 12 (co-primary endpoint), statistically significant differences from placebo in change from baseline were seen for both FF/VI and FF
  - difference compared with placebo: FF/VI 172mL (95% CI: 87, 258; p<0.001); FF 136mL (51, 222; p=0.002)
  - the treatment difference between FF/VI and FF was not statistically significant: 36mL (–48, 120; p=0.405).

Table 1. Patient demographics and baseline lung function (ITT population)

	Placebo once daily (N=203)	FF 100mcg once daily (N=205)	FF/VI 100/25mcg once daily (N= 201)
Mean age, years (range)	38.1 (12–72)	40.4 (12–84)	40.7 (12–82)
Female, n (%)	111 (55)	126 (61)	116 (58)
% reversibility of FEV$_1$(a), L, mean (SD)	27.47 (18.747)	30.66 (19.739)	27.98 (15.977)
Pre-dose FEV$_1$ (L), mean (SD)	2.334 (0.6257)	2.290 (0.6165)	2.344 (0.6420)
%predicted FEV$_1$, mean (SD)	70.20 (10.142)	70.49 (11.011)	70.62 (11.879)

(a) Screening values

- For serial (0–24h) weighted mean (wm) FEV$_1$ at Week 12 (co-primary endpoint; subset of patients, n=309), statistically significant differences were seen for both FF/VI (302mL; 95% CI: 178, 426; p<0.001) and FF (186mL; 62, 310; p=0.003) vs. placebo
  - the treatment difference between FF/VI and FF was not statistically significant (116mL; –5, 236; p=0.060)

- improvement in serial FEV_1 at Week 12 was maintained over 24h with FF/VI and FF (Fig. 2).

Figure 1. Adjusted mean change from baseline at Week 12 in (a) trough FEV_1 and (b) serial $wmFEV_1$ (ITT population)

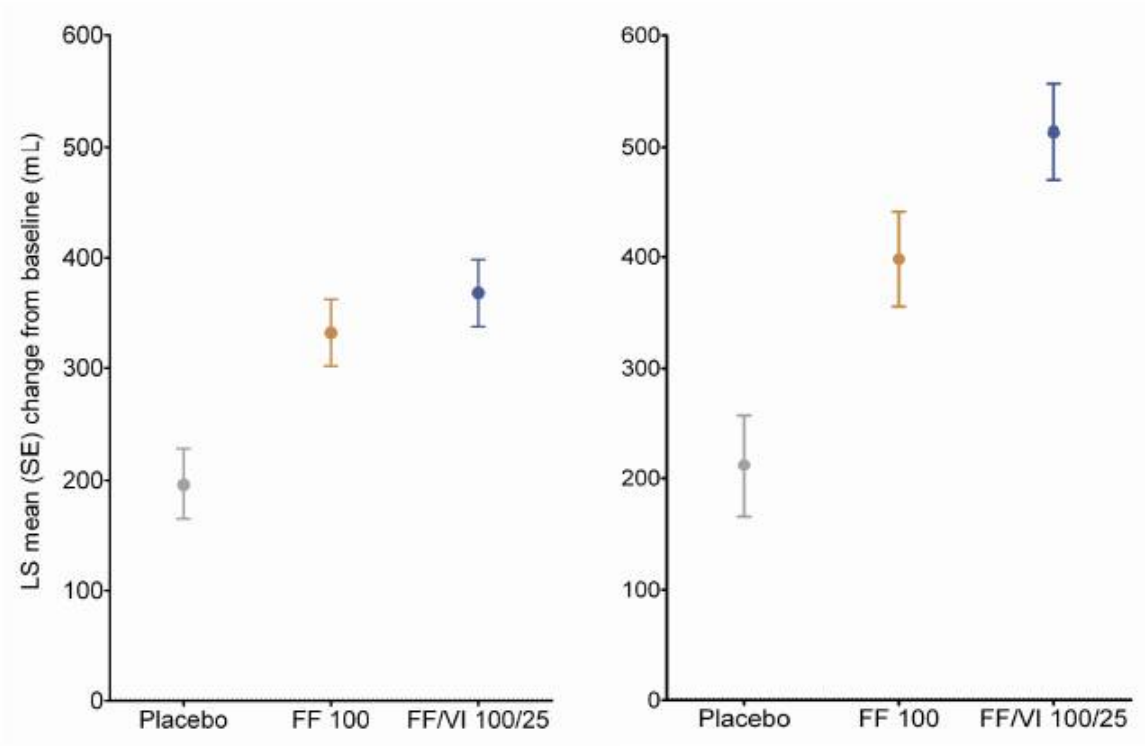
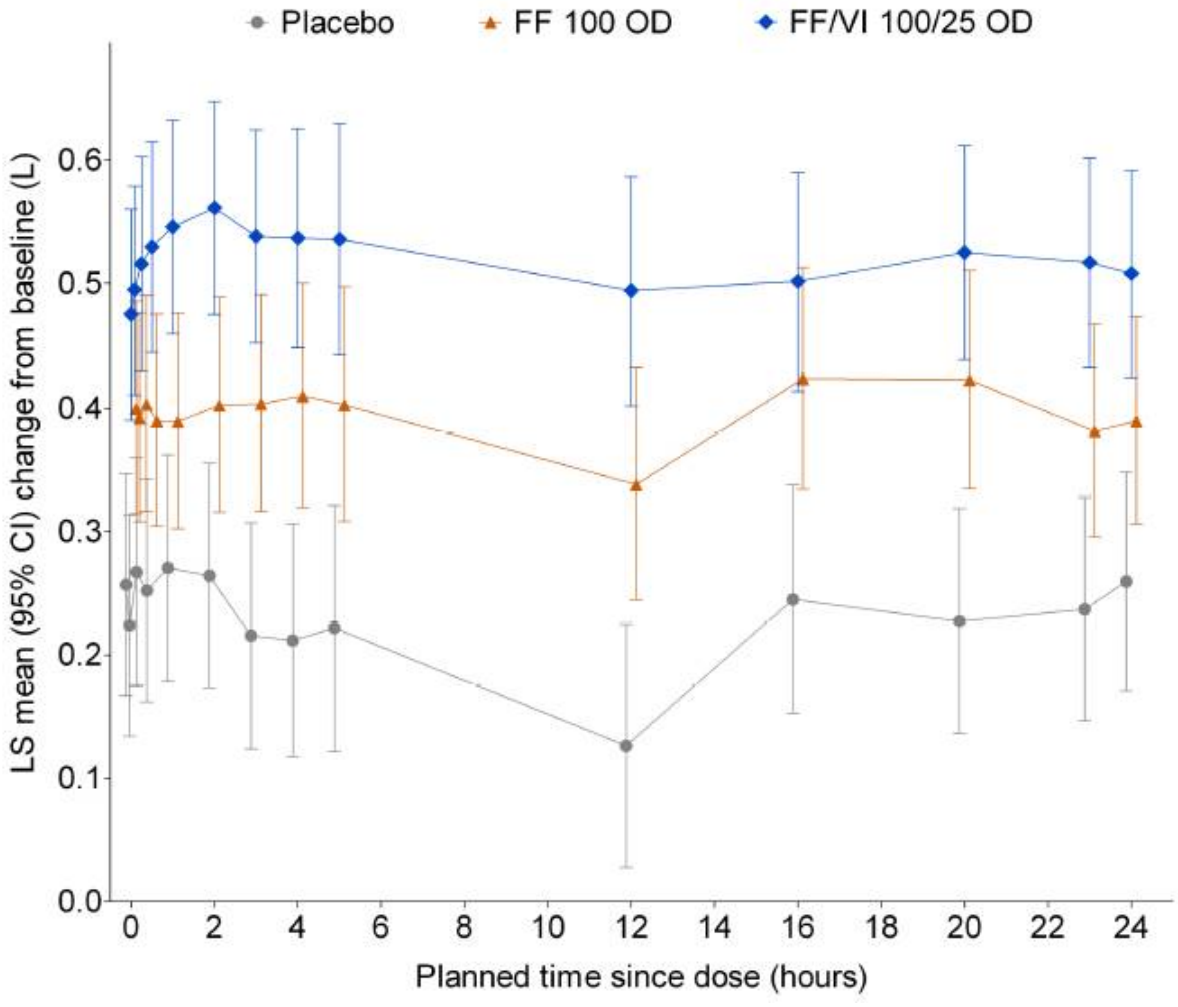


Figure 2. 0–24h FEV_1 change from baseline at Week 12 (ITT population)



Powered secondary

- An increase from baseline relative to placebo was seen in % rescue-free 24-h periods during the 12-week treatment period (powered secondary endpoint) with FF/VI and FF (treatment difference compared with placebo: FF/VI 19.3% [95% CI: 13.0, 25.6]; FF 8.7% [2.4, 15.0])
    - a greater increase was seen with FF/VI than FF: 10.6% (4.3, 16.8).

Safety

- Overall incidence of on-treatment adverse events (AEs) was low (Table 2).
- One on-treatment serious AE (SAE) was reported (pancreatitis) by one patient on FF; this SAE was not considered treatment related.
- More patients had on-treatment severe asthma exacerbations on placebo (9, 4%) than FF/VI (1, <1%) or FF (4, 2%).
- Adjusted ratios relative to placebo for change from baseline in 24-h urinary cortisol excretion at Week 12 was 0.82 for FF/VI and 0.86 for FF.

Table 2. On-treatment AEs, treatment-related AEs and SAEs (ITT population)

n (%)	Placebo once daily (N=203)	FF 100mcg once daily (N=205)	FF/VI 100/25mcg once daily (N=201)
Any on-treatment AE	43 (21)	52 (25)	59 (29)
On-treatment AE ≥3% (any treatment group)			
Nasopharyngitis	15 (7)	14 (7)	20 (10)
Headache	8 (4)	9 (4)	10 (5)
Treatment-related AEs	3 (1)	10 (5)	14 (7)
AEs leading to permanent discontinuation of study drug or withdrawal	1 (<1)(a)	0	2 (<1)(b)
Any SAE	0	2 (<1)(c)	2 (<1)(d)

(a)considered treatment-related; (b)one withdrawal was due to an AE of moderate skin rash and was considered treatment-related; (c)one SAE reported on-treatment (pancreatitis) and one post-treatment (appendicitis); (d)one SAE was reported pre-treatment (cystitis) and one post-treatment (moderate severity of prostate cancer)

CONCLUSIONS

- Significant improvement in lung function was observed with FF/VI 100/25mcg and FF 100mcg compared with placebo in patients with persistent asthma.
- Addition of VI to FF did not significantly improve FEV_1, but a numerical increase was observed. The high placebo response in evening trough FEV_1 may have influenced the interpretation of efficacy of the active therapies in this study.

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POSTER P2092

Safety and tolerability of the novel inhaled corticosteroid (ICS) fluticasone furoate (FF) in combination with the long-acting beta$_2$ agonist (LABA) vilanterol (VI) administered once daily in patients with asthma

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INTRODUCTION

- LABAs are recommended in combination with ICS for patients who remain symptomatic on low-to-medium dose ICS alone.(1),(2)
- The ICS, FF, in combination with the LABA, VI, represents a novel ICS/LABA combination suitable for once-daily dosing, which is in development for the treatment of asthma and COPD.

OBJECTIVES

- To assess the safety and tolerability of two doses of FF/VI (100/25mcg and 200/25mcg) administered once daily over 52 weeks in patients with asthma.

METHODS

- Phase III, randomised, multi-centre, double-blind, double-dummy, active comparator, parallel group study.
- Patients (aged ≥12 years) were using ICS (500–1000mcg/day or equivalent) for ≥4 weeks prior to Visit 1 (screening).
- Patients received FF/VI once daily in the evening or FP 500mcg twice daily (morning and evening) for 52 weeks; FF/VI was administered via novel dry powder inhaler and FP was administered by DISKUS™/ACCUHALER™
  - high-dose FP (500mcg) was selected to elicit a safety signal for comparison with FF/VI.
- Safety evaluations included: adverse events (AEs), oral candidiasis, non-fasting glucose and potassium levels, urinary cortisol (UC), heart rate (HR) measured by ECG and by 24-h Holter monitoring (Holter monitoring was conducted in a subset of patients; ≥50% each group), pulse rate and ophthalmic assessments.

RESULTS

- Patient baseline demographics and screening lung function are shown in Table 1.
- Most patients in the intent-to-treat population (ITT) had 'normal' or 'no change' from baseline in 24-h urine-free cortisol excretion at any post-baseline visit (76–81% FF/VI; 70% FP).
- Statistically significant UC suppression was seen with FP compared with both FF/VI groups at Weeks 12 and 28, but not at Week 52 (Table 2).
- Non-fasting glucose and potassium levels were similar across groups.

- Increases in pulse rate at Week 52 (10 min post-dose) were reported with FF/VI vs. FP (FF/VI 100/25mcg; 3.4bpm, p=0.002; FF/VI 200/25mcg; 3.4bpm, p=0.003).

Table 1. Patient baseline demographics and screening lung function (ITT population)

	FF/VI 100/25mcg once daily (N=201)	FF/VI 200/25mcg once daily (N=202)	FP 500mcg twice daily (N=100)
Age, years			
Mean (SD)	39.7 (15.85)	38.5 (15.64)	38.6 (15.97)
Female, n (%)	130 (65)	124 (61)	62 (62)
Race, n (%)			
White	135 (67)	134 (66)	68 (68)
Asian	50 (25)	51 (25)	26 (26)
African American	15 (7)	17 (8)	6 (6)
Other(a)	1 (<1)	0	0
Duration of Asthma, yr			
Mean (SD)	14.76 (11.316)	16.31 (12.768)	14.32 (12.976)
Min/Max	0.4, 58.0	0.3, 62.0	0.3, 56.3

Screening lung function(b)			
Pre-bronchodilator FEV_1 (L), mean (SD)	2.305 (0.6613)	2.290 (0.6545)	2.353 (0.6719)
% predicted FEV_1 (%), mean (SD)	74.2 (13.48)	74.1 (14.13)	75.2 (12.46)

(a)African American/African heritage and White. (b)total of 74 (37%) of patients allocated to FF/VI 100/25mcg, 78 (39%) of patients allocated to FF/VI 200/25mcg and 38 (38%) of patients allocated to FP had historical documentation of FEV_1 reversibility

Table 2. Statistical analysis of 24-h UC excretion at Weeks 12, 28 and 52 (UC population)

	FF/VI 100/25mcg once daily (N=143)	FF/VI 200/25mcg once daily (N=143)	FP 500mcg twice daily (N=76)
Week 12	n=129	n=129	n=71
FF/VI vs. FP			
Ratio	1.67	1.52	
95% CI	(1.34, 2.08)	(1.22, 1.89)	—
p-value	<0.001	<0.001	
Week 28	n=128	n=121	n=56
FF/VI vs. FP			
Ratio	1.65	1.43	
95% CI	(1.29, 2.13)	(1.11, 1.84)	—
p-value	<0.001	0.006	
Week 52	n=125	n=127	n=60
FF/VI vs. FP			
Ratio	1.05	1.09	
95% CI	(0.83, 1.33)	(0.87, 1.38)	—
p-value	0.674	0.444	

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

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· No significant effects with FF/VI vs. FP were observed on QTc(F) or HR with Holter monitoring (Table 3).

Table 3. Mean (0–24h) HR by Holter monitor by visit for patients with ≥16h of recorded data (ITT population)

n, mean (SD)	FF/VI 100/25mcg once daily (N=201)	FF/VI 200/25mcg once daily (N=202)	FP 500mcg twice daily (N=100)
Screening	111	116	49
	79.0 (8.23)	79.1 (9.55)	79.8 (8.75)
Day 1	104	113	47
	78.6 (7.89)	78.7 (9.45)	77.4 (7.66)
Week 28	95	90	39
	77.8 (8.90)	77.5 (9.01)	74.9 (8.54)
Week 52	88	82	37
	78.8 (8.72)	78.0 (10.15)	74.8 (8.62)

AEs and ophthalmic assessments

· AEs were reported by 66–69% of patients on FF/VI and 73% on FP (Table 4).

· Eleven on-treatment serious AEs were reported; one (worsening hepatitis on FP) was considered treatment related.

· No clinically significant differences between groups were reported on the ophthalmic assessments (posterior subcapsular opacity, cortical opacity, nuclear colour, nuclear opalescence, intraocular pressure and visual acuity).

Table 4. Overview of AEs and the most common (≥5%) on-treatment AEs (ITT population)

n (%)	FF/VI 100/25mcg once daily (N= 201)	FF/VI 200/25mcg once daily (N= 202)	FP 500mcg twice daily (N= 100)
Any on-treatment AE	139 (69)	134 (66)	73 (73)
Headache	39 (19)	35 (17)	23 (23)
Upper respiratory tract infection	34 (17)	30 (15)	18 (18)
Nasopharyngitis	25 (12)	19 (9)	10 (10)
Cough	9 (4)	11 (5)	13 (13)
Oropharyngeal pain	7 (3)	12 (6)	11 (11)
Pyrexia	8 (4)	13 (6)	6 (6)
Oral candidiasis(a)	12 (6)	11 (5)	2 (2)
Back pain	8 (4)	13 (6)	3 (3)
Extrasystoles(b)	4 (2)	15 (7)	3 (3)
Bronchitis	7 (3)	9 (4)	5 (5)
Upper abdominal pain	8 (4)	11 (5)	1 (1)

Respiratory tract infection	6 (3)	5 (2)	7 (7)
Sinusitis	9 (4)	4 (2)	5 (5)

Table 4. Continued

	FF/VI 100/25mcg once daily (N=201)	FF/VI 200/25mcg once daily (N=202)	FP 500mcg twice daily (N=100)
Any drug-related AE(c),(d)	27 (13)	29 (14)	14 (14)
AEs leading to withdrawal from the study(d)	5 (2)	3 (1)	6 (6)
Any on-treatment serious AE	3 (1)(e)	1 (<1)(f)	7 (7)(g)
Any treatment-related serious AE	0	0	1 (1)
Deaths	0	0	0

(a) Oropharyngeal candidiasis was reported by three patients (1%) on FF/VI 100/25mcg, two (<1%) on FF/VI 200/25mcg and one (1%) on FP. (b) Bigeminy or trigeminy on Holter recording. (c) Investigator's judgment of causality. (d) Includes on-treatment and post-treatment AEs. (e) Myalgia (muscular chest pain), haemorrhagic dengue fever, asthma exacerbation. (f) Acute pyelonephritis. (g) Pneumonia, deep vein thrombosis, asthma exacerbation (n=2), fibroadenoma of breast, breast cancer, worsening of hepatitis B (worsening hepatitis B considered by investigator to be treatment related)

CONCLUSIONS

- FF/VI (100/25mcg or 200/25mcg) administered once daily over 52 weeks was well tolerated by patients ≥12 years with asthma.
- Safety findings that were observed reflected the expected pharmacologic activity of the ICS and LABA components.

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POSTER P2123

Efficacy and safety of once-daily fluticasone furoate (FF) in patients with persistent asthma: a 24-week randomised trial

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INTRODUCTION

- Inhaled corticosteroids (ICS) are considered the most effective therapy for all severities of persistent asthma.(1)
- FF is a new ICS under development as once-daily monotherapy for asthma and in combination with the long-acting beta$_2$ agonist vilanterol as a once-daily treatment for asthma and COPD.

OBJECTIVES

- To evaluate the efficacy and safety of once-daily FF 100mcg vs. placebo, with twice-daily fluticasone propionate (FP) 250mcg as an active control, in patients with persistent asthma uncontrolled on a stable low-to-mid dose of ICS ($\leq$500mcg FP equivalent total daily dose).

METHODS

- Multi-centre, randomised, placebo-controlled, double-blind, double-dummy, parallel-group study.
- Patients: age $\geq$12 years; asthma for $\geq$12 weeks; pre-bronchodilator FEV$_1$ 40–90% predicted; $\geq$12% and $\geq$200mL evening reversibility of FEV$_1$ following salbutamol.
- Following a 4-week run-in, patients were randomised (1:1:1) to receive one of the following for 24 weeks
  - FF 100mcg once daily (evening dosing) via novel dry powder inhaler
  - FP 250mcg twice daily via DISKUS™/ACCUHALER™
  - placebo.

RESULTS

Study population and demographics (Table 1)

- Of 1036 patients screened, 349 were randomised (ITT population=343) and 255 completed the study.

Efficacy

- Mean SE change from baseline in trough evening (pre-bronchodilator and pre-dose) FEV$_1$ at 24 weeks (primary endpoint; ANCOVA analysis): FF 161mL (39.8), FP 159mL (40.6), placebo 15mL (39.4)
  - treatment differences (95% CI) vs. placebo were statistically significant: FF 146mL (36, 257; p=0.009), FP 145mL (33, 257; p=0.011)
  - Fig. 1 shows the 24-week time course for trough FEV$_1$ (repeated measures analysis).

Table 1. Baseline characteristics (ITT population)

	Placebo N=115	FF 100 OD N=114	FP 250 BD N=114
Age (yr)	40.3 (17.68)	40.1 (16.17)	41.4 (15.64)
Female, %	59	55	63
% Predicted baseline FEV$_1$	72.32 (10.871)	72.18 (10.387)	73.04 (11.936)
% Reversibility	25.43 (12.959)	27.32 (15.252)	25.07 (14.537)
% Symptom-free 24h, mean	3.9	7.9	7.0
% Rescue-free 24h, mean	18.5	13.3	17.1

Values are mean (SD) unless otherwise stated

- Significant increase from baseline in % rescue-free 24-h periods (powered secondary endpoint) with FF (14.8%) and FP (17.9%) vs. placebo (both p<0.001)

- the 24-week time course is illustrated in Fig. 2.

- Numerical treatment differences in favour of FF and FP vs. placebo for secondary endpoints
  - evening PEF, L/min (95% CI)*†: FF=5.8 (–1.9, 13.6); FP=8.3 (0.6, 16.1)
  - morning PEF, L/min (95% CI)*†: FF=12.1 (4.0, 20.2); FP=7.6 (–0.5, 15.7)
  - symptom-free 24-h periods, % (95% CI)*: FF=8.9 (1.1, 16.7); FP=8.8 (1.1, 16.6)
  - change from baseline in Total AQLQ12+ at Week 24, score (95% CI)*: FF=0.33 (0.09, 0.57); FP=0.16 (–0.08, 0.41).
- Change from baseline in Asthma Control Test™ ('Other' endpoint) at Week 24, score (95% CI)*: FF=1.4 (0.4, 2.5); FP=1.1 (0.1, 2.1).

Safety

- On-treatment and treatment-related adverse events (AEs) were higher with FF vs. FP and placebo (Table 2).
- Most frequently reported treatment-related AEs were oral candidiasis and oropharyngeal candidiasis (for both: FF 3%, FP <1%, placebo 0%) (oropharyngeal examinations were performed at each clinic visit).

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*A lack of significance in the original analysis (including outlier†) in evening PEF between FF 100mcg and placebo meant that statistical inference could not be drawn on the subsequent efficacy endpoints in the hierarchy (daily AM PEF, symptom-free 24-h periods and AQLQ12+ score). Confidence intervals for comparisons are shown to describe the data more fully

†Data are from a sensitivity analysis with an outlier removed (due to a malfunctioning mouthpiece on the peak flow meter)

- Incidence of on-treatment severe asthma exacerbations: FF 3%, FP 2%, placebo 7%; none resulted in hospitalisation.
- Statistically significant urinary cortisol suppression was seen with FF (ratio=0.76; p=0.030) and FP (0.77; p=0.036) relative to placebo.

Figure 1. Repeated measures analysis of change from baseline in trough FEV_1 over 24 weeks (ITT Population)

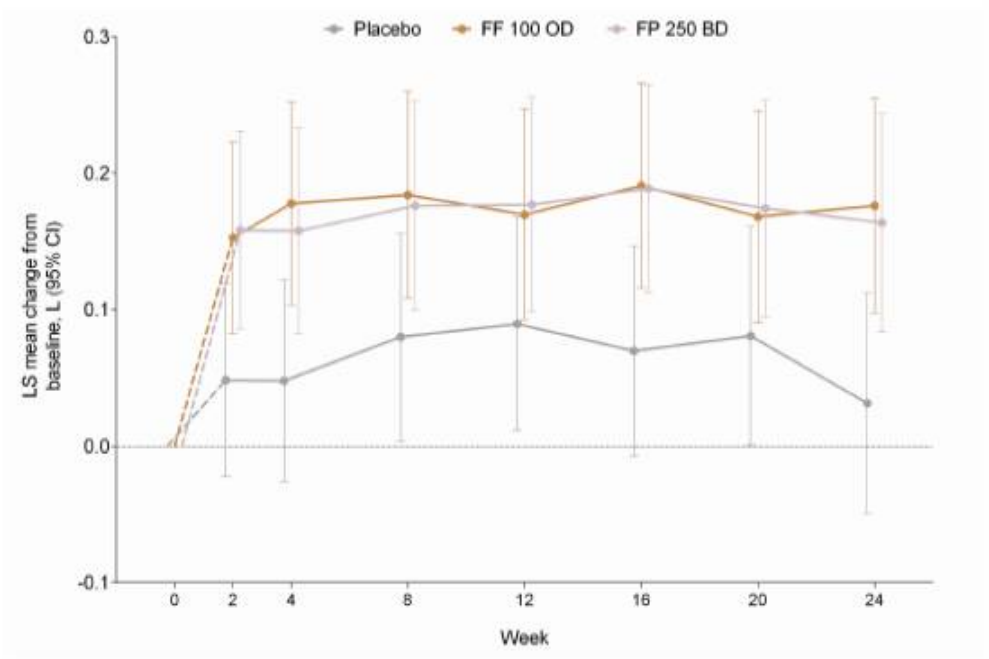

Figure 2. Change from baseline in % rescue-free 24h periods over time (ITT population)

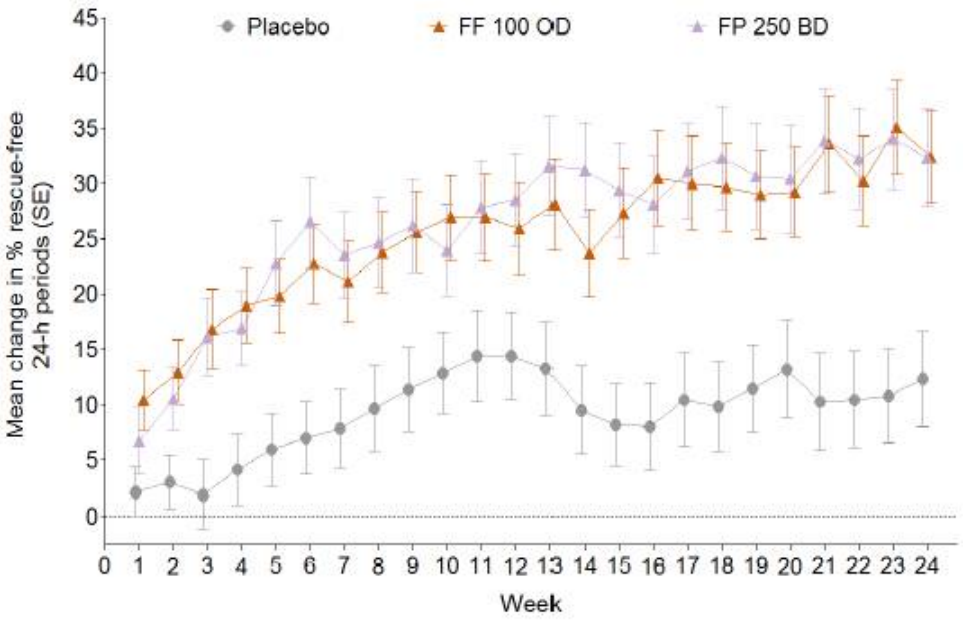

Table 2. Summary of AEs and frequent on-treatment AEs (ITT population)

n (%)	Placebo (N=115)	FF 100 OD (N=114)	FP 250 BD (N=114)
On-treatment AEs	46 (40%)	60 (53%)	48 (42%)
Bronchitis	7 (6%)	8 (7%)	4 (4%)
Headache	5 (4%)	7 (6%)	7 (6%)
Nasopharyngitis	6 (5%)	9 (8%)	4 (4%)
Upper respiratory tract infection	6 (5%)	7 (6%)	6 (5%)
Drug-related AEs	7 (6%)	11 (10%)	7 (6%)
AEs leading to permanent discontinuation of study drug or withdrawal from study	2 (2%)	3 (3%)	3 (3%)
On-treatment SAEs*	2 (2%)	4 (4%)	1 (<1%)

AEs occurring in ≥5% of patients in any treatment group are presented

*There were 9 on-treatment SAEs in 7 patients (none were fatal or considered treatment-related): FF: abscess, Crohn's disease, epididymal cyst, Escherichia bacteraemia, prostate cancer and pyelonephritis; FP: supraventricular tachycardia; placebo: meningitis and pyelonephritis

CONCLUSIONS

- FF 100mcg administered once a day significantly improved trough FEV_1 to a similar extent to FP 250mcg twice a day, and reduced rescue medication use relative to placebo.
- FF was well tolerated and had a similar AE profile to FP.

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POSTER P2151

The pharmacokinetics (PK) and pharmacodynamics (PD) of the fluticasone furoate (FF) and vilanterol (VI) combination in subjects with severe renal impairment

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INTRODUCTION

- FF/VI, a novel inhaled corticosteroid/long-acting beta$_2$-agonist combination (ICS/LABA) is being developed as a once-daily inhaled treatment for asthma and COPD.
- Elimination of both FF and VI occurs mainly via hepatic metabolism. However, renal impairment can inhibit some pathways of hepatic metabolism leading to increases in drug concentrations.
- It is recommended that all drugs intended for chronic administration (even if cleared predominantly by the hepatic route) should be subjected to pharmacokinetic assessment in patients with renal impairment.(1),(2)
- The present study was designed to investigate the effect of severe renal impairment on the pharmacokinetics, pharmacodynamics and safety of FF/VI in combination.

OBJECTIVES

- To investigate the effect of severe renal impairment on the pharmacokinetics, pharmacodynamics and safety of FF/VI.

METHODS

- An open-label, parallel-group repeat dose study.
- Subjects with severe renal impairment (n=9; creatinine clearance (CrCL): <30 mL/min) and matched (by gender, ethnicity, age and BMI) healthy subjects (n=9; CrCL: >80 mL/min).
- Inhaled FF/VI 200/25 µg once daily for 7 days.
- FF and VI pharmacokinetic parameters were assessed on Days 1 and 7.
- Systemic PD effects of FF (0–24h serum cortisol) and VI (0–4h heart rate and serum potassium) were assessed on Day 7.
- For each pharmacokinetic parameter of interest, point estimates and corresponding 90% confidence intervals (CIs) were constructed for the ratio of the geometric means of the severe renal impairment group: healthy subject group.
- For the pharmacokinetic comparisons between the two groups, non-inferiority was defined as when the upper 90% CI for the geometric mean ratio on Day 7 (severe renal impairment : healthy subjects) was <2.

RESULTS

- Nine white healthy subjects (8 male:1 female; mean age 55.4 yrs; mean weight 82.8kg; mean BMI 26.6 kg/m(2); mean CrCL 109.7 mL/min) and nine white subjects with severe renal impairment (8 male:1 female; mean age 55.8 yrs; mean weight 82.9 kg; mean BMI 27.3 kg/m(2); mean CrCL 24.0 mL/min) completed the study.
- There were no withdrawals.

Figure 1. Mean FF concentration-time profiles on Day 1 and Day 7 after administration of FF/VI 200/25 µg to subjects with severe renal impairment and healthy subjects (semi-log scale)

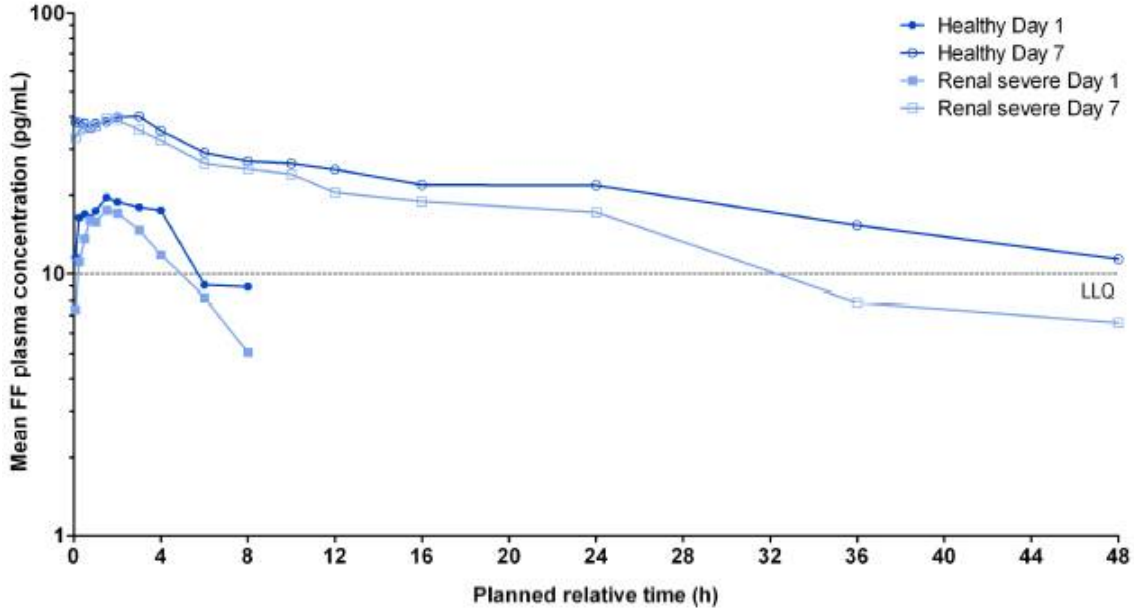
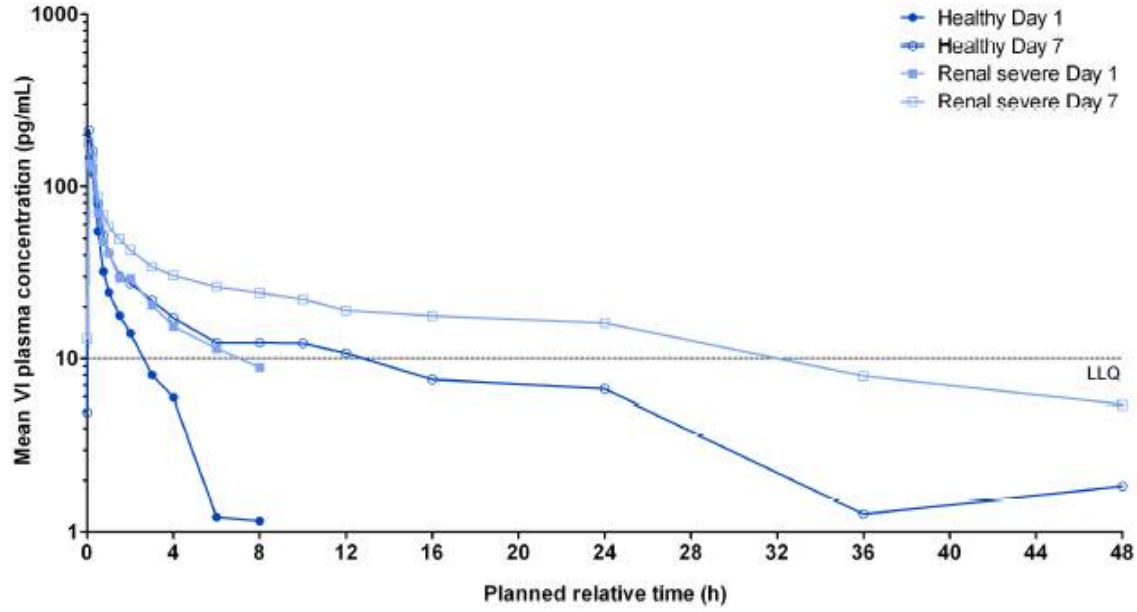


Figure 2. Mean VI concentration-time profiles on Day 1 and Day 7 after administration of FF/VI 200/25 µg to subjects with severe renal impairment and healthy subjects (semi-log scale)



- Following inhaled FF/VI administration maximum FF plasma concentrations were observed at on average 1.5 to 3 hours post-dose (Table 1 and Figure 1). Maximum VI plasma concentrations were observed at on average 5 minutes post-dose (Table 1 and Figure 2).

- Non-inferiority was demonstrated for both FF and VI $AUC_{(0–24)}$ and C_{max} values in subjects with severe renal impairment compared with healthy subjects (Table 2).

- Accumulation was similar in healthy subjects and subjects with severe renal impairment. Average FF accumulation was 86% and 123% for AUC and 97% and 105% for C_{max} and for VI was 84% and 75% for AUC and 42% and 30% for C_{max}, respectively.

- There was no evidence of a difference between subjects with severe renal impairment and healthy subjects in systemic effects that might be attributable to the administration of either a LABA (difference of adjusted means [90% CI]: heart rate 0.30 [–7.30, 7.90] and serum potassium 0.40 [–0.02, 0.81]) or an ICS (ratio of adjusted geometric means [90% CI]: 24 hour serum cortisol 1.03 [0.79, 1.33]) .

- No adverse events were reported in either group.

Table 1. Summary of pharmacokinetic parameters for plasma FF and VI

Parameter	Group	Day	FF GM (95% CI)	VI GM (95% CI)
$AUC_{(0–24)}$ (pg.h/mL)	Healthy	7	609.1 (406.5, 912.6)	386.3 (312.1, 478.3)
	SRI		554.1 (381.0, 806.0)	604.3 (510.5, 715.3)
$AUC_{(0–8)}$ (pg.h/mL)	Healthy	1	131.8 (88.8, 195.8)	103.4 (55.4, 192.8)
	SRI		126.1 (46.9, 339.3)	181.1 (121.6, 269.8)
	Healthy	7	252.9 (162.1, 394.5)	190.5 (98.6, 368.1)
	SRI		229.7 (160.1, 330.0)	316.6 (261.1, 383.8)

$t_{½}$ (h)	Healthy	7	35.1 (30.7, 40.1)	ND
	SRI		34.6 (25.8, 46.3)	ND
Cmax (pg/mL)	Healthy	1	19.5 (12.1, 31.7)	107.8 (42.6, 272.3)
	SRI		18.0 (10.9, 29.7)	126.7 (81.8, 196.3)
	Healthy	7	38.4 (21.2, 69.8)	152.9 (56.4, 414.5)
	SRI		36.9 (26.0, 52.5)	164.7 (118.1, 229.7)
t_{max} (h)(a)	Healthy	1	1.75 [0.08–3.00]	0.08 [0.08–0.25]
	SRI		1.75 [0.75–4.00]	0.08 [0.08–0.25]
	Healthy	7	3.00 [0.25–4.00]	0.08 [0.08–0.08]
	SRI		1.50 [0.25–3.00]	0.08 [0.08–0.25]

(a)Median [range]
GM = geometric mean; CI = confidence interval;
$AUC_{(0–8)}$ = area under the concentration-time curve from time 0 to 8 hours;
$AUC_{(0–24)}$ = AUC from time 0 to 24 hours; C_{max}: maximum observed concentration;
$t_{½}$ = half-life; ND = not determined; SRI = severe renal impairment

Table 2. Statistical comparison of FF and VI pharmacokinetic parameters between subjects with severe renal impairment and healthy subjects

Parameter	Group	Day	FF ratio of GM (90% CI)	VI ratio of GM (90% CI)
$AUC_{(0–8)}$ (pg.h/mL)	SRI/Healthy	1	0.96 (0.54, 1.70)	1.42 (0.90, 2.25)
$AUC_{(0–24)}$ (pg.h/mL)	SRI/Healthy	7	0.91 (0.60, 1.38)	1.56 (1.27, 1.92)
C_{max} (pg/mL)	SRI/Healthy	1	0.92 (0.55, 1.54)	0.80 (0.56, 1.14)
	SRI/Healthy	7	0.96 (0.57, 1.61)	0.70 (0.49, 1.00)
$t_{½}$ (h)	SRI/Healthy	7	0.98 (0.79, 1.23)	ND

GM = geometric mean; CI = confidence interval;
$AUC_{(0–8)}$ = area under the concentration-time curve from time 0 to 8 hours;
$AUC_{(0–24)}$ = AUC from time 0 to 24 hours; C_{max}: maximum observed concentration;
$t_{½}$ = half-life; ND = not determined; SRI = severe renal impairment

CONCLUSIONS

- There was no evidence of clinically relevant increases in FF or VI systemic exposure or systemic pharmacodynamic effects in subjects with severe renal impairment compared with healthy subjects.

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POSTER P2157

The pharmacokinetics (PK) and pharmacodynamics (PD) of the fluticasone furoate (FF) and vilanterol (VI) combination in subjects with hepatic impairment

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INTRODUCTION

- FF/VI, a novel inhaled corticosteroid/long-acting beta$_2$-agonist combination (ICS/LABA) is being developed as a once-daily inhaled treatment for asthma and COPD.
- FF and VI both undergo extensive first-pass metabolism and are predominantly metabolised in the liver via cytochrome P450 3A4 (CYP3A4).(1),(2)
- Hepatic dysfunction can lead to substantial alterations in drug absorption, distribution and elimination(3),(4) and the Food and Drug Administration and the European Medicines Agency both recommend that the effect of liver disease on the pharmacokinetics of drugs under development is studied.(5),(6)

OBJECTIVES

- To investigate the effect of hepatic impairment (HI) on the pharmacokinetics, pharmacodynamics and safety of FF/VI.

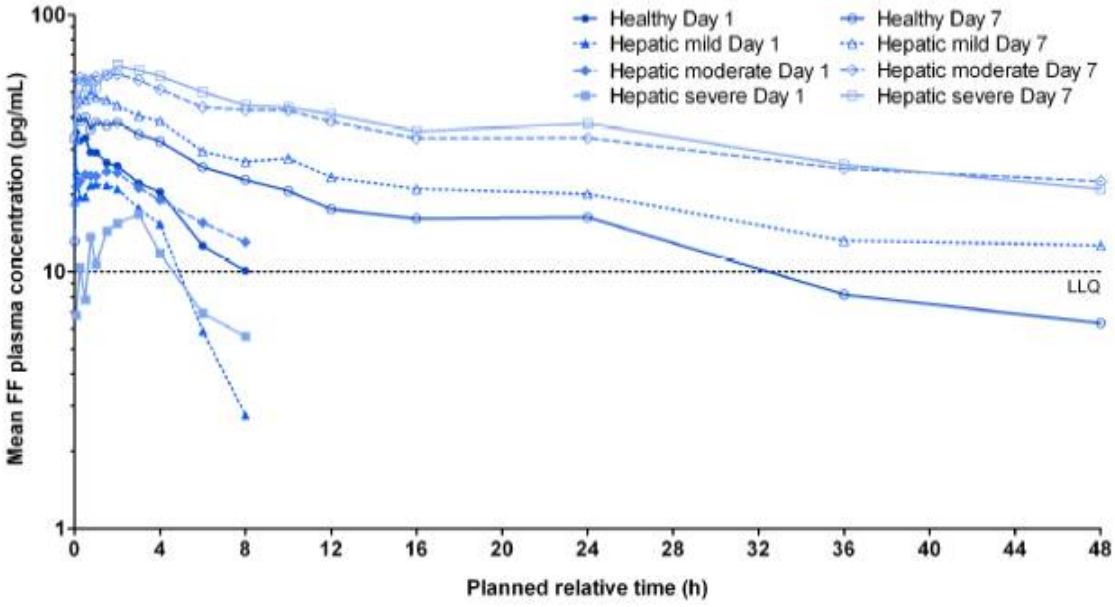
METHODS

- Open-label, parallel-group repeat dose study.
- Subjects with mild (n=9; Child-Pugh A) and moderate (n=9; Child-Pugh B) hepatic impairment, and healthy subjects (n=9) received the FF/VI 200/25 mcg combination (as two inhalations of FF/VI 100/12.5 mcg) via a novel dry powder inhaler once daily for 7 days.
- An interim review showed subjects with moderate hepatic impairment to have 65% higher FF $AUC_{(0–24)}$ values than healthy subjects, hence the FF/VI dose was subsequently reduced to 100/12.5 mcg in subjects with severe hepatic impairment (n=8; Child-Pugh C).
- PK parameters of FF and VI were assessed on Days 1 and 7.
- Systemic PD effects of FF (0–24 hour serum cortisol) and VI (0–4 hour heart rate and serum potassium) were assessed on Day 7.
- PK concentrations and parameters were dose-normalised by multiplying the values for the severe hepatic impairment cohort by 2, putting the data on the same scale as the other 3 groups.
- PK parameter point estimates and corresponding 90% confidence intervals (CIs) were constructed for the ratio of the geometric means (each hepatically impaired group : healthy subject group).
- For the PK comparisons between the two groups, non-inferiority was defined as an upper 90% CI of <2 for the geometric mean ratio (hepatically impaired : healthy) on Day 7.

RESULTS

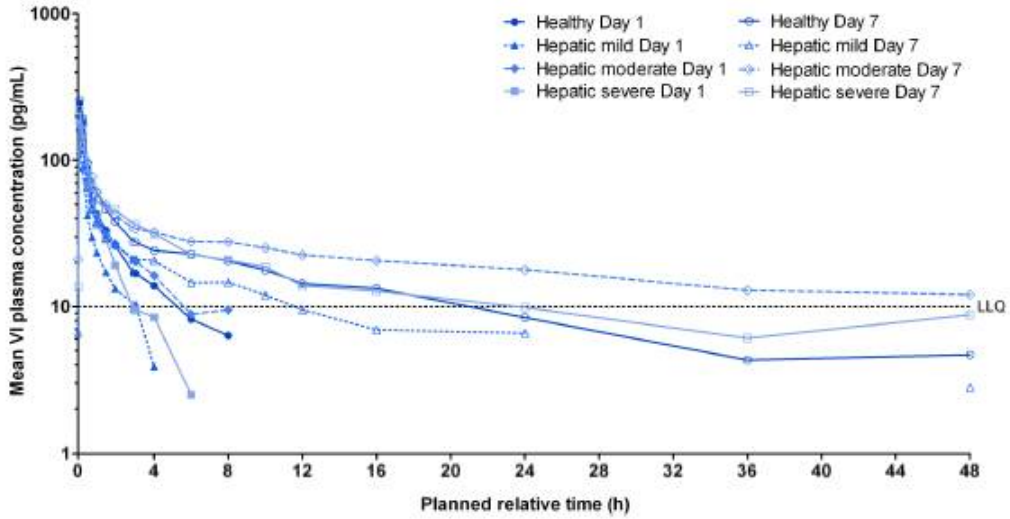
- Thirty-five subjects were enrolled. Demographic characteristics were generally similar across treatment groups, although the mean age of the severe hepatic impairment group was slightly greater than the other groups (57.8 years versus 50.3–52.1 years).
- Only one adverse event occurred (mild back pain in a healthy subject). There were no withdrawals.
- Following repeat inhaled FF/VI administration FF C_{max} was observed at on average 0.5 to 3 hours post-dose (Figure 1). VI C_{max} was observed at on average 5 minutes post-dose across all groups (Figure 2).
- Non-inferiority was established for all VI PK comparisons between hepatically impaired and healthy subjects as all upper 90% CI limits were <2 (Table 1).
- Non-inferiority between treatment groups was not demonstrated in terms of FF $AUC_{(0–24)}$, as the upper 90% CI limits for the ratios were all >2 (all hepatically impaired groups : healthy subjects [Table 1]).
- The FF elimination $t_{½}$ was longer in hepatically impaired subject groups (mean 30.9 to 53.5 hours) compared with healthy subjects (mean 23.9 hours).
- Higher accumulation (Day 7 : Day 1) of FF and VI occurred in subjects with hepatic impairment than in healthy subjects in terms of $AUC_{(0-8)}$ and C_{max} (Table 2).

Figure 1. Mean FF plasma concentration-time profiles (Day 1 and Day 7) after administration of FF/VI to subjects with hepatic impairment and healthy subjects (semi-log scale)



Note: Data for subjects with severe hepatic impairment normalised to 200/25 mcg

Figure 2. Mean VI plasma concentration-time profiles (Day 1 and Day 7) after administration of FF/VI to subjects with hepatic impairment and healthy subjects (semi-log scale).



Note: Data for subjects with severe hepatic impairment normalised to 200/25 mcg

- There was no evidence of a difference (HI - healthy subjects) in systemic beta-agonist PD effects. Differences (90% CI) in heart rate for mild, moderate and severe HI were: 3.8 bpm (–1.2, 8.8), 3.2 bpm (–1.7, 8.1) and –2.4 bpm (–7.7, 3.0) and for serum potassium were 0.04 mmol/L (–0.19, 0.27), –0.11 mmol/L (–0.34, 0.12) and 0.15 mmol/L (–0.10, 0.40), respectively.

- No clinically relevant effects on weighted mean (0–24 hour) serum cortisol were noted in subjects with mild hepatic impairment, or subjects with severe hepatic impairment to whom a lower dose of FF/VI 100/12.5 mcg was given.

- In subjects with moderate hepatic impairment, there was an average decrease of 34% (90% CI: 11% decrease to 51% decrease) in weighted mean (0–24 hour) serum cortisol, compared with healthy subjects.

Table 1. Statistical comparison of PK parameters between subjects with hepatic impairment and healthy subjects

			Comparison with healthy subjects Ratio of GM (90% CI)	
Parameter	**Day**	**Group**	**Fluticasone furoate**	**Vilanterol**
$AUC_{(0–8)}$ (pg.h/mL)	1	Mild HI	0.67 (0.33, 1.35)	0.40 (0.26, 0.62)
		Moderate HI	0.98 (0.49, 1.98)	0.93 (0.58, 1.48)
		Severe HI	0.18 (0.09, 0.38)	0.58 (0.37, 0.91)
$AUC_{(0–24)}$ (pg.h/mL)	7	Mild HI	1.34 (0.82, 2.20)	0.66 (0.40, 1.08)
		Moderate HI	1.83 (1.11, 2.99)	1.33 (0.92, 1.91)
		Severe HI	1.75 (1.05, 2.91)	0.72 (0.43, 1.20)
C_{max} (pg/mL)	1	Mild HI	0.81 (0.57, 1.15)	0.47 (0.33, 0.69)
		Moderate HI	0.81 (0.57, 1.16)	0.74 (0.50, 1.11)
		Severe HI	0.60 (0.42, 0.86)	0.74 (0.50, 1.09)

C_{max} (pg/mL)	7	Mild HI	1.18 (0.83, 1.69)	0.63 (0.43, 0.91)
		Moderate HI	1.43 (1.00, 2.04)	0.78 (0.52, 1.17)
		Severe HI	1.37 (0.95, 1.98)	0.83 (0.57, 1.23)

GM = geometric mean; CI = confidence interval; HI = Hepatic impairment

Table 2. Determination of accumulation of FF and VI in subjects with hepatic impairment and healthy subjects

Parameter	Group	Fluticasone furoate Day 7:Day 1 ratio of GM (90% CI)	Vilanterol Day 7:Day 1 ratio of GM (90% CI)
$AUC_{(0–8)}$ (pg.h/mL)	Healthy	1.60 (1.05, 2.44)	1.50 (1.201 1.85)
	Mild HI	2.89 (1.89, 4.40)	2.57 (2.07, 3.18)
	Moderate HI	2.59 (1.70, 3.96)	1.81 (1.42, 2.30)
	Severe HI	NE	2.18 (1.73, 2.73)
C_{max} (pg/mL)	Healthy	1.21 (0.90, 1.61)	1.09 (0.89, 1.35)
	Mild HI	1.77 (1.32, 2.36)	1.44 (1.17, 1.78)
	Moderate HI	2.12 (1.59, 2.84)	1.15 (0.91, 1.46)
	Severe HI	2.76 (2.03, 3.75)	1.23 (0.99, 1.54)

GM = geometric mean; CI = confidence interval; HI = Hepatic impairment
NE = not estimated (insufficient quantifiable data on Day 1 due to low dose)
Note: Data for subjects with severe hepatic impairment normalised to 200/25 mcg

CONCLUSIONS

- In subjects with hepatic impairment there was no increase in VI systemic exposure or beta-agonist mediated systemic effects.
- FF exposure was increased, on average, <2-fold in subjects with HI and was associated with a reduction in serum cortisol of approximately 30% compared with healthy subjects.

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POSTER P2090

The efficacy of inhaled fluticasone furoate (FF) and vilanterol (VI) administered in combination in asthma is comparable when administered in the morning or evening

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INTRODUCTION

- FF/VI, a novel inhaled corticosteroid/long-acting beta$_2$-agonist combination (ICS/LABA), is being developed as a once-daily inhaled treatment for asthma and COPD.
- Phase IIb studies in subjects with asthma demonstrated that both FF and VI were efficacious when dosed once daily(1),(2). Phase III clinical studies in asthma with FF/VI were conducted with evening dosing.
- This study was conducted to compare the efficacy of FF/VI when administered in the morning (AM) or evening (PM) in subjects with asthma. The results provide supporting information to understand the implications of time of dosing on the therapeutic response to FF/VI.

OBJECTIVES

- To investigate the effect of time of day of dosing (AM or PM) on the efficacy of FF/VI (100/25mcg).

METHODS

- This was a randomised, double-blind, placebo-controlled, repeat-dose, three-way crossover study.
- Subjects had asthma ($\geq$60% predicted FEV$_1$; receiving inhaled corticosteroids [ICS] ± short-acting beta$_2$-agonist [SABA] for 12 weeks prior to screening [total ICS dose 200-500 mcg/day fluticasone propionate or equivalent]).
- ICS were stopped and subjects were switched to SABA only for 2 weeks prior to dosing and throughout the study.
- Subjects received the following treatments for 14 (±2) days
  - FF/VI 100/25 mcg once daily (AM dosing) with placebo (PM)
  - FF/VI 100/25 mcg once daily (PM dosing) with placebo (AM)
  - Placebo (AM and PM).
- FF/VI doses were administered at approximately 09:00 h (AM) and 21:00 h (PM). Dosing started with the PM dose on Day 1. The final FF/VI doses were administered PM on Day 14 and AM on Day 15. The washout period was 14–21 days.

- FEV$_1$ was measured on the last study day (i.e. on the nominal ‘Day 14’ which was Day 14 (±2) days).
- FEV$_1$ was determined every 3 h for 0–24 h on Day 14 (i.e. from approximately 21:00 h on Day 14 until 21:00 h on Day 15).
- The primary endpoint was Day 14 weighted mean FEV$_1$ (0–24 h).
- Secondary endpoints included Day 14 trough FEV$_1$ (AM and PM) and mean pre-treatment peak expiratory flow (PEF).

RESULTS

Table 1. Demographics (N=26)

Characteristic	Value
Mean age, years (range)	38.1 (24–64)
Gender, F/M: n (%)	8/18 (31/69)
Height, cm: mean (range)	171.5 (153–186)
Race: n (%)	
White – White/Caucasian/European Heritage	25 (96)
Native Hawaiian or Other Pacific Islander	1 (4)

Primary endpoints

- Weighted mean FEV$_1$ (Day 14; 0–24h) was clinically significantly higher after both AM and PM dosing with FF/VI 100/25 mcg compared with placebo (Table 2). The values were similar for AM or PM dosing and the AM-PM difference was not considered to be clinically significant.

- FF/VI dosed AM or PM resulted in clinically significant increases in FEV_1 compared with placebo at all time points 0–24 h on Day 14 (Figure 1). There was no discernible difference between AM and PM dosing with FF/VI despite the final AM dose being administered in the middle of the 24 h assessment period.

- There was little evidence of diurnal variation in FEV_1 (Day 14: 0–24 h) with either AM or PM dosing with FF/VI. There was no evidence of the early morning nadir in FEV_1 seen with placebo between approximately 6–12 h post-PM dose (03:00 h–09:00 h; Figure 1).

Figure 1. Mean (95% CI) FEV_1 (L) on Day 14 following administration of FF/VI (100/25 mcg) AM or PM and placebo in subjects with asthma (n=26)

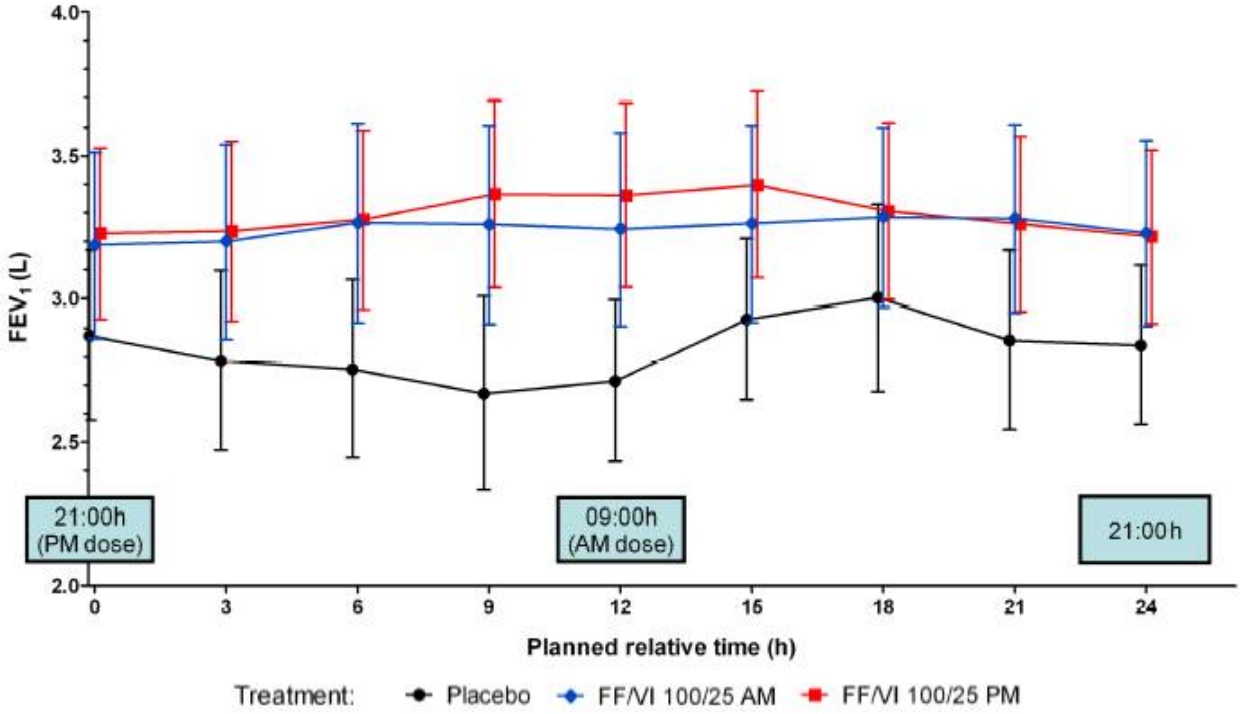


Table 2. Summary of statistical analysis of FEV_1 (L) weighted mean (Day 14; 0–24 h)

Treatment	Adjusted Mean (L)	Difference from Placebo (90% CI)	Difference from FF/VI PM (90% CI)
FF/VI AM	3.188	0.377 (0.293, 0.462)	-0.044 (-0.125, 0.036)
FF/VI PM	3.233	0.422 (0.337, 0.507)	N/A
Placebo	2.811	N/A	N/A

N/A – not applicable

Secondary endpoints

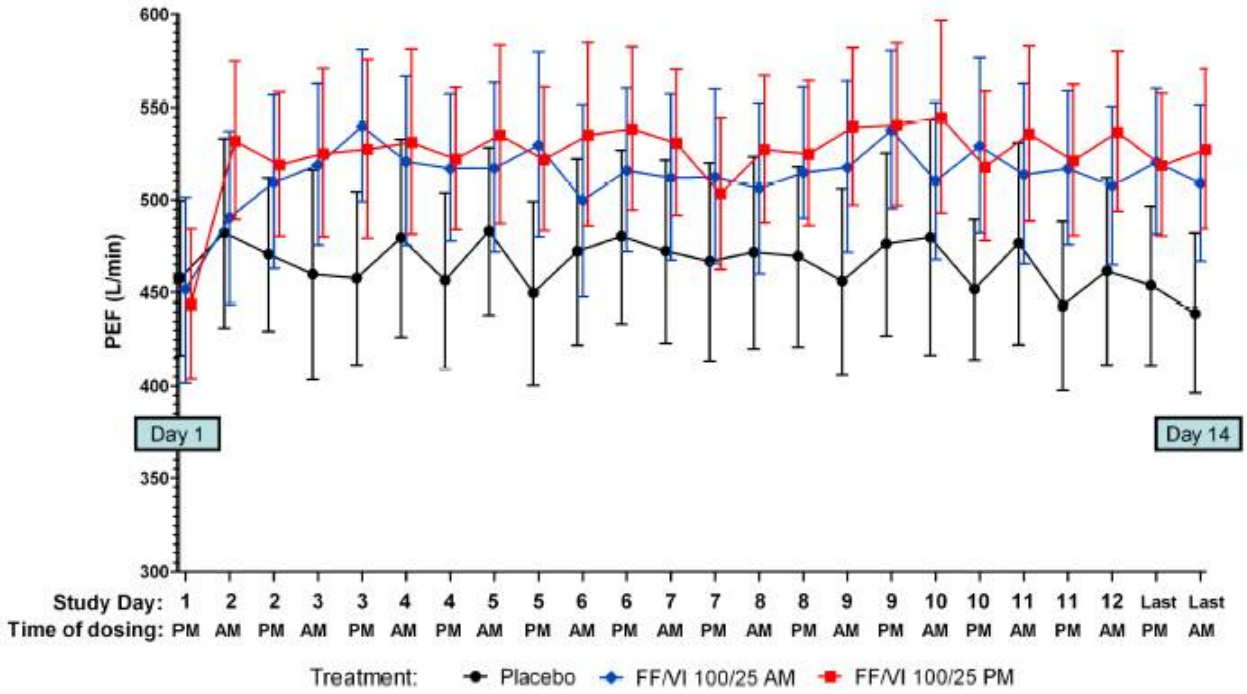
- Mean (90% CI) AM trough FEV_1 on Day 14 improved by 0.403 L (0.272, 0.533) with AM dosing compared with placebo.

- Mean (90% CI) PM trough FEV_1 on Day 14 improved by 0.309 L (0.205, 0.413) with PM dosing compared with placebo.

- FF/VI AM or PM produced clinically significant increases in pre-treatment PEF after the first dose, which were maintained throughout the 14 day treatment period (Figure 2).

- AM and PM dosing with FF/VI 100/25 mcg for 14 days were well tolerated in subjects with asthma. No serious adverse events were reported. There were no withdrawals due to worsening asthma or asthma adverse events.

Figure 2. Mean (95% CI) PEF (L/min) following AM or PM FF/VI (100/25 mcg) administration and placebo in subjects with asthma (Day 1-14; n=26)



CONCLUSIONS

· The efficacy of FF/VI (100/25mcg) was comparable when dosed in the morning or evening in subjects with persistent asthma.

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POSTER P2161

Efficacy of fluticasone furoate (FF) and vilanterol (VI), separately and in combination (FF/VI), in an allergen challenge model

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INTRODUCTION

- In sensitised asthma patients the response to allergen exposure is often evident as a bi-phasic decline in lung function.
- The early asthmatic response (EAR) starts shortly after a single inhaled allergen challenge, and the late asthmatic response (LAR) commences 2–4h later; (1),(2) the LAR is associated with development of non-specific airway hyper-responsiveness (AHR).(3)
- FF(4) and VI(5) are promising agents for a combined, long-acting, once-daily ICS/LABA treatment of asthma.

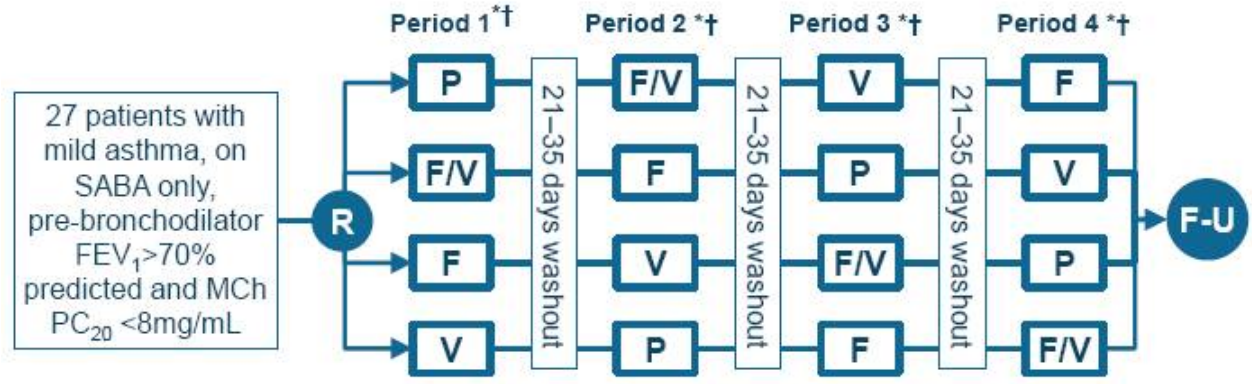
OBJECTIVES

- Primary: to compare the effect of FF/VI combination on EAR (vs. FF or VI monotherapy) and LAR (vs. placebo).
- Secondary: to compare the effects of treatments on AHR (more detailed results presented separately).(6)

METHODS

- Randomised, double-blind, 4-way complete crossover study.
- Following a 2-week run-in, patients received 21-days treatment administered in the morning via a novel dry powder inhaler (Fig. 1).
- Forced expiratory volume in 1 sec (FEV_1) was measured at 5, 10, 15, 20, 30, 45, 60 minutes and every 30 minutes until 10h post-final dose of allergen
  - EAR: minimum (min) FEV_1 (0–2h post-allergen challenge); LAR: $wmFEV_1$ (4–10h)
  - treatment differences were assessed by a mixed effects ANCOVA model.

Figure 1. Study design



F/V = FF/VI 100/25mcg; F = FF 100mcg; V = VI 25mcg; P = Placebo; R = Randomisation; F-U = Follow-Up
* Allergen challenge on Day 21, 1h post-final dose
† Assessment of AHR on Day 22, 24-h post-allergen challenge (25h post-dose) using doubling concentrations of methacholine (MCh) to induce a 20% fall in FEV_1 (PC_{20})

RESULTS

Study population and demographics

- Patient demographics, baseline lung function and allergen details are summarised in Table 1.
- Of the 27 randomised patients, 26 completed the study; one withdrew consent and four protocol deviations during treatment Period 1 (received incorrect allergen bolus dose) led to those data being excluded from the analysis.

Table 1. Patient demographics, baseline lung function and allergen details

Patient demographics

Age (years), mean (range)	30.8 (18–49)
Female, n (%)	8 (30)
White race, n (%)	25 (93)

Lung function

Pre-bronchodilator FEV_1 (L), mean (range)	3.7 (2.7–5.0)
Pre-bronchodilator FEV_1 (% pred), mean (range)	92.3 (71.3–119.8)
Methacholine PC_{20}, mg/mL	<8

Allergen, n (%)

House dust mite	15 (56)
Cat hair/dander	10 (37)
Birch tree	1 (4)
Grass pollen	1 (4)

Pre-challenge lung function

- FEV_1 improved from Day 1 to 21 prior to allergen challenge with FF/VI (230mL [145, 315]), FF (116mL [30, 202]) and VI (183mL [95, 272]) but declined by 61mL [–147, 24] with placebo (Fig. 2).

Allergen challenge

- At all time points assessed, FF/VI generally exhibited the greatest mean attenuation of the allergen-induced response (Fig. 2).
- FF/VI and FF were superior to placebo on the EAR and LAR; VI was superior to placebo on the LAR only. FF/VI was superior to FF and VI on the EAR and to VI on the LAR (Fig. 3).
- Alleviation of the AHR relative to placebo was seen with FF/VI and FF, but not with VI. FF/VI was superior to FF and VI (Fig. 4).

Figure 2. Absolute FEV_1 from Day 1 to 21, over the allergen challenge time course, up to pre-methacholine challenge on Day 22

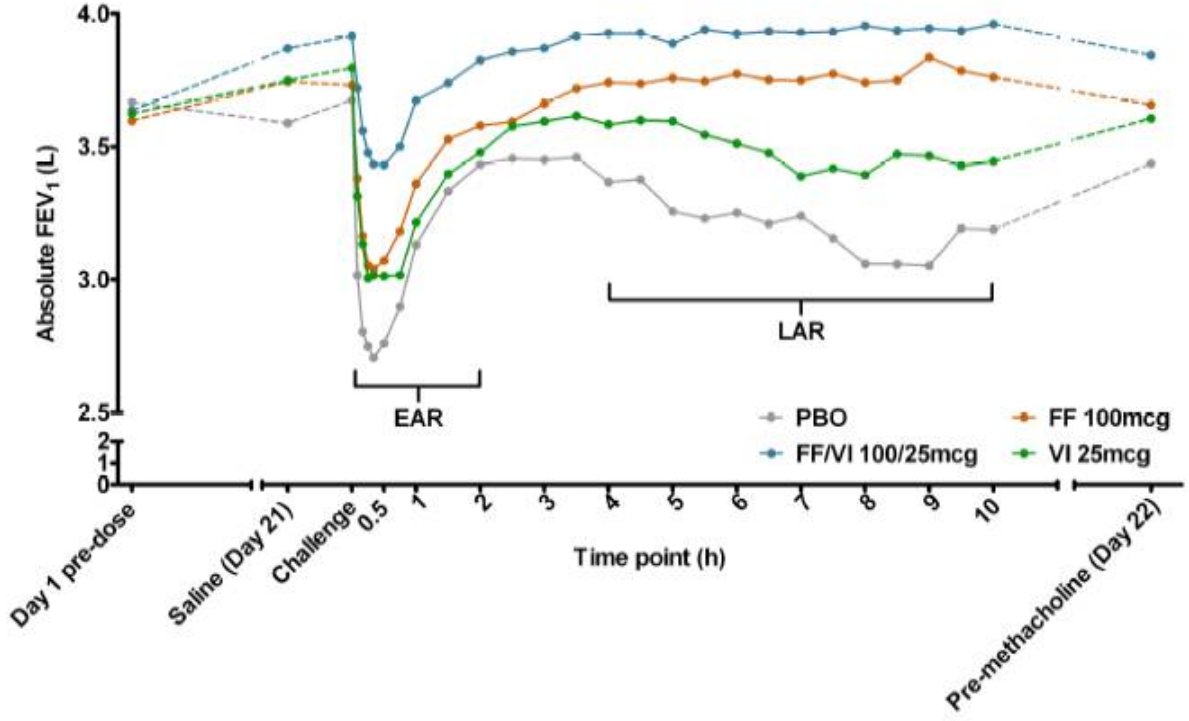
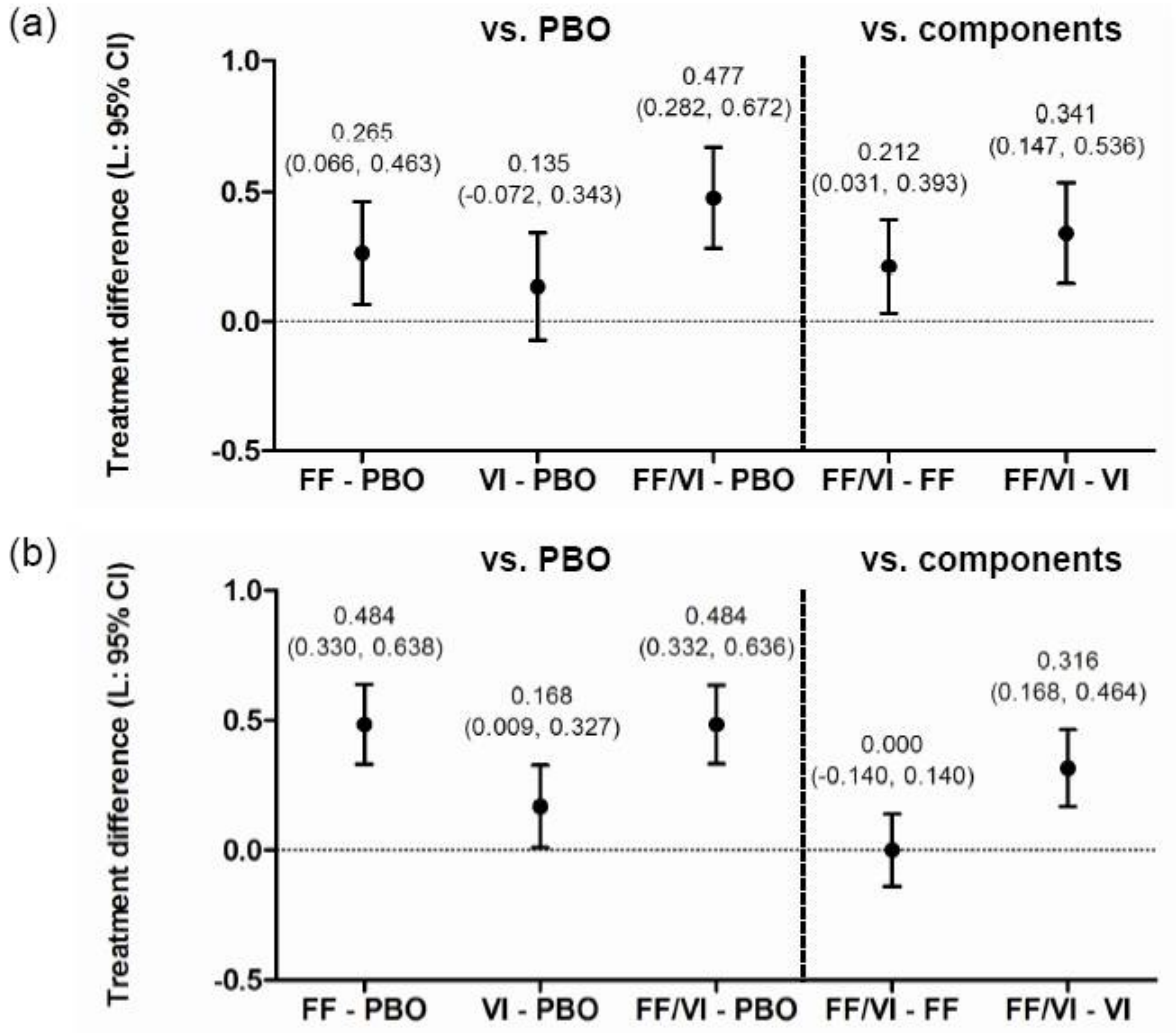
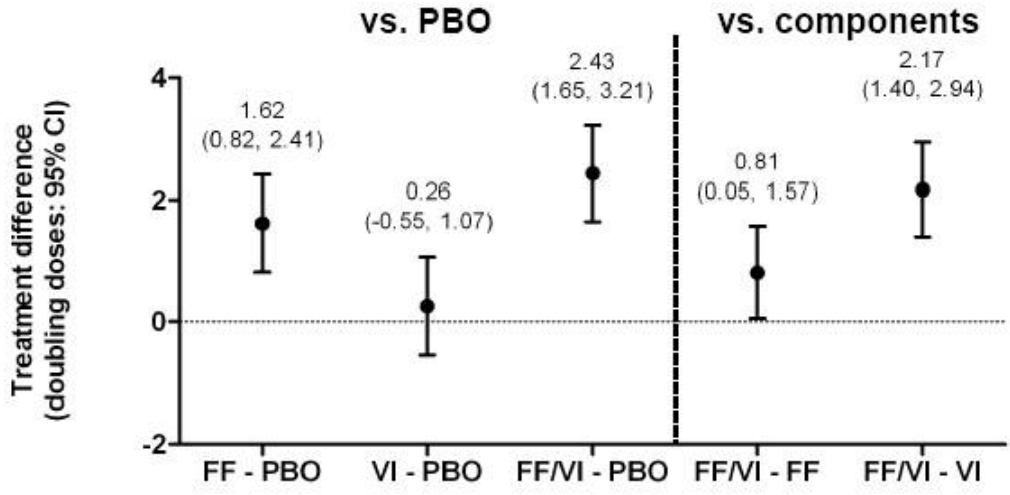


Figure 3. Treatment differences for allergen challenge on (a) the EAR assessed by minimum FEV_1 ($minFEV_1$) and (b) the LAR assessed by $wmFEV_1$



PBO=placebo

Figure 4. Treatment differences for doubling doses of methacholine required to achieve PC_{20} 24h post-allergen challenge



Adverse events and withdrawals

· No serious adverse events (AE) or withdrawals were reported.

· The number of treatment-related AEs were similar between FF/VI, FF, VI and placebo.(6)

CONCLUSIONS

· FF was highly effective in reducing both the EAR and LAR, and the addition of VI to FF further reduced the allergen-induced EAR.

· Adding VI to FF also provided further reduction of AHR as measured by methacholine responsiveness 24h after the allergen provocation.

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POSTER P2121

Umeclidinium (GSK573719) dose response and dosing interval in COPD

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INTRODUCTION

- Umeclidinium (UMEC; GSK573719) is a new, long-acting muscarinic antagonist in development as a COPD treatment.
- In two previous studies, no clear dose response was identified for UMEC over the dose range of 62.5mcg to 1000mcg once daily (OD).(1),(2)

OBJECTIVES

- To further characterise the dose-response of UMEC at doses of 15.6mcg to 125mcg OD, and to explore efficacy and safety at doses of 15.6 to 125mcg OD and 15.6mcg and 31.25mcg twice daily (BID) compared with tiotropium OD or placebo in subjects with COPD.

METHODS

Study design and population

- Randomised, double-blind, placebo-controlled, incomplete block, crossover study (AC4115321; NCT01372410) .
- Eligible subjects were male or female, aged 40–80 years with a history of COPD, current or former cigarette smoking of $\geq$10 pack-years, and a forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio of <0.70 and a post-salbutamol FEV_1 of $\geq$35 and $\leq$70% of predicted.

Treatment

- Subjects were randomised to sequences consisting of three 7-day treatment periods, separated by 10–14 day washouts
  - four OD UMEC doses (15.6, 31.25, 62.5, 125mcg) or two BID UMEC doses (15.6, 31.25mcg) were administered via dry powder inhaler
  - placebo and open-label OD tiotropium (18mcg) were comparators
  - each subject received 3 out of 8 possible treatments.

Endpoints

- Primary endpoint
  - trough FEV_1 on Day 8, defined as the mean FEV_1 value obtained 23 and 24h after morning dosing on Day 7 of each treatment period
  - *post hoc* analysis was performed without data from one investigative site due to poor compliance with good clinical practice standards.
- Secondary endpoint
  - serial FEV_1 over 24h on Day 7.
- Safety and pharmacokinetics were also assessed.

Model-based analysis

- OD and BID regimens were modelled jointly based on total daily dose. A population dose response model was applied and simulated based on the population variability of the parameters to provide an expected response over the dose range. A secondary efficacy analysis was performed with ANCOVA.

RESULTS

Demographics

- 244 subjects were screened, 163 were randomised and received treatment (modified intent-to-treat population), and 147 completed the study.
- Demographic characteristics of the study population included
  - 85 (52%) female
  - age, mean (range): 59.5 (41–80) years
  - body mass index (range): 27.4 (14.7–35.3) kg/m^2

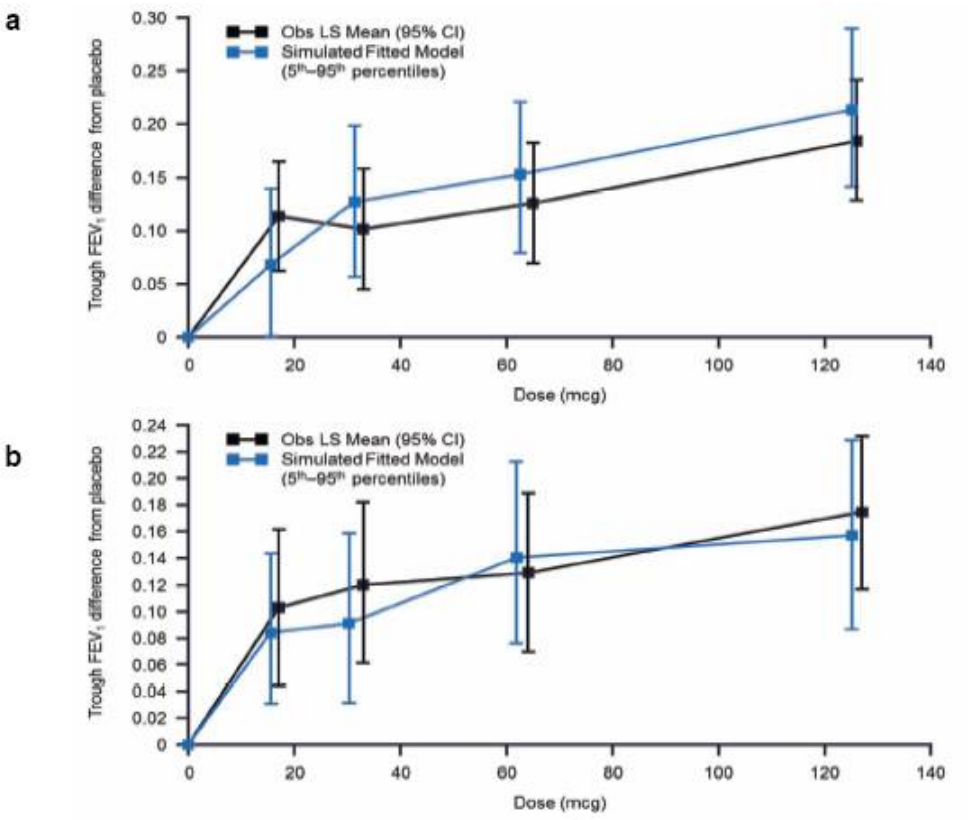
- sixty-four percent of patients were current smokers with a mean smoking history of 38.2 years, and a mean smoking pack–years of 49.4
- GOLD Stage II and III with post-bronchodilator mean percent predicted FEV_1 of 51.1% (35%–69%) and mean post-bronchodilator FEV_1/FVC ratio of 52.3% (27%–70%)
- mean post-salbutamol FEV_1 was 1.554L and FVC was 3.001L.

- Concurrent use of inhaled corticosteroids was 18% to 30% (UMEC), 20% (placebo), 25% (tiotropium).
- Mean treatment compliance was ≥99.3%.

Final dose response model

- A population physiological E_{max} model best characterised the relationship between UMEC doses and trough FEV_1 on Day 8
  - a clear monotonic dose response for UMEC was observed
  - a potency (ED_{50}) estimate of 37mcg OD (95% CI: 18–57) was demonstrated with good precision (coefficient of variation [CV]: 14%); a maximum intrinsic efficacy at trough of 0.185L (95% CI: 0.153, 0.218) after OD dosing was predicted
  - no difference in dose response was noted between OD and BID regimens.
- The simulated median (5^{th}–95^{th} percentiles) estimates of FEV_1 (OD regimen) were plotted over the curve for the observed least square (LS) mean FEV_1 (95% confidence [CI]) response values (**Figure 1**)
  - simulated dose-response predictions were generally higher than the derived LS Mean data.
- Results of the *post hoc* analysis of the primary endpoint were similar (**Figure 1b**).

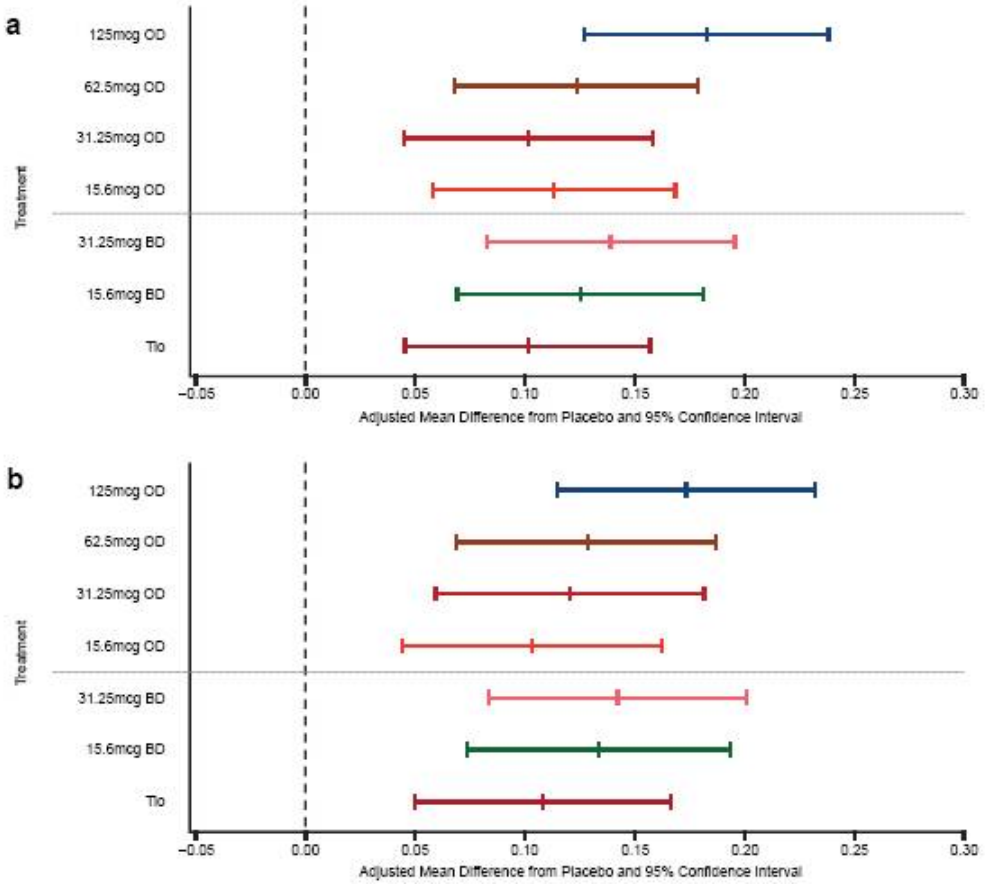
FIGURE 1. OBSERVED LS MEAN TROUGH FEV_1 AND SIMULATED MEDIAN. (A)mITT POPULATION (B) mITT POPULATION EXCLUDING SUBJECTS FROM ONE SITE



Trough FEV_1 on Day 8

- Statistically significant increases from baseline in trough FEV_1 were demonstrated for all OD and BID UMEC doses and tiotropium compared with placebo (**Figure 2**)
  - results from the *post hoc* analysis were similar.
- Dose ordering was observed with the largest improvements over placebo for 62.5mcg and 125mcg OD doses.

FIGURE 2. TROUGH FEV_1 (L) ON Day 8. (A) mITT POPULATION (B) mITT POPULATION EXCLUDING SUBJECTS FROM ONE SITE



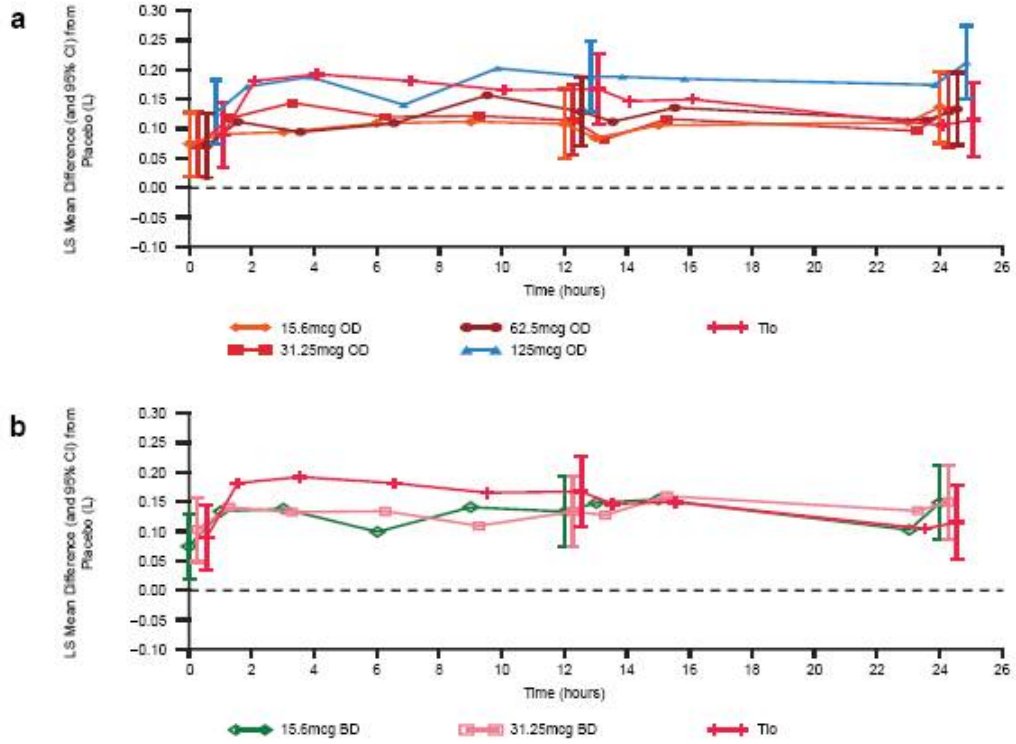
Serial FEV_1 over 24h on Day 7

- Statistically significant improvements in FEV_1 values at all time points on Day 7 were demonstrated for UMEC OD and BID doses and tiotropium (**Figure 3**) compared with placebo .
- The improvements in FEV_1 from placebo observed at time points over the first 12h were maintained at time points over the second 12h for all OD doses of UMEC.
- UMEC 125mcg OD had more consistent increases in FEV_1 from baseline across almost all time points over 24h compared with other UMEC doses or tiotropium.
- UMEC BID dosing did not offer additional benefit over OD dosing. No additional increase in FEV_1 was noted after the second dose at 12h.

Safety

- Incidence of overall adverse events (AEs) was higher for UMEC 125mcg OD (18%) than for placebo (8%), tiotropium (4%), other UMEC doses (5–12%).
- The most frequent AEs were headache, nasopharyngitis, dysgeusia, or sinusitis
  - headache occurred in 0%–7% of subjects and the other AEs occurred in $\leq$4% of subjects.

FIGURE 3. SERIAL FEV_1 ON DAY 7. (A) UMEC OD AND TIOTROPIUM AND (B) UMEC BID AND TIOTROPIUM



- Two non-drug related, non-fatal SAEs were reported (acute respiratory failure, 15.6mcg OD; myocardial infarction, 31.25mcg OD); neither SAE was related to treatment. Both subjects were withdrawn from the study and both SAEs resolved.

- Four COPD exacerbations were reported: 1 in placebo, 2 in 15.6mcg OD, and 1 in 125mcg OD**.** Each of the exacerbations was treated with corticosteroids and resolved following treatment; these subjects were withdrawn from the study.

Pharmacokinetics

- UMEC C_{max} occurred early (median t_{max} of 5–15min) followed by rapid clearance and elimination.

- Following 7 days of repeat dose treatment, there was a 1.2–1.7 -fold accumulation.

CONCLUSIONS

- Based on the population E_{max} dose response model of trough FEV_1 data, UMEC is a potent bronchodilator with geometric mean potency of 37mcg (95% CI: 18, 57) and a predicted maximum intrinsic efficacy at trough of 0.185L (95% CI: 0.153, 0.218) after OD dosing.

- A dose ordering was demonstrated over the lower dose range of 15.6 to 125mcg OD.

- A once-daily dosing interval was confirmed.

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A Randomized, Crossover Study to Examine the Pharmacodynamics and Safety of a New Antimuscarinic TD-4208 in Patients with COPD

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ABSTRACT

Background: TD-4208 is a potent and selective inhaled muscarinic antagonist with functional lung selectivity and long duration in preclinical models of bronchoconstriction. It is currently in development for maintenance treatment of airflow obstruction in patients with COPD.

Aims: To investigate the bronchodilatory profile, safety and tolerability of nebulized TD-4208 in subjects with COPD.

Methods: Thirty-two patients aged 40-75 years of age with moderate or severe COPD were randomized in a double-blind, complete 4-way crossover study. Single doses of 350 µg or 700 µg TD-4208, active-control ipratropium bromide (500 µg) or placebo were administered using a PARI LC Plus nebulizer in each period. Baseline and serial post-dose spirometry assessments (0-25 hours) were performed. Safety evaluation included adverse events, vital signs, ECGs, and clinical laboratory results.

Results: A statistically significant improvement in peak FEV_1 versus placebo of 174 mL (95% CI: 112, 235), 169 mL (95% CI: 108, 231) and 176 mL (95% CI: 114, 237) for TD-4208 350 µg, 700 µg, and ipratropium 500 µg, respectively, was observed ($p<0.001$ for each comparison). Similar to ipratropium, onset of action of TD-4208 was rapid. TD-4208 bronchodilation was sustained over the 25-hour monitoring period. FEV_1 difference from placebo at 12 hours was 113 mL , 123 mL, and 15 mL; p <0.001, <0.001 and 0.659, and at 24 hours was 103 mL, 137 mL , and -24 mL; p 0.001, <0.001 and 0.327, for TD-4208 350 µg, 700 µg, and ipratropium 500 µg, respectively. Adverse events were generally mild and occurred with similar frequencies in all treatments, with the most common being headache and dyspnea. There were no serious adverse events.

Conclusions: TD-4208 was well tolerated and demonstrated significant peak bronchodilation with rapid onset that was sustained over 24 hours suggesting a once daily dosing regimen.

INTRODUCTION

- Muscarinic receptors mediate a variety of physiological processes including maintenance of airway tone, mucus secretion, and regulation of further ACh release.
- The expression and function of muscarinic receptors may be altered in chronic lung disease, leading to increases in airway hyper-reactivity, bronchoconstriction, and mucus hypersecretion.(1)
- Treatment with bronchodilators is central to the management of COPD, either as-needed in mild cases, or daily for patients with persistent symptoms.(2)
- Long-acting inhaled muscarinic antagonist (LAMA) bronchodilators are convenient and more effective for symptom relief than short-acting bronchodilators.(2)
- Despite increased therapeutic options, there remains a need for improved bronchodilator agents for treating COPD and asthma.
- TD-4208 is a novel, long-acting, inhaled muscarinic antagonist that is being developed as a once daily treatment of COPD and asthma.(3),(4)

AIMS

Primary Objective:

- To investigate the bronchodilatory effect of single nebulized doses of TD-4208 in male and female subjects with COPD

Key Secondary Objectives:

- To explore the duration of bronchodilatory effect of TD-4208
- To evaluate the safety and tolerability profile of TD-4208
- To evaluate single dose pharmacokinetics of TD-4208

METHODS

Key Eligibility Criteria:

- Male and female aged 40 to 75 years
- COPD meeting GOLD guidelines (2)

- FEV_1/FVC ratio <0.70
- FEV_1 35 to 80% predicted post-bronchodilator
- ≥12% (and ≥200 mL) response in FEV_1 post ipratropium bromide
- No recent exacerbations/infections (< 6 weeks prior to screening)
- Not taking high-dose steroids (≥ 5 mg prednisone or ≥1000 µg fluticasone)

Study Design and Assessments:

- Single-dose, randomized, double-blind, active and placebo-controlled, four-period complete crossover study
- 21 day screening period followed by four in-house treatment periods with 25 hour intense monitoring (spirometry, safety and pharmacokinetics)
- Washout of 7 to 12 days between doses
- Single doses of TD-4208 350 and 700 mg, active-control agent ipratropium bromide (500 mg), and placebo, each administered using a PARI LC® Plus nebulizer with a PARI PRONEB® Ultra II Compressor
- Maintenance bronchodilators and steroids were discontinued for 12 to 72 hours prior to each dosing period depending on their duration of action

Pharmacodynamic Endpoints:

- Primary PD endpoint:
  - Change in peak FEV_1 relative to period baseline
- Key secondary PD endpoint:
  - FEV_1 value at 24 hours postdose (trough)

PATIENTS

- 32 subjects diagnosed with COPD were enrolled
- All subjects received each study treatment and completed all follow-up assessments

Table 1. Demographic and Clinical Characteristics

	N = 32
Age (mean ± SD)	62.0 ± 7.46
Sex M/F	22/10
Race (W/Other)	28/4
BMI (mean ± SD)	27.7 ± 8.02
FEV_1 % predicted (mean ± SD)	50.5 ±13.74
FEV_1 (L) (mean ± SD)	1.9 ± 0.48
FEV_1 % response post-ipratropium (mean ± SD)	23.7 ± 8.75

PHARMACODYNAMIC RESULTS

Figure 1. FEV_1 Change from Baseline

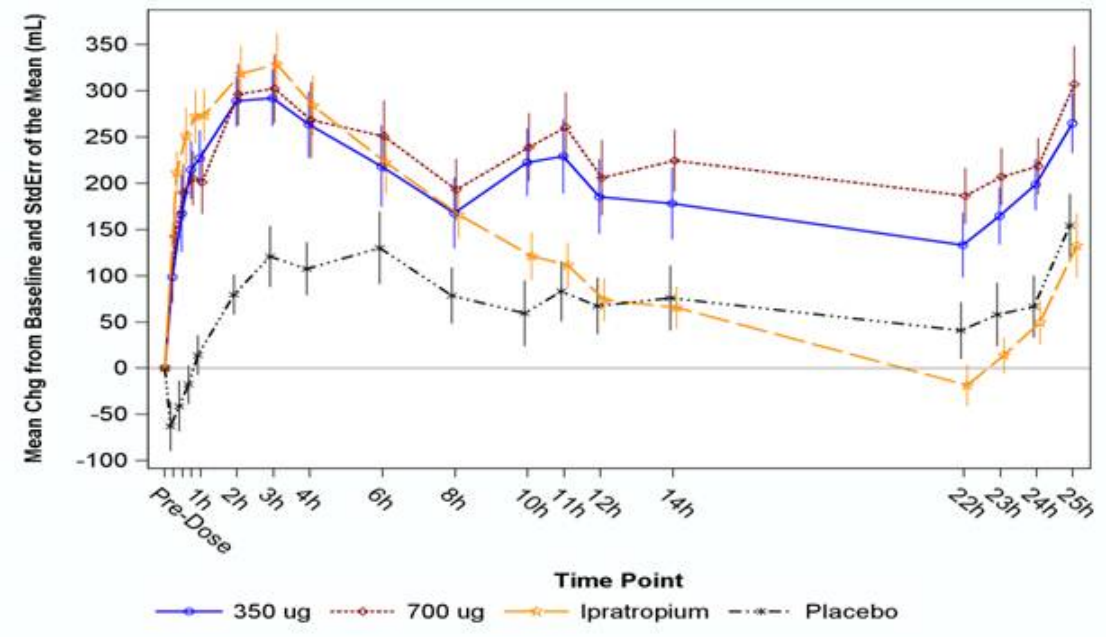
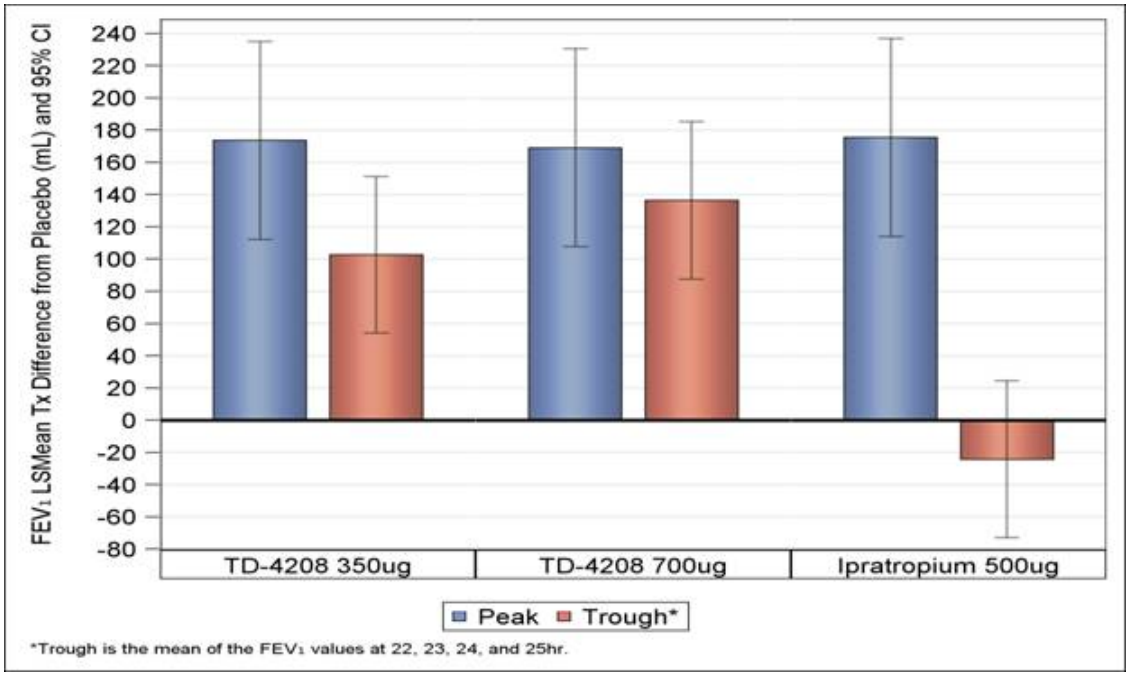


Figure 2. Mean FEV_1 Peak and Trough*



PHARMACOKINETIC RESULTS

- Mean C_{max} values were 0.12 and 0.25 ng/mL for the 350 and 700 µg doses
- Median T_{max} values were 0.3 and 0.3 hours, respectively
- Mean half-lives ($t_{1/2}$) of 3.8 and 6.7 hours, respectively

SUMMARY OF ADVERSE EVENTS

- Adverse events were generally mild
- Adverse events occurred with similar frequencies in all treatments
- Most common were headache and dyspnea
- No dry mouth reported
- No patient discontinued because of an adverse event
- There were no serious adverse events and no deaths

Table 2. Treatment-Emergent Adverse Events in ≥2 Patients (Safety Subjects)

	Placebo (N=32)	350 mcg (N=32)	700 mcg (N=32)	Ipra. (N=32)	Total (N=32)
Any AEs	16 (50.0%)	11 (34.4%)	12 (37.5%)	11 (34.4%)	23 (71.9%)
Nasopharyngitis	1 (3.1%)	0	0	1 (3.1%)	2 (6.3%)
ECG T wave peaked	1 (3.1%)	2 (6.3%)	1 (3.1%)	1 (3.1%)	2 (6.3%)
Gout	1 (3.1%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	2 (6.3%)
Headache	6 (18.8%)	2 (6.3%)	3 (9.4%)	2 (6.3%)	9 (28.1%)
Dyspnoea	3 (9.4%)	0	2 (6.3%)	4 (12.5%)	6 (18.8%)
Nasal congestion	1 (3.1%)	1 (3.1%)	0	0	2 (6.3%)

CONCLUSIONS

- TD-4208 demonstrated significant peak bronchodilation with rapid onset
- The bronchodilation for both doses of TD-4208 was sustained for the 24 hour period
- TD-4208 was well tolerated
- TD-4208 is suitable for development as a once daily inhaled agent for COPD and asthma

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