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 8, 2013**

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 8, 2013 at the European Respiratory Society (ERS) Annual Congress 2013 in Barcelona, Spain, GlaxoSmithKline (GSK) presented posters containing information from Phase 3 studies of umeclidinium/vilanterol (UMEC/VI) in chronic obstructive pulmonary disease (COPD). UMEC/VI is a combination of two investigational bronchodilator molecules - GSK573719 or umeclidinium, a long-acting muscarinic antagonist (LAMA) and vilanterol (VI), a long-acting beta$_2$ agonist (LABA), administered using the ELLIPTA™ inhaler. UMEC/VI is under regulatory review by the U.S. Food and Drug Administration (FDA), European Medicines Agency and the Japanese Ministry of Health, Labor and Welfare. Marketing applications for UMEC/VI have been submitted to regulatory authorities in a number of other countries worldwide.

In addition, GSK presented data on ELLIPTA™ from Phase 3 asthma studies of FF/VI, the treatment combination of fluticasone furoate (FF), an inhaled corticosteroid, and VI, and FF monotherapy. FF/VI, known in the United States as BREO™ ELLIPTA™ (100/25mcg), is approved by the FDA as an inhaled long-term, once-daily maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. It is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. It is not indicated for the relief of acute bronchospasm or the treatment of asthma. FF/VI is not currently approved or licensed in the European Union or anywhere outside of the U.S. and Canada.

GSK also presented a poster containing information from a Phase 2 study of GSK961081 in patients with COPD. GSK961081 (‘081) is an investigational, single molecule bifunctional bronchodilator with both muscarinic antagonist and beta$_2$ receptor agonist activities.

UMEC/VI and FF/VI are in development under the LABA collaboration agreement between Glaxo Group Limited and Theravance, Inc. ‘081 is in development under the strategic alliance between Glaxo Group Limited and Theravance, Inc.

The posters are filed as Exhibits 99.1 to 99.4 to this report and are incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit	Description
Exhibit 99.1	Long-term safety and tolerability of umeclidinium/vilanterol and umeclidinium in COPD
Exhibit 99.2	Effects of a combination of vilanterol and umeclidinium on exercise endurance in subjects with COPD: two randomised clinical trials
Exhibit 99.3	Ease of use of a two-strip dry powder inhaler (DPI) to deliver fluticasone furoate/vilanterol (FF/VI) and FF alone in asthma
Exhibit 99.4	Population pharmacokinetics and pharmacodynamics of GSK961081 (MABA) in patients with moderate to severe 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 8, 2013

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

EXHIBIT INDEX

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99.3	Ease of use of a two-strip dry powder inhaler (DPI) to deliver fluticasone furoate/vilanterol (FF/VI) and FF alone in asthma
99.4	Population pharmacokinetics and pharmacodynamics of GSK961081 (MABA) in patients with moderate to severe COPD

Poster No. P760

Long-term safety and tolerability of umeclidinium/vilanterol and umeclidinium in COPD

James Donohue,(1) Dennis Niewoehner,(2) Jean Brooks,(3) Dianne O'Dell,(4) Alison Church(4)

(1)University of North Carolina, North Carolina, USA; (2)VA Medical Center, Minneapolis, USA; (3)GlaxoSmithKline, Stockley Park, Uxbridge, UK; (4)GlaxoSmithKline, Respiratory, Research Triangle Park, North Carolina, USA

INTRODUCTION

- Current Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines recommend treatment with one or more long-acting bronchodilators for patients with moderate-to-very severe chronic obstructive pulmonary disease (COPD).(1),(2)
- Umeclidinium (UMEC) is a long-acting muscarinic antagonist in development, as monotherapy and as a combination bronchodilator with the long-acting β_2-agonist vilanterol (UMEC/VI), for the maintenance treatment of COPD.

AIMS

- To evaluate the long-term safety and tolerability of once-daily UMEC/VI 125/25 mcg (delivering 113/22 mcg) and UMEC 125 mcg (delivering 113 mcg) in patients with COPD.

METHODS

Study design and treatment

- This was a 52-week, multicentre, double-blind, placebo-controlled, parallel-group study (DB2113359; NCT01316887). A follow-up phone contact was conducted 1 week after the final study visit.
- Eligible patients were current/former smokers ≥40 years of age, with a smoking history ≥10 pack-years, clinically established COPD, post-salbutamol forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio <0.70 and post-salbutamol FEV_1 ≥35% and ≤80% predicted.
- Patients were randomised 2:2:1 to once-daily UMEC/VI 125/25, UMEC 125 and placebo. Concurrent use of inhaled corticosteroids (ICS) and rescue use of salbutamol was allowed.
- All treatments were administered via the ELLIPTA™* dry powder inhaler.
- All patients provided written informed consent prior to study participation. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study endpoints

- These included: incidence of adverse events (AEs), laboratory parameters and electrocardiography (ECG) parameters.
- Additionally, COPD exacerbations (incidence and time to first exacerbation), rescue medication use, trough FEV_1, trough FVC and the incidence of AEs of special interest (cardiovascular and ocular effects, effects on glucose and potassium, tremor, urinary retention, gallbladder disorders, pneumonia, intestinal obstruction, anticholinergic syndrome) were also assessed.

RESULTS

Patient demographics and baseline characteristics

- Of the 563 patients randomised to treatment, 562 received treatment and were included in the intent-to-treat population.
- Patient demographics, baseline characteristics and co-morbid conditions were similar across the treatment groups (Table 1).

TABLE 1. PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

	UMEC/VI 125/25 (N=226)	UMEC 125 (N=227)	Placebo (N=109)	Total
Age, years	61.4 (9.01)	61.7 (9.10)	60.1 (8.28)	61.3 (8.92)
Males, n (%)	156 (69)	145 (64)	73 (67)	374 (67)
Ethnicity, n (%)				
Hispanic/Latino	19 (8)	17 (7)	7 (6)	43 (8)
Not Hispanic/Latino	207 (92)	210 (93)	102 (94)	519 (92)
Smoking pack-years	43.7 (27.49)	39.2 (21.24)	42.8 (24.71)	41.7 (24.63)
Pre-bronchodilator FEV_1, L	1.498 (0.5255)	1.432 (0.5120)	1.579 (0.5714)	1.487 (0.5311)

Post-salbutamol FEV_1, L	1.647 (0.5138)	1.594 (0.4884)	1.724 (0.5691)	1.641 (0.5164)
Post-salbutamol % predicted FEV_1	55.0 (12.10)	54.2 (11.81)	55.1 (11.68)	54.7 (11.89)
Reversible to salbutamol, n (%)(a)	78 (35)	72 (32)	36 (33)	186 (34)
ICS use, n (%)	80 (35)	73 (32)	40 (37)	193 (34)
Cardiovascular risk factors, n (%)(b)	151 (67)	155 (68)	70 (64)	376 (67)

All data presented as mean (standard deviation) unless otherwise stated.

(a)Reversible defined as an increase in FEV_1 ≥12% and ≥0.2 L following administration of salbutamol.
(b)Current medical history of angina pectoris, diabetes, hyperlipidaemia, hypertension, myocardial infarction or stroke (no events of myocardial infarction/stroke were reported).

AEs

- A similar incidence of on-treatment AEs was reported for UMEC/VI 125/25 and placebo, with a higher incidence reported for UMEC 125 (Table 2). Similar incidences of serious AEs (SAEs; 6—7%) and drug-related AEs (12—13%) were observed across all groups.
- Headache was the most common AE in each treatment group (8—11%; Table 2).

TABLE 2. AE AND SAE OVERVIEW

AE category	UMEC/VI 125/25 (N=226)	UMEC 125 (N=227)	Placebo (N=109)
Any on-treatment AEs	**120 (53)**	**132 (58)**	**57 (52)**
AEs occurring in ≥5% of any study group			
Headache	20 (9)	25 (11)	9 (8)
Nasopharyngitis	11 (5)	20 (9)	5 (5)
Ventricular extrasystoles	11 (5)	12 (5)	5 (5)
Hypertension	8 (4)	4 (2)	5 (5)
Influenza	6 (3)	5 (2)	5 (5)
Any SAEs	**14 (6)**	**17 (7)**	**7 (6)**

Data expressed as n, (%).

- No individual on-treatment AE in any special interest group was reported by >5% of patients; incidences were generally similar across treatment groups.
  - Pneumonia special interest AE group: a higher incidence was reported for UMEC 125 (5%) compared with UMEC/VI 125/25 or placebo (both 2%). Specifically, pneumonia itself was only reported with UMEC 125 (3%).
  - Glucose effects special interest AE group: a higher incidence was reported with UMEC/VI 125/25 (4%) compared with placebo (0%).
- Fewer AEs leading to permanent discontinuation or withdrawal were observed with UMEC/VI 125/25 (8%) and UMEC 125 (9%) compared with placebo (11%).

- Five deaths occurred during the study, 4 (2%) in the UMEC 125 group (spine metastases, liver metastases, pneumonia, cardiac failure) and 1 (<1%) in the placebo group (coronary artery insufficiency).
- None of the deaths were considered to be related to the study drug by the reporting investigator.

Laboratory and ECG parameters

- No clinically-meaningful effects on vital signs or laboratory assessments were reported for active treatments compared with placebo.
- The proportions of patients with ≥1 abnormal, clinically significant post-baseline 12-lead or Holter ECG interpretation were generally similar across treatment groups (12-lead: 23—26%; Holter 52—55%).
- Individual ECG abnormalities with an incidence ≥2% greater than placebo include:
  - Holter (atrial arrhythmias): ectopic supraventricular beats (UMEC 125: 9%), sustained supraventricular tachycardia (UMEC 125: 5%) (Table 3) and ectopic supraventricular rhythm (UMEC 125: 4%).
  - 12-lead: frequent ventricular depolarisation (UMEC/VI 125/25: 5%; UMEC 125: 6%), ectopic supraventricular beats (UMEC/VI 125/25: 3%; UMEC 125: 4%), right bundle branch block (UMEC 125/25: 4%), first degree atrioventricular block (UMEC 125: 3%).
- Mean changes from baseline in heart rate were generally small across treatment groups at all visits, with no evidence of a treatment-related effect.

TABLE 3. POST-RANDOMISATION ABNORMALITIES FROM ABNORMAL, CLINICALLY SIGNIFICANT HOLTER ECGS(a)

	UMEC/VI 125/25 (N=206)	UMEC 125 (N=198)	Placebo (n=90)
Any event	114 (55)	109 (55)	47 (52)
Bigeminy	74 (36)	60 (30)	25 (28)

Ventricular couplets	62 (30)	54 (27)	32 (36)
Non-sustained ventricular tachycardia (<100 beats/min, 3—30 beats)	22 (11)	16 (8)	11 (12)
Premature ventricular complex (>1000/24 h)	17 (8)	16 (8)	5 (6)
Ectopic supraventricular beats	7 (3)	17 (9)	4 (4)
Trigeminy	12 (6)	10 (5)	5 (6)
Sustained supraventricular tachycardia (>100 beats/min, >30 beats)	5 (2)	9 (5)	2 (2)

Data expressed as n, (%).

(a)Based on events occurring in ≥5% of patients in any treatment group.

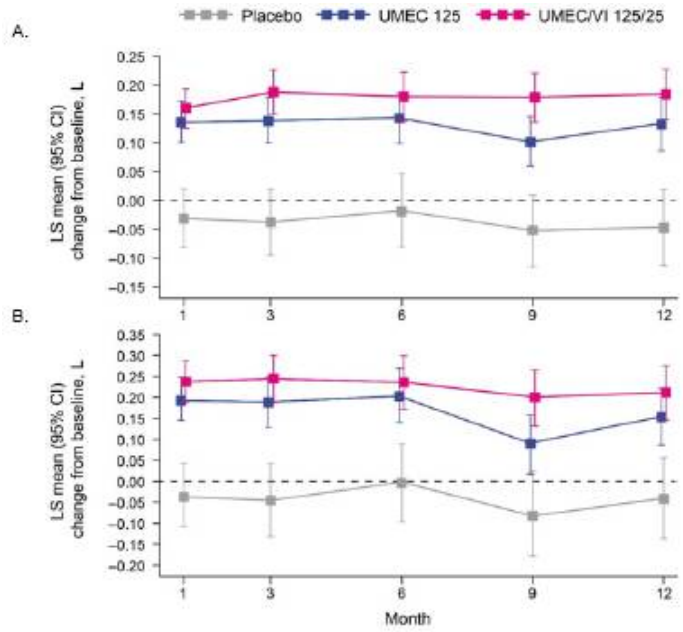
COPD exacerbations and rescue medication use

- COPD exacerbations were fewer with active treatments compared with placebo (13—15% *vs* 24%), as were COPD exacerbations leading to hospitalisation (6—7% *vs* 12%).
- Less rescue medication was required with active treatments (1.6—2.2 puffs/day) compared with placebo (2.6 puffs/day).

Trough FEV_1 and FVC

- Greater mean changes from baseline in trough FEV_1 were shown for UMEC/VI 125/25 and UMEC 125 compared with placebo at all study visits (Figure 1).
- At 52 weeks, UMEC/VI 125/25 and UMEC 125 improved trough FEV_1 by 0.231 L and 0.178 L, respectively; trough FVC was improved by 0.252 L and 0.194 L.

FIGURE 1. LS MEAN CHANGE FROM BASELINE IN TROUGH FEV_1 (A) AND FVC (B)



CI, confidence interval; LS, least squares.

CONCLUSIONS

- UMEC/VI 125/25 and UMEC 125 were well tolerated over 52 weeks of treatment in patients with COPD.
- Both treatments also provided improvements in lung function and rescue medication use compared with placebo.
- These safety and tolerability data are supportive of the use of once-daily UMEC/VI 125/25 and UMEC 125 as long-term maintenance treatments for COPD.

REFERENCES

(1) GOLD 2013. Available at: *http://www.Goldcopd.org/* [Accessed August 2013].
(2) Celli BR, Macnee W. *Eur Respir J* 2004; 23:932—946.

ACKNOWLEDGEMENTS

· The presenting author, Professor James Donohue, is a consultant and advisor for Boehringer Ingelheim, Forest Laboratories, GlaxoSmithKline, Mylan, Novartis, Sunovion, and is a consultant for Pneumrx on the data safety monitoring board. JB, DO and AC are employees of GlaxoSmithKline and hold stocks/shares in the company. DN has received fees from AstraZeneca, Boehringer Ingelheim, Forest Research, GlaxoSmithKline, Merck and Novartis, for serving on advisory boards or endpoint committees of clinical trials.

· This study was sponsored by GlaxoSmithKline (ClinicalTrials.gov: NCT01316887; protocol number: DB2113359).

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Presented at the Annual Congress of the European Respiratory Society (ERS), Barcelona, Spain, 7–11 September, 2013

Poster No. P761

Effects of a combination of vilanterol and umeclidinium on exercise endurance in subjects with COPD: two randomised clinical trials

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INTRODUCTION

Exercise intolerance is a feature of patients with chronic obstructive pulmonary disease (COPD) and is associated with poor outcomes in this disease.

OBJECTIVES

Two crossover studies were designed to examine the effect of the combination of inhaled umeclidinium/vilanterol (UMEC/VI) at two different doses (125/25 mcg and 62.5/25 mcg) on exercise performance, expiratory flows and lung volumes. The two component bronchodilators UMEC (both 125 and 62.5 mcg doses) and VI were also characterised.

METHODS

Study population key details

Current and former smokers ≥40 years of age with a smoking history of ≥10 pack-years and a diagnosis of moderate-to-severe stable COPD (post-bronchodilator forced expiratory volume in one second [FEV_1]/forced vital capacity [FVC] <70% and FEV_1 ≥35% and ≤70% predicted). Stable/regular doses of inhaled corticosteroids (ICS) were allowed. A score of ≥2 on the Modified Medical Research Council Dyspnoea Scale at Visit 1 was required along with a resting functional residual capacity (FRC) of ≥120% predicted. The presence of co-morbid respiratory conditions or a current diagnosis of asthma were exclusionary.

Trial design

Two identical multicentre, randomised, double-blind, placebo-controlled crossover studies involving incomplete treatment block were designed (DB2114417, NCT01328444; DB2114418, NCT01323660). Eligible patients were randomised to receive one of the 26 treatment sequences consisting of two of the following treatments: UMEC/VI 125/25, UMEC/VI 62.5/25, UMEC 125, UMEC 62.5, VI 25 or placebo, once daily via the ELLIPTA™* inhaler. Baseline patient demographics are shown in Table 1. The duration of each treatment period was 12 weeks with 12 clinic visits.

Co-primary endpoints of exercise endurance time (EET) and FEV_1

EET using endurance shuttle walking test(1) 3 hours post-dose at Week 12, defined as the EET obtained 3 hours after dosing at Week 12; FEV_1 clinic visit trough FEV_1 at Week 12.

Secondary endpoints

Clinic visit trough and 3-hour post-dose measurements of lung volumes at Week 12.

Safety analyses

Safety endpoints included adverse events (AEs), vital signs, 12-lead electrocardiogram (ECG), clinical chemistry, haematology and the incidence of exacerbations.

RESULTS

TABLE 1. STUDY POPULATIONS BASELINE DEMOGRAPHICS

	DB2114417	DB2114418
ITT population	(N=348)	(N=307)
Mean age, years (SD)	61.6 (8.3)	62.6 (7.9)
Sex, female, n (%)	153 (44)	139 (45)
Current smoker at screening*, n (%)	220 (63)	186 (61)
Smoking pack-years, mean (SD)	48.7 (25.3)	47.4 (24.7)
ICS use at screening, n (%)	98 (28)	121 (39)
Post-salbutamol % predicted FEV_1, mean (SD)	51.3 (9.7)	51.3 (10.0)
Post-salbutamol FEV_1/FVC, mean (SD)	49.3 (10.2)	47.9 (10.2)
GOLD stage, n	348	304
I, n (%)	0	2 (<1)
II, n (%)	185 (53)	158 (52)
III, n (%)	163 (47)	143 (47)
IV, n (%)	0	1 (<1)
Reversible to salbutamol, n (%)	120 (34)	118 (39)
Reversible to salbutamol and ipratropium, n (%)	187 (55)	198 (66)
% reversibility to salbutamol, mean (SD)	12.6 (15.6)	16.2 (14.0)
% reversibility to salbutamol and ipratropium, mean (SD)	20.3 (18.9)	24.6 (17.1)

% predicted normal FRC, mean (SD)					153.6 (32.0)	151.6 (31.2)	

*Patient was reclassified as a current smoker if he/she smoked within 6 months of screening GOLD, Global initiative for chronic Obstructive Lung Disease; ITT, intent-to-treat; SD, standard deviation.

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TABLE 2. LS MEAN CHANGE FROM BASELINE AND *VS* PLACEBO FOR EET AT WEEK 12

EET, (s)		Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	VI 25	UMEC 62.5	UMEC 125
DB2114417	n	145	131	130	63	43	44
	LS mean change from baseline (SE)	36.7 (13.2)	58.6 (13.8)	69.1 (14.0)	26.7 (19.7)	63.2 (23.9)	49.8 (23.8)
	Difference from Placebo (95% CI)		21.9 (–14.2, 58.0)	32.4 (–3.9, 68.8)	–10 (–55.5, 35.4)	26.5 (–25.9, 78.9)	13.1 (–38.9, 65.1)
DB2114418	n	117	115	109	54	37	32
	LS mean change from baseline (SE)	0.1 (16.7)	69.5 (17.1)	65.9 (17.5)	30.7 (24.8)	25.1 (30.2)	74.8 (31.6)
	Difference from Placebo (95% CI)		69.4 (24.5,114.4)**	65.8 (20.3, 111.3)**	30.6 (–26.8, 88.0)	25 (–41.0, 91.0)	74.7 (6.0, 143.4)*

n is the number of patients with analysable data at Week 12; *p<0.05; **p<0.01. CI, confidence interval; LS, least squares; SE, standard error. Note: analysis performed using a repeated measures model with covariates of period walking speed, mean walking speed, period, treatment, visit, smoking status, centre group, visit by period walking speed, visit by mean walking speed and visit by treatment interactions.

EET

Study DB2114417 did not achieve clinically relevant or statistically significant improvements of EET *vs* placebo for UMEC/VI 125/25 or 62.5/25 (Table 2).

Study DB2114418 showed clinically important and statistically significant improvements in EET for UMEC/VI 125/25 and UMEC/VI 62.5/25 *vs* placebo (Table 2).

VI showed similar improvements in EET from baseline across both studies but less than the combination, whereas UMEC 62.5 and UMEC 125 were more variable across the studies (Table 2).

Both studies showed similar improvements from baseline for both doses of UMEC/VI, but Study DB2114417 showed a large placebo effect. This placebo effect was visible from Day 2 and continued throughout the study (Figure 1). DB2114418 showed little placebo effect throughout the study (Figure 2).

Lung function

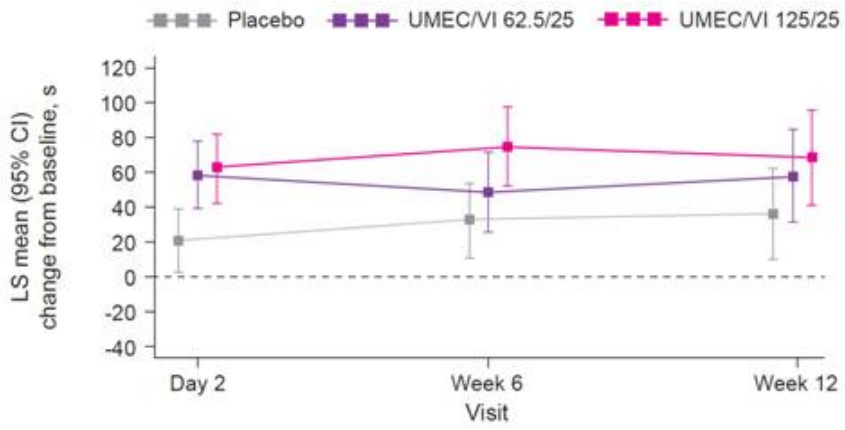
In Study DB2114417, numerical improvements were observed for trough FEV_1 for both doses of UMEC/VI (125/25 and 62.5/25) compared with placebo (Table 3). In Study DB2114418, statistically significant improvements in trough FEV_1 were demonstrated for UMEC/VI 125/25 and for UMEC/VI 62.5/25 compared with placebo (Table 3). The trough FEV_1 data for VI showed a consistent improvement across both studies, whilst UMEC 62.5 and UMEC 125 were more variable across the studies (Table 3).

TABLE 3. LS MEAN CHANGE FROM BASELINE FOR FEV_1 AT WEEK 12

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	VI 25	UMEC 62.5	UMEC 125
Trough FEV_1, (L)						
DB2114417						
n	148	130	132	64	43	44
LS mean change from baseline (SE)	–0.032 (0.015)	0.178 (0.016)	0.136 (0.016)	0.067 (0.022)	0.054 (0.026)	0.108 (0.026)
Difference from Placebo (95% CI)		0.211 (0.172, 0.249)***	0.169 (0.129, 0.209)***	0.099 (0.050, 0.148)***	0.087 (0.030, 0.143)**	0.140 (0.084, 0.196)***
DB2114418						
n	119	117	112	56	38	33
LS mean change from baseline (SE)	–0.043 (0.016)	0.200 (0.016)	0.218 (0.016)	0.069 (0.022)	0.101 (0.027)	0.212 (0.029)
Difference from Placebo (95% CI)		0.243 (0.202, 0.284)***	0.261 (0.220, 0.303)***	0.112 (0.061, 0.163)***	0.144 (0.086,0.203)***	0.255 (0.193, 0.318)***

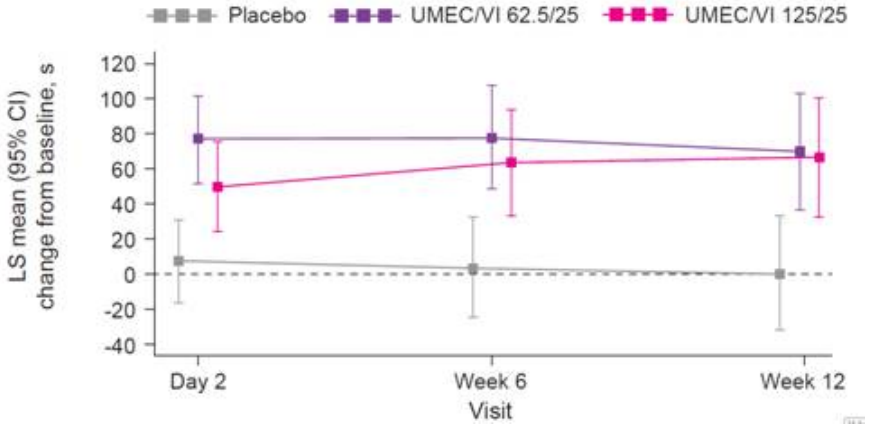
**p<0.01; ***p<0.001.

FIGURE 1. LS MEAN CHANGE FROM BASELINE FOR EET DURING THE STUDY (DB2114417)



Note: EET analyses (Figures 1 and 2) performed using a repeated measures model with covariates of period walking speed, mean walking speed, period, treatment, visit, smoking status, centre group, visit by period walking speed, visit by mean walking speed and visit by treatment interactions.

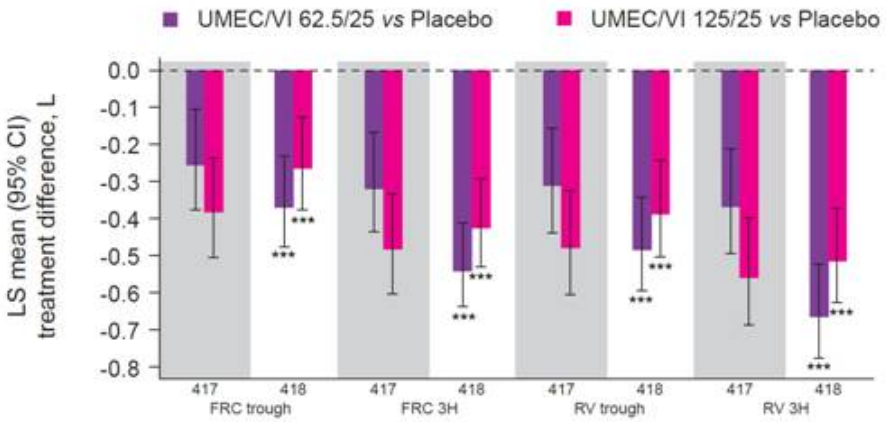
FIGURE 2. LS MEAN CHANGE FROM BASELINE FOR EET DURING THE STUDY (DB2114418)



Lung volumes for UMEC/VI

In Study DB2114417, numerical improvements were observed for both trough and 3-hour post-dose FRC, residual volume (RV) and inspiratory capacity (IC) for both doses of UMEC/VI compared with placebo (Figure 3; data not shown for IC). In Study DB2114418, statistically significant improvements in trough and 3-hour post-dose FRC, RV and IC were demonstrated for both doses of UMEC/VI compared with placebo.

FIGURE 3. LS MEAN CHANGE FROM PLACEBO IN BASELINE TROUGH AND POST-DOSE FRC (L), AND RV (L) FOR UMEC/VI (DB2114417/DB2114418) ITT POPULATION



***p<0.001.

Note: analysis performed using a repeated measures model with covariates of period baseline, mean baseline, period, treatment, visit, smoking status, centre group, visit by period baseline, visit by mean baseline and visit by treatment interactions.

Safety

AEs were distributed evenly between treatments within each study with an overall higher incidence in Study DB2114418 across all treatments including placebo (Table 4). The most common AEs overall were headache, nasopharyngitis and sinusitis (pooled data). There was one death in Study DB2114417 with UMEC 125 (reported as ‘death’) and one in Study DB2114418 with UMEC/VI 62.5/25 (reported as ‘cancer’). Neither was considered related to study medication by the reporting investigator.

TABLE 4. SUMMARY OF ON-TREATMENT AEs REPORTED BY ≥3% OF PATIENTS WITHIN ANY TREATMENT (DB2114417) OR BY 2 OR MORE PATIENTS (DB2114418) ITT POPULATION

	Number (%) of patients					
	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	VI 25	UMEC 62.5	UMEC 125
DB2114417	N=170	N=152	N=144	N=76	N=49	N=50
On-treatment AEs	46 (27)	35 (23)	46 (32)	22 (29)	6 (12)	14 (28)
Preferred term						
Nasopharyngitis	10 (6)	5 (3)	8 (6)	3 (4)	1 (2)	1 (2)
Headache	7 (4)	3 (2)	2 (1)	4 (5)	0	1 (2)
Sinusitis	3 (2)	0	4 (3)	0	0	2 (4)
Dry mouth	0	0	0	0	0	2 (4)
DB2114418	N=151	N=130	N=128	N=64	N=40	N=41
On-treatment AEs	59 (39)	57 (44)	52 (41)	23 (36)	12 (30)	22 (54)
Preferred term						
Nasopharyngitis	10 (7)	8 (6)	2 (2)	1 (2)	4 (10)	4 (10)
Headache	8 (5)	3 (2)	6 (5)	1 (2)	1 (3)	4 (10)
Cough	3 (2)	2 (2)	5 (4)	2 (3)	0	1 (2)
Arthralgia	2 (1)	6 (5)	0	0	1 (3)	1 (2)
Back pain	5 (3)	0	2 (2)	2 (3)	0	1 (2)
Sinusitis	3 (2)	2 (2)	0	3 (5)	0	2 (5)
Dyspnoea	6 (4)	0	1 (<1)	1 (2)	0	1 (2)
Upper respiratory tract infection	1 (<1)	3 (2)	3 (2)	2 (3)	0	0
Musculoskeletal pain	0	0	1 (<1)	2 (3)	0	1 (2)
Toothache	1 (<1)	1 (<1)	0	0	0	2 (5)
Osteoarthritis	2 (1)	0	0	0	1 (3)	0

CONCLUSIONS

- Both dose combinations of UMEC/VI improved exercise endurance from baseline but improvements against placebo were seen only in Study DB2114418.
- Both dose combinations of UMEC/VI were effective bronchodilators, improving lung function in COPD patients with resting hyperinflation.
- Both dose combinations of UMEC/VI improved lung volumes.
- Safety and tolerability profiles of UMEC/VI 125/25 and 62.5/25 were similar to the monotherapies and placebo.

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Placeholder for QR code

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Ease of use of a two-strip dry powder inhaler (DPI) to deliver fluticasone furoate/vilanterol (FF/VI) and FF alone in asthma

Poster No. P701

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INTRODUCTION

- Difficulty in inhaler use, and incorrect use, are associated with two types of poor adherence to prescribed asthma treatment(1),(2)
  - intentional non-adherence: the patient chooses not to take the medication
  - non-intentional (unconscious) non-adherence: the patient does not receive the prescribed dose of medication because of incorrect inhaler use.
- The ELLIPTA™ DPI is a handheld inhaler with built-in dose counter, approved for the delivery of fluticasone furoate (FF) alone and in combination with vilanterol (VI), and in development for other new inhaled therapies
  - US approval granted for FF/VI treatment of COPD on 10 May 2013.

OBJECTIVES

- To assess the perception of the ease of use of the ELLIPTA DPI among patients with asthma participating in randomised clinical trials.
- To assess participating patients' competence in the use of the ELLIPTA DPI, as judged by trial investigators.

METHODS

- All participants completed one of the following studies of FF/VI or FF dosed once daily via the ELLIPTA DPI (Figure 1).

Figure 1. The ELLIPTA DPI

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- Clinical studies from which participants (Table 1) were recruited
  - HZA106827 (NCT01165138), a 12-week study of FF/VI 100/25mcg, FF 100mcg and placebo
  - FFA114496 (NCT01431950), a 24-week study of FF 100mcg and FF 200mcg
  - FFA115283 (NCT01436071), a 12-week study of FF 50mcg and placebo.

Table 1. Participant demographics and lung function characteristics

	HZA106827 (N=609)	FFA114496 (N=219)	FFA115283 (N=222)
Age, years	39.7 (16.6)	46.4 (15.4)	35.2 (15.1)
Female sex, n (%)	353 (58)	148 (68)	133 (60)
Duration of asthma, years	12.1 (11.4)	20.5 (15.5)	16.6 (12.0)
Pre-bronchodilator FEV_1, L	2.23 (0.60)	1.97 (0.58)	2.49 (0.69)
% predicted FEV_1, L	67.59 (11.22)	65.32 (12.33)	76.02 (11.37)
% FEV_1 reversibility to salbutamol	28.7 (18.3)	32.3 (18.5)	24.5 (10.1)

Data for intent-to-treat population. All data are mean (SD) unless otherwise stated
Lung function data were recorded at the screening visit
FEV_1, forced expiratory volume in one second

Inhaler user assessment

- Trial investigators assessed patients' competence in the usage of the ELLIPTA DPI at baseline, and again at Week 2 and Week 4 of the treatment period.
- Patients who did not use the DPI correctly were provided with additional instruction in its use.

RESULTS

Ease of use questionnaire (Table 3)

- Across the three trials, 94% of patients reported the ELLIPTA DPI to be easy or very easy to use.
- 96% reported that it was easy or very easy to tell how many doses of medication were left in the inhaler using the ELLIPTA DPI's built-in dose counter.

Table 3. Ease of use questionnaire results

	HZA106827	FFA114496	FFA115283	Total
n	570	213	206	989
How do you rate the ease of use of the inhaler?				
Very easy	362 (64)	146 (69)	132 (64)	640 (65)
Easy	157 (28)	64 (30)	68 (33)	289 (29)
Neutral	43 (8)	3 (1)	4 (2)	50 (5)
Difficult	7 (1)	0	2 (<1)	9 (1)
Very difficult	1 (<1)	0	0	1 (<1)
How easily are you able to tell how many doses of medication are left in the inhaler?				
Very easy	419 (74)	169 (79)	144 (70)	732 (74)
Easy	126 (22)	42 (20)	51 (25)	219 (22)
Neutral	22 (4)	2 (<1)	8 (4)	32 (3)
Difficult	3 (<1)	0	1 (<1)	4 (1)
Very difficult	0	0	2 (<1)	2 (<1)

All data are n (%)

Inhaler use assessment (Table 4)

- 95% of patients used the ELLIPTA DPI correctly as adjudicated by the investigator after a single demonstration of correct usage at the baseline (Week 0) visit.
- >99% of patients used the DPI correctly at Week 2 and at Week 4.

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Table 4. Inhaler use assessment results

	HZA106827	FFA114496	FFA115283	Total
Week 0*				
n	609	218	222	1049
Patient used inhaler correctly	578 (95)	206 (94)	216 (97)	1000 (95)
One further instruction required	22 (4)	11 (5)	5 (2)	38 (4)
Two further instructions required	8 (1)	1 (<1)	1 (<1)	10 (1)
>2 further instructions required	1 (<1)	0	0	1 (<1)
Week 2				
n	593	215	216	1024
Patient used inhaler correctly	593 (100)	211 (98)	216 (100)	1020 (>99)
One further instruction required	0	3 (1)	0	3 (<1)
Two further instructions required	0	1 (<1)	0	1 (<1)
>2 further instructions required	0	0	0	0
Week 4				
n	569	213	206	988
Patient used inhaler correctly	569 (100)	210 (99)	205 (>99)	984 (>99)
One further instruction required	0	3 (1)	1 (<1)	4 (<1)
Two further instructions required	0	0	0	0
>2 further instructions required	0	0	0	0

*After one demonstration of correct usage at the baseline clinic visit

CONCLUSIONS

- Patients with asthma participating in clinical trials using the ELLIPTA DPI found the inhaler to be easy to use, and its dose counter to be intuitive and clearly readable.
- Few instances of incorrect use of the DPI were reported.
- The findings reported here suggest that the ELLIPTA DPI is perceived positively and used correctly by patients with asthma.

Placeholder for QR code

Presented at the European Respiratory Society Annual Congress, Barcelona, Spain, 7–11 September 2013

Poster No.1248

Population pharmacokinetics and pharmacodynamics of GSK961081 (MABA) in patients with moderate to severe COPD

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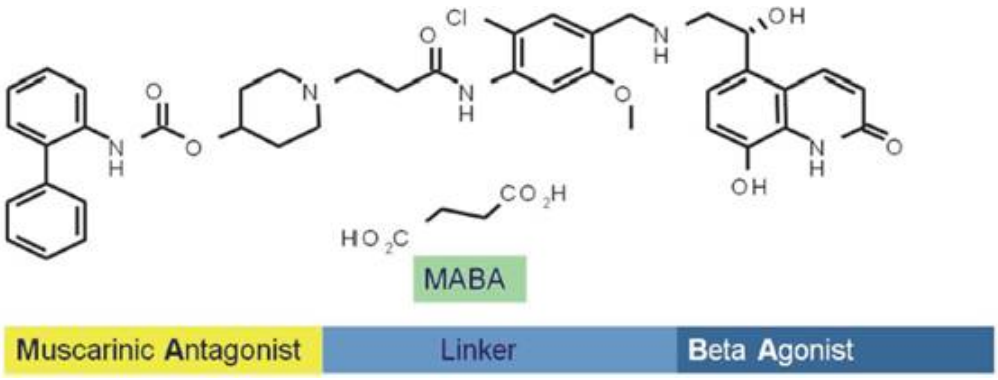
INTRODUCTION

- GSK961081 is a potent bi-functional molecule that has demonstrated both anti-muscarinic receptor activity (MA) and beta2-adrenergic agonist activity (BA) in pre-clinical and clinical investigation [1,2,3].



- In COPD trials, GSK961081 has shown clinically meaningful bronchodilation with rapid onset of action with a good safety and tolerability profile [4,5].

OBJECTIVES

- To characterise the population pharmacokinetics (PK) and pharmacodynamics (PD) of GSK961081 in moderate to severe COPD subjects.

METHODS

- Data were obtained from a 4-week, multicentre, randomised, double-blind, double dummy, placebo and salmeterol controlled parallel group study [5].
- Once (OD) and twice (BD) daily GSK961081 DISKUS™ dosing regimens were assessed;
  - OD doses: 100, 400 & 800 mcg
  - BD doses: 100, 200 & 400 mcg
- Trough FEV1 at day 29 was the primary endpoint.
- Plasma GSK961081 concentrations were an additional endpoint.
  - Blood samples were collected on Day 28: Pre AM dose (-1h to 0min) and post AM dose between 0-30min, 30min-2h, 2-6h and 6-11h. Pre PM dose (-1h to 0min) and post PM dose between 0-30min, 30min-2h, 2-6h and 6-11h. PK subset subjects only.
  - PK bioanalysis was performed using a validated high performance liquid chromatography/mass spectrometry (HPLC-MS/MS) method with a lower limit of quantification (LOQ) of 25 pg/mL.

FIGURE 1. PK and PD Models

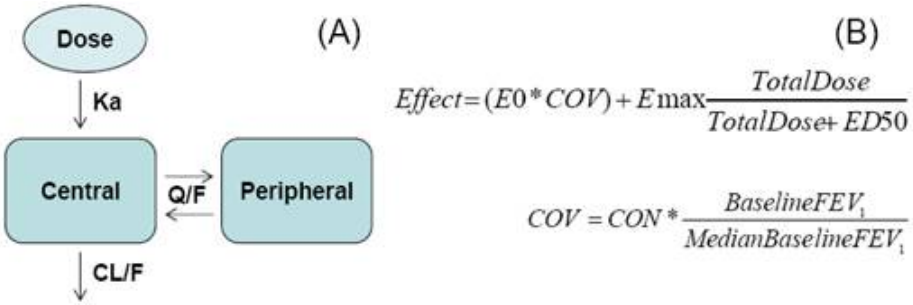


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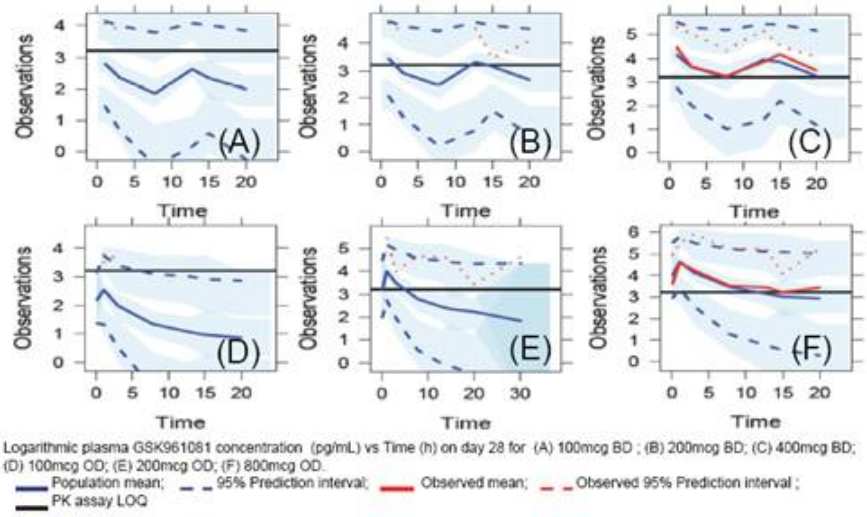
FIGURE 2. Final PK Model



PK and PD Analyses

- The software NONMEM 7 (ICON Development Solutions) was used.
    - M3 methodology was used to handle non-quantifiable (NQ) PK data [6,7].
- Models were prioritised using objective function values, plausibility of parameters and graphical checking.
- Stepwise covariate model building was used (PD model only).
- A 2-compartment PK model with first-order absorption was selected and fitted to the PK data (Figure 1A).
- To characterise the dose-response curve an Emax model was selected and fitted to the PD data (Figure 1B).

TABLE 1. PK Model Parameters

PK Parameter	Estimate	95% CI	RSE%
Clearance, CL/F (L/h)	944	750, 1188	1.72
Central volume, V2/F (L)	523	337, 829	3.71
Absorption rate constant, Ka (h^{-1})	0.411	0.313, 0.535	15.2
Peripheral volume, V3/F (L)	21375	12088, 36316	2.90
Inter-compartment clearance, Q/F (L/h)	1408	1035, 1915	2.17

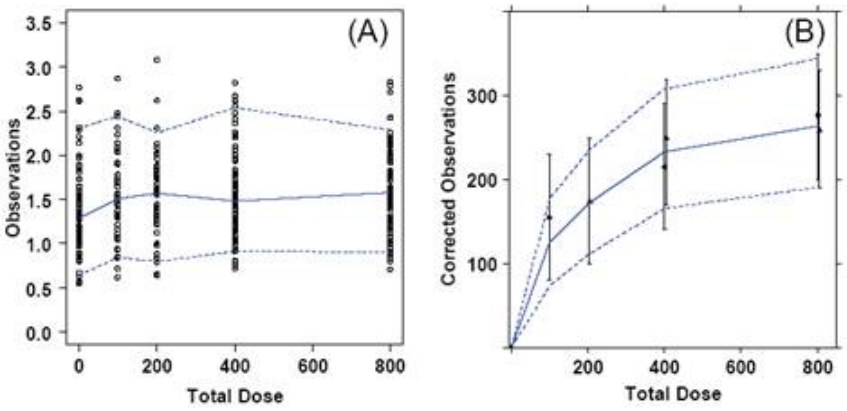
CI: Confidence interval; %RSE: Relative standard error.

RESULTS

PK

- Greater than 50% of PK data per treatment group was NQ; except for at 800mcg QD (27% NQ) and 400mcg BD (30% NQ);
    - Therefore the PK model was selected based on these two treatment groups only (N=47).
- The PK model well characterised the observed 800mcg OD and 400mcg BD data (Figure 2(C) and (F)).
- PK model parameters were estimated with good precision (%RSE<20%) (Table 1).
- Covariates were not included in the PK model.
- Evaluation of the PK model using the data not used in model building (N=139) showed a good fit (Figure 2(A),(B),(D) and (E)).

FIGURE 3. Final PD Model (Trough FEV1, day 29)



(A) Day 29 trough FEV1 (L) vs Total daily dose (mcg). o Observed data; ▬ Population mean; - - 95% Prediction interval.
(B) Day 29 placebo corrected change from baseline trough FEV1 (mL) vs Total daily dose (mcg). OD (■) or BD (▲) LSMean (95% confidence interval) ; ▬ Population median; - - 95% Prediction interval

PD

- The PD model gave a good fit to the observed data (Figure 3(A)) (N=347).
- PD model parameters were estimated with precision%RSE≤50% (Table 2).
- Dosing regimen, age, weight, sex, height and inhaled corticosteroid use were not identified as statistically significant covariate effects.
- Baseline FEV1 was identified as a statistically significant covariate effect on E0.
- The PD model concurred well with the primary endpoint analysis (Figure 3(B) and [5]) based on post-hoc derived placebo corrected change from baseline.

TABLE 2. PD Model Parameters

PD Parameter	Estimate	95% CI	RSE%
Emax (L)	0.293	0.207, 0.379	14.9
ED50 (mcg)	152	2.45, 302	50.2
Intercept , E0 (L)	0.0650	0.0233, 0.107	32.8
Baseline, COV (L)	19.0	5.24, 32.8	36.9

CI: Confidence interval; %RSE: Relative standard error.

CONCLUSIONS

- The PK model described will be used as a tool for guiding GSK961081 clinical development.
  - The model performed well and in addition was able to account for Non Quantifiable data.
  - Covariate inclusion in the model will be re-visited once additional PK data is available.
- The PD model described will be used as a tool for guiding dose selection for GSK961081 in Phase III trials.
  - There was no influence of dosing regimen on the PD model; indicating there was no apparent difference between OD and BD dosing for day 29 trough FEV1 (primary end point).

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