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): **May 19, 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 May 19, 2013 at the American Thoracic Society International Conference in Philadelphia, Pennsylvania, GlaxoSmithKline plc (GSK) presented posters containing information from a Phase 3 study of the combination treatment fluticasone furoate/vilanterol (FF/VI) and a Phase 1 study of umeclidinium bromide (UMEC) monotherapy and UMEC/VI combination. FF/VI, known in the United States as BREO™ ELLIPTA™ (100/25mcg), recently gained U.S. Food and Drug Administration approval as an inhaled long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (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 remains in development elsewhere in the world for the maintenance treatment of asthma and COPD, with pending marketing authorization applications in a number of countries. It is not currently approved or licensed in the European Union or anywhere outside of the U.S. 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 Theravance, Inc. (the "Company"). The Company also presented a poster containing information from a Phase 2 study of TD-4208, its internally-discovered investigational LAMA for the treatment of COPD. The posters are filed as Exhibits 99.1 to 99.3 to this report and are incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit	**Description**

Exhibit 99.1	Long-acting bronchodilators and arterial stiffness in patients with COPD
Exhibit 99.2	A placebo- and moxifloxacin-controlled thorough QT study of umeclidinium monotherapy and umeclidinium/vilanterol combination in healthy subjects
Exhibit 99.3	Single-dose Pharmacokinetics of TD-4208, a Novel Long-acting Muscarinic Antagonist, 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: May 19, 2013

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

EXHIBIT INDEX

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Long-acting bronchodilators and arterial stiffness in patients with COPD

POSTER NO. 225

***D.B. Rubin*(1), J.-L. Pepin(2), J.R. Cockcroft(3), D. Midwinter(4), S. Sharma(1), S. Andreas(5)**

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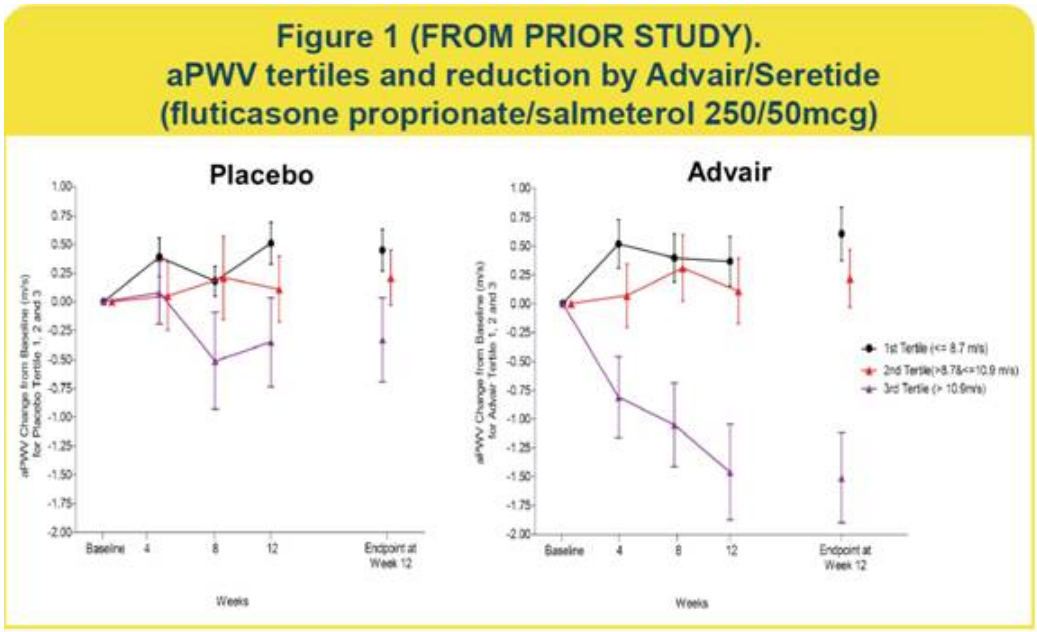
INTRODUCTION

- Increased arterial stiffness as measured by aortic pulse wave velocity (aPWV) independently predicts cardiovascular (CV) events and mortality(1) and is elevated in COPD patients.(2)
- A post-hoc analysis of a clinical trial with Advair/Seretide (250/50mcg) suggested that a long-acting beta agonist/inhaled corticosteroid (LABA/ICS) lowers aPWV in patients with baseline aPWV values >11 meters per second (m/s)(3) (Figure 1). These results prompted the current investigation.



OBJECTIVES

- As LABA/ICS and tiotropium (TIO) may have a different impact on CV events, the purpose of this study was to compare the effect of fluticasone furoate/vilanterol (FF/VI) with TIO on aPWV.

METHODS

- This multicenter, randomized, double-blind, double-dummy, parallel group study compared FF/VI 100/25mcg and TIO 18mcg both once daily over 12 weeks.
- aPWV was measured by sequentially recording ECG-gated carotid and femoral artery waveforms.
- The primary endpoint was aPWV change from baseline at 12 weeks. Other endpoints included trough FEV_1 and St. George Respiratory Questionnaire for COPD (SGRQ-C). Primary analysis was intent-to-treat (ITT).

RESULTS

Table 1. Screening/baseline characteristics (ITT)*

	N=257
Demographics	
Age, years	67.3 (7.28)
Female sex, %	14
White race, %	100
Smoking history	
Smoking pack years	43.6 (22.55)
Current smokers at screening, %	46
Cardiovascular history/risk factors, %	87
aPWV at screening (m/s)	12.91 (1.902)
Augmentation index at screening (%)	26.3 (10.76)

Lung function at screening	
Pre-bronchodilator FEV_1 (L)	1.271 (0.4559)
Percent predicted post-bronchodilator FEV_1 (%)	46.5 (14.15)
Percent reversibility in FEV_1 (%)	8.5 (12.56)
Post-bronchodilator FEV_1/FVC (%)	51.3 (11.13)
Proportion reversible (%)	16
Inspiratory capacity at baseline (L)	2.123 (0.6499)

Data are mean (SD) and from the baseline visit unless otherwise stated

*There were no differences in characteristics between patients randomized to FF/VI vs TIO

Table 2. Change from baseline in FEV_1 (L) (ITT)

Trough FEV_1 (L) at Day 84	**FF/VI 100/25 N=127**	**TIO N=130**
n[1]	117	122
n[2]	112	112
LS mean	1.406	1.368
LS mean change (SE for mean/mean change)	0.117 (0.0221)	0.080 (0.0219)
FF/VI versus TIO		
Difference (95% CI)	0.037 (-0.024, 0.099)	
P-value	0.232	

n[1] = number of subjects with analyzable data for one or more time points
n[2] = number of subjects with analyzable data at the given time point
LS = least square

Figure 2. Adjusted mean change from baseline aPWV (m/s) (ITT)

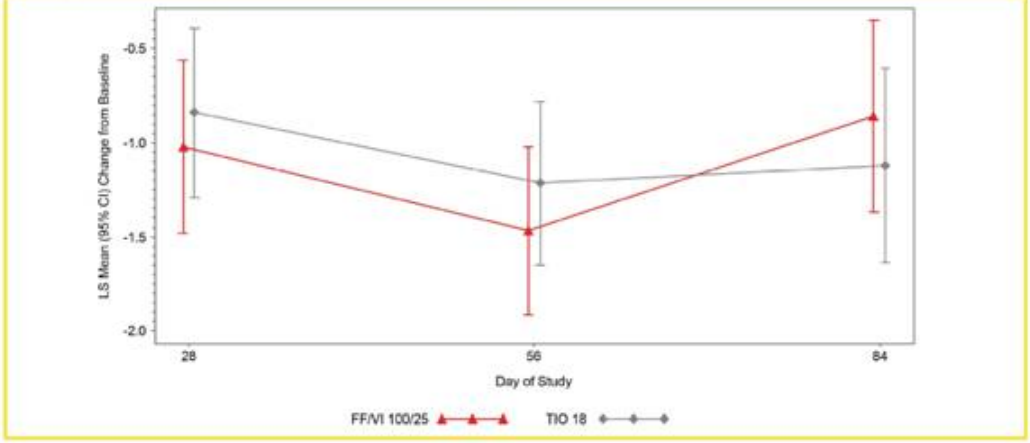


Figure 3. Raw mean change from baseline aPWV (m/s) (ITT)

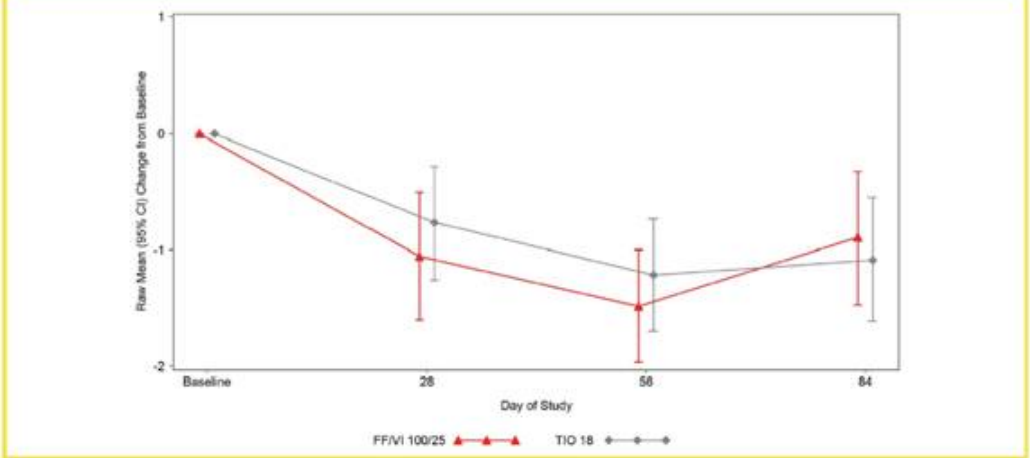


Table 3. Change in SGRQ (ITT)

SGRQ*	FF/VI 100/25 N=127	TIO N=130
Total, n[1] : n[2]	123 : 106	128 : 108
Mean baseline (SD)	50.36 (18.582)	47.97 (18.150)
Mean change from baseline (SD)	–6.03 (13.235)	–4.97 (11.503)
Symptoms Domain, n[1] : n[2]	126 : 108	130 : 112
Mean baseline (SD)	66.79 (21.338)	64.12 (19.204)
Mean change from baseline (SD)	–8.57 (17.983)	–5.09 (17.303)
Activity Domain, n[1] : n[2]	125 : 108	129 : 109
Mean baseline (SD)	59.99 (20.063)	58.75 (19.715)
Mean change from baseline (SD)	–4.72 (16.412)	–3.43 (14.631)
Impacts Domain, n[1] : n[2]	126 : 110	129 : 111
Mean baseline (SD)	39.33 (20.443)	36.90 (20.171)
Mean change from baseline (SD)	–5.84 (14.481)	–5.70 (12.863)

n[1] = number of subjects with baseline data
n[2] = number of subjects with Day 84 and baseline data
*SGRQ scores derived from SGRQ-C questionnaire

OTHER ANALYSES

- **Post-hoc analysis indicates both FF/VI and TIO lower aPWV ~1m/s, a MCID, without an impact on MAP.**
- **Responders (>1m/s) did not reveal distinguishing characteristics.**
- **Mean arterial pressure (MAP) was unchanged over the trial and including the MAP in the statistical model did not change the magnitude of the treatment effect.**
- **There was an inconsistent treatment difference for current smokers compared with former smokers over time**
  - at Days 56 and 84, the treatment difference numerically favored FF/VI for former smokers, whereas the reverse was true for current smokers
  - at Day 28 there was no apparent difference between groups for current smokers.

CONCLUSIONS

- **FF/VI and TIO have similar impact on reduction of aPWV.**
- **The COPD phenotype selected by the inclusion criterion of a aPWV >11m/s is associated with a history and/or risk of cardiovascular disease.**
- **HYPOTHESIS: We speculate that bronchodilators lower aortic stiffness by improving the inflation reflex that lowers vascular sympathetic tone. (4) Further studies exploring this mechanism are warranted.**

REFERENCES

(1) Eur Heart J 2006;27:2588.
(2) Am J Respir Crit Care Med 2007;176:1208.
(3) Resp Med 2011;105:1322.
(4) Chest 2005;128:3618.

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- The presenting author, David Rubin, is employed by and holds stock in GlaxoSmithKline.
- Funded by GlaxoSmithKline (HZC115247, NCT013958888).
- Editorial support (in the form of assembling tables) was provided by David Cutler, PhD at Gardiner-Caldwell Communications (Macclesfield, UK) and was funded by GlaxoSmithKline.

Presented at the American Thoracic Society Annual Congress, Philadelphia, PA, USA, 17—22 May 2013

Poster No. F71

A placebo- and moxifloxacin-controlled thorough QT study of umeclidinium monotherapy and umeclidinium/vilanterol combination in healthy subjects

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INTRODUCTION

· Umeclidinium (UMEC, GSK573719) is a new long-acting muscarinic antagonist (LAMA) currently under development as a once-daily inhaled bronchodilatory therapy for COPD,(1) alone or in combination with vilanterol (VI), a long-acting beta$_2$ agonist (LABA).(2)

OBJECTIVE

· To investigate the effect of UMEC monotherapy and UMEC/VI combination therapy on QT interval prolongation.

METHODS

Study design

· A randomized, placebo- and moxifloxicin-controlled, four-way, incomplete-block crossover study in healthy subjects (ClinicalTrials.gov: NCT01521377; study number: DB2114635).

Treatment

· Treatments were:

· UMEC/VI 125/25mcg for 10 days + placebo tablet (Day 10 only)
· UMEC 500mcg for 10 days + placebo tablet (Day 10 only)
· UMEC/VI 500/100mcg for 10 days + placebo tablet (Day 10 only)
· placebo for 10 days + placebo tablet (Day 10 only)
· placebo for 10 days + moxifloxacin 400mg tablet (Day 10 only).

Endpoints

· Primary endpoints were:

· effect of UMEC/VI 125/25mcg on QT interval using Fridericia's correction (QTcF) compared with placebo after 10 days
· effect of UMEC 500mcg on QTcF compared with placebo after 10 days.

· Secondary endpoints included effects of UMEC 500/100mcg and moxifloxacin 400mcg on QTcF and QT interval corrected for heart rate (HR) of the individual subject (QTcI) and of UMEC/VI 125/25mcg and UMEC 500mcg on QTcI compared with placebo, and 0–4h change from baseline in ECG ventricular HR.

· Pharmacokinetic and pharmacodynamic profiles of UMEC administered as a monotherapy and in combination with VI were characterized.

· The relationship between plasma concentrations of UMEC and VI and QTcF interval was explored using non-linear mixed effect modelling.

RESULTS

· Of the 103 subjects randomized, 86 (83%) completed the study as planned. Reasons for withdrawal: 11 withdrew consent; 3 adverse events (AEs); 2 investigator discretion; 1 met protocol-defined stopping criteria.

QTc analysis

· Analysis of QT interval, QTcB (QT interval corrected using Bazett's formula), QTcF and QTcI vs RR interval were explored to determine the most appropriate QT correction for this study. The primary endpoint, QTcF, provided the best correction as indicated by scatterplots of corrected QT vs RR. The QTcI also provided an adequate correction.

TABLE 1. SUBJECT BASELINE DEMOGRAPHICS

	Subjects (N=103)
Age, years	33.1 (19–63)
Sex: male, n (%)	55 (53)
Race, n (%)	
White	68 (66)
African American/African	21 (20)

Central/South Asian	10 (10)
Other	4 (4)
BMI, kg/m²	23.4 (19.2–29.5)
Height, cm	171.7 (153–195)
Weight, kg	69.3 (46.4–102.1)

Values are mean (range) unless otherwise stated

QTcF and QTcI: treatment vs placebo (Day 10)

· Treatment differences from placebo in adjusted mean change from baseline QTcF and QTcI interval over 24h are shown in **Table 2**.

· Moxifloxacin 400mg produced a clinically significant increase in QTcF from the 1h timepoint onwards. Assay sensitivity was demonstrated.

TABLE 2. ADJUSTED MEAN (90% CI) CHANGE FROM BASELINE QTcF COMPARED WITH PLACEBO (DAY 10)

	QTcF Treatment Difference (90% CI)(msec)				QTcI Treatment Difference (90% CI) (msec)			
Time	**Mox 400mcg**	**UMEC 500mcg**	**UMEC/VI 125/25mcg**	**UMEC/VI 500/100mcg**	**Mox 400mcg**	**UMEC 500mcg**	**UMEC/VI 125/25mcg**	**UMEC/VI 500/100mcg**
Pre-dose	–2.3 (–4.1, –0.4)	–1.5 (–3.3, 0.3)	–2.5 (–4.3, –0.7)	–2.2 (–4.1, –0.4)	–2.5 (–4.3, –0.6)	–2.8 (–4.6, –0.9)	–3.4 (–5.3, –1.6)	–4.9 (–6.7, –3.0)
5min	–1.4 (–3.8, 1.0)	–2.1 (–4.4, 0.3)	1.6 (–0.8, 3.9)	4.2 (1.8, 6.5)	–1.6 (–4.1, 0.8)	–3.3 (–5.8, –0.8)	–1.4 (–3.9, 1.1)	–4.6 (–7.1, –2.0)
10min	–1.6 (–3.7, 0.5)	–2.9 (–5.0, –0.9)	4.3 (2.2, 6.4)	**6.4** (4.3, 8.5)	–2.1 (–4.5, 0.3)	–4.0 (–6.5, –1.6)	–0.4 (–2.7, 2.0)	–5.5 (–7.9, –3.0)
30min	4.8 (2.8, 6.7)	–0.8 (–2.8, 1.1)	4.2 (2.3, 6.1)	**8.2** (6.2, **10.2**)	3.8 (1.5, 6.0)	–1.8 (–4.0, 0.4)	1.6 (–0.6, 3.7)	0.5 (–1.7, 2.7)
1h	**8.1** (6.2, 9.9)	–1.0 (–2.9, 0.8)	–0.8 (–2.6, 1.0)	0.5 (–1.4, 2.3)	**6.3** (4.3, 8.3)	–1.8 (–3.8, 0.2)	–2.1 (–4.1, –0.1)	–4.3 (–6.3, –2.2)
2h	**7.7** (6.0, 9.4)	–2.1 (–3.8, –0.4)	–1.5 (–3.2, 0.1)	–0.8 (–2.5, 0.9)	**6.3** (4.3, 8.3)	–3.5 (–5.5, –1.5)	–3.2 (–5.2, –1.2)	–5.4 (–7.4, –3.4)
4h	**9.7** (8.0, **11.3**)	–1.8 (–3.5, –0.1)	–0.9 (–2.6, 0.8)	–0.6 (–2.3, 1.1)	**8.3** (6.4, **10.1**)	–3.8 (–5.7, –1.9)	–2.6 (–4.5, –0.8)	–5.3 (–7.2, –3.4)
8h	**9.0** (7.4, **10.5**)	–1.0 (–2.5, 0.6)	–0.5 (–2.0, 1.1)	–0.4 (–1.9, 1.2)	**7.8** (6.0, 9.6)	–2.4 (–4.2, –0.6)	–1.4 (–3.2, 0.3)	–5.4 (–7.2, –3.7)
12h	**5.7** (4.1, 7.3)	–0.8 (–2.5, 0.8)	–1.0 (–2.6, 0.6)	0.3 (–1.4, 1.9)	3.9 (2.0, 5.7)	–2.2 (–4.1, –0.4)	–2.0 (–3.8, –0.1)	–3.9 (–5.8, –2.0)
16h	4.6 (2.9, 6.3)	–1.8 (–3.6, –0.1)	–1.2 (–3.0, 0.5)	–1.1 (–2.8, 0.6)	3.3 (1.4, 5.3)	–3.5 (–5.5, –1.5)	–2.2 (–4.2, –0.2)	–4.7 (–6.7, –2.7)
24h	4.7 (3.1, 6.3)	–1.1 (–2.7, 0.5)	–1.2 (–2.8, 0.4)	–1.6 (–3.2, 0.0)	4.3 (2.5, 6.2)	–2.0 (–3.9, –0.1)	–2.1 (–4.0, –0.3)	–4.8 (–6.7, –3.0)

Bold red values represent a mean treatment difference of >5msec or an upper CI >10msec

· Outcomes of categorical analysis of maximum observed QTcF values and maximal change from baseline in QTcF are provided in **Table 3**.

TABLE 3. QTcF CATEGORICAL ANALYSIS (DAY 10, 0–24H)

Maximum QTcF absolute values

	Absolute QTcF (msec)			
Treatment	**≤450 n (%)**	**>450–480 n (%)**	**>480–500 n (%)**	**>500 n (%)**
Placebo	76 (100)	0	0	0
Moxifloxacin 400mcg	69 (96)	3 (4)	0	0
UMEC 500mcg	73 (100)	0	0	0
UMEC/VI 125/25mcg	73 (99)	1 (1)	0	0
UMEC/VI 500/100mcg	70 (100)	0	0	0

Maximal change from baseline QTcF

	Change in absolute QTcF (msec)		
Treatment	**≤30 n (%)**	**>30–60 n (%)**	**>60 n (%)**

Placebo	74 (99)	1 (1)	0
Moxifloxacin 400mcg	69 (97)	2 (3)	0
UMEC 500mcg	71 (100)	0	0
UMEC/VI 125/25mcg	71 (99)	1 (1)	0
UMEC/VI 500/100mcg	68 (99)	1(1)	0

Note: Day 10 pre-dose included in calculation of maximums

Heart rate (Day 10)

- Transient increases in HR compared with placebo were observed with UMEC/VI 125/25mcg (maximal increase [90% CI]: 8.4bpm [7.0, 9.8]) and UMEC/VI 500/100mcg (20.3bpm [18.9, 21.7]). The maximal increase in HR occurred 10min post-dose and reduced rapidly thereafter.
- UMEC 500mcg did not increase HR compared with placebo at any timepoint.
- Exploratory analyses suggested an association between HR increase and VI maximal plasma concentration (C_{max}).

Pharmacokinetics

- UMEC and VI exposures were dose proportional across therapeutic and supratherapeutic treatments.

Concentration-QT analysis

- Simulations of the model typical parameters were carried out at the geometric mean observed C_{max} for each treatment (**Table 4**).
- Decreased QTcF following UMEC monotherapy, along with increased QTcF observed for the combination therapies, suggest the effect is possibly attributable to the VI component of the combination treatment.

TABLE 4. QTcF MODEL SIMULATION

Treatment	Observed geometric mean C_{max}*((pg/mL)		Mean (90% PI) QTcF prolongation (msec)		
	UMEC	VI	UMEC	VI	Total
UMEC 500mcg	1531	NA	–2.38 (–3.82, –0.85)	NA	–2.38 (–3.82, –0.85)
UMEC/VI 125/25mcg	321	335	–0.50 (–0.80, –0.18)	**5.89** (4.89, 6.91)	**5.39** (4.40, 6.47)
UMEC/VI 500/100mcg	1290	1394	–2.01 (–3.22, –0.72)	**7.23** (5.88, 8.55)	**5.22** (3.72, 6.80)

PI=prediction interval, NA=not applicable
*Geometric means of individual C_{max} values. These exclude the five subjects who were missing ECG data and only include time-matched PK obs
Bold red values represent a mean treatment difference of >5msec or an upper CI >10msec

Safety

- The most common (≥10% of subjects) AEs are shown in **Table 5**. Four AEs led to study withdrawal: one gastroenteritis considered unrelated to treatment (UMEC/VI 125/25mcg); one palpitations/chest pain considered potentially treatment related (UMEC/VI 500/100mcg); one contact dermatitis considered unrelated to treatment (placebo); one increase in alanine aminotransferase meeting pre-defined stopping criteria considered potentially treatment related (placebo). These four AEs resolved.
- There were no serious AEs, and no vital sign readings were reported as an AE. There were no clinically significant ECG abnormalities or laboratory findings.

TABLE 5. ADVERSE EVENTS

Term	Placebo (n=77)	Mox 400mg (n=74)	UMEC 500mcg (n=76)	UMEC/VI 125/25mcg (n=78)	UMEC/VI 500/100mcg (n=76)	Total (N=103)
Any AE, n (%)	35 (45)	29 (39)	38 (50)	31 (40)	45 (59)	85 (83)
Most frequent (≥10% subjects), n (%)						
Headache	17 (22)	17 (23)	14 (18)	18 (23)	16 (21)	49 (48)
Oropharyngeal pain	3 (4)	1 (1)	9 (12)	3 (4)	6 (8)	21 (20)
Palpitations	2 (3)	1 (1)	0	1 (1)	15 (20)	17 (17)
Dizziness	2 (3)	2 (3)	4 (5)	4 (5)	4 (5)	16 (16)
Nausea	2 (3)	9 (12)	2 (3)	1 (1)	1 (1)	13 (13)
Cough	2 (3)	4 (5)	1 (1)	1 (1)	6 (8)	11 (11)
Dry throat	1 (1)	0	5 (7)	2 (3)	3 (4)	10 (10)
Rhinitis	0	3 (4)	3 (4)	2 (3)	2 (3)	10 (10)
Any drug-related AE	18 (23)	24 (32)	28 (37)	25 (32)	36 (47)	72 (70)

CONCLUSIONS

- No clinically significant effects on QTcF were observed following a 10-day dosing period with a therapeutic dose of UMEC/VI (125/25mcg) or a supratherapeutic dose of UMEC monotherapy (500mcg).
- A transient increase in QTcF was observed following supratherapeutic UMEC/VI (500/100mcg) at the 30min post-dose timepoint only; QTcF was similar to placebo from 1h post-dose.
- All UMEC and UMEC/VI treatments were found to be well tolerated on the basis of AEs, vital signs, ECG and laboratory safety data.

REFERENCES

(1) Decramer M, et al. *Respir Physiol Neurobiol* 2013;185:393–99.

(2) Kelleher D, et al. *PLoS ONE* 2012;7:e50716.

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- The presenting author, Dennis Kelleher, is employed by and holds stock in GlaxoSmithKline.
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- The authors would like to acknowledge the site staff and subjects that took part in the study (Hammersmith Medicines Research, London, UK).

Presented at the American Thoracic Society Annual Congress, Philadelphia, PA, USA, 17–22 May 2013

Single-dose Pharmacokinetics of TD-4208, a Novel Long-acting Muscarinic Antagonist, in Patients with COPD

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ABSTRACT

Rationale: TD-4208 is a potent and selective inhaled muscarinic antagonist with functional lung selectivity and long duration of action in preclinical models of bronchoconstriction. It is currently in development for maintenance treatment of airflow obstruction in patients with COPD. We have previously reported the 24 hour bronchodilation profile of single doses of TD-4208 in subjects with COPD. This analysis evaluates the single dose pharmacokinetics of nebulized TD-4208 and its metabolite THRX-195518.

Methods: Thirty-two patients aged 45-75 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. Plasma protein binding and in vitro equilibrium binding studies at the hM_2 and hM_3 receptors were conducted.

Results: TD-4208 was rapidly absorbed (median T_{max} 0.3 hr) after inhaled administration and was followed by a rapid initial decline of plasma concentrations. TD-4208 was rapidly converted to a major metabolite, THRX-195518, (median T_{max} 0.3 hr) and the metabolite was steadily eliminated. The metabolite to parent ratio for C_{max} and AUC_{0-12} ranged from 3- to 5-fold for both dose levels. Minimal renal elimination was observed for both TD-4208 or THRX-195518 (TD-4208 CL_{renal} values for 350 and 700 µg doses, 6.0 ± 4.2 and 4.3 ± 3.1 L/hr, respectively). Mean plasma C_{max}, AUC_{0-12} and amount excreted in urine increased in an approximately dose proportional manner for both compounds. The unbound fraction in plasma for TD-4208 and THRX-195518 was 26% and 64%, respectively. THRX-195518 exhibited 10- and 6-fold less potency than TD-4208 at the hM_3 and hM_2 receptors, respectively. Based on the plasma pharmacokinetics, plasma protein binding, and binding affinity of parent and metabolite at the hM_3 receptor, minimal systemic M_3 receptor occupancy is anticipated following 350 and 700 µg doses of TD-4208. These results are consistent with the previously reported 24 hour bronchodilation observed for both single doses of TD-4208 and a safety and tolerability profile at these dose levels that was similar to placebo.

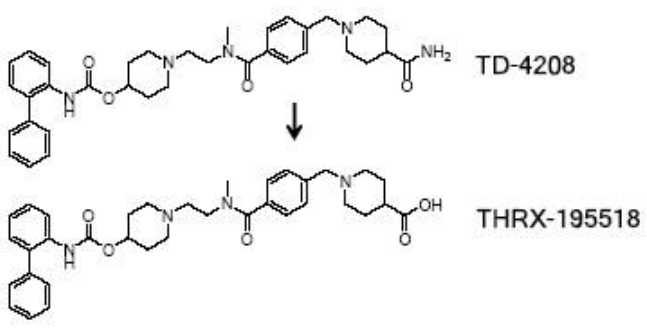
Conclusions: Single 350 and 700 microgram doses of nebulized TD-4208, which produce sustained bronchodilation, result in low systemic exposures. TD-4208 is rapidly cleared and extensively converted to the pharmacologically less-active metabolite, THRX-195518. Both compounds have minimal projected systemic M_3 receptor occupancy and negligible renal elimination.

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).
- 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).
- Antagonism of extra-pulmonary muscarinic receptors has the potential to cause off-target effects (e.g. M_3 receptor mediated dry mouth) therefore an ideal PK profile would show minimal systemic exposures and low M_3 receptor occupancies.

- THRX-195518 is a major metabolite of TD-4208 in preclinical species and human hepatocyte incubations. In healthy human subjects, maximum plasma concentrations of THRX-195518 are similar to those of TD-4208. Due to weaker muscarinic receptor potencies, THRX-195518 is not expected to significantly contribute to the pharmacodynamic effects of inhaled TD-4208.

Figure 1. TD-4208 Metabolic Scheme



AIMS

Primary Objectives:

- Evaluate single dose pharmacokinetics of TD-4208 and its major metabolite THRX-195518 in subjects with COPD.
- Predict systemic M_3 receptor occupancies using plasma pharmacokinetics and in vitro receptor binding affinity data.

METHODS

Study Design

- 32 subjects diagnosed with COPD were enrolled in a 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).
- Single doses of TD-4208 350 and 700 µg, active-control agent ipratropium bromide (500 µg), and placebo, each administered using a PARI LC® Plus nebulizer with a PARI PRONEB® Ultra II compressor.
- Washout of 7 to 12 days between doses.

Table 1. Subject Demographics

	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

Pharmacokinetics

- Plasma samples were obtained from each period predose and at 15, 30, and 45 minutes postdose and 1, 2, 3, 4, 6, 8, 10, 12, 22, and 24 hours postdose
- Total urine collections were obtained during each period from 0 to 12 and 12 to 24 hours postdose.
- TD-4208 and THRX-195518 were quantified using a validated liquid chromatography with tandem mass spectrometry method
- Receptor occupancies (RO) were calculated using the following equations:

$$\text{Fractional Receptor Occupancy (FRO)} = \frac{[\text{free ligand}]}{[\text{free ligand}] + Ki}$$

$$\%RO = 100 \times (FRO\ TD\text{-}4208 + FRO\ THRX\text{-}195518 - (FRO\ TD\text{-}4208 \times FRO\ THRX\text{-}195518)$$

RESULTS

Figure 2. Plasma Pharmacokinetics

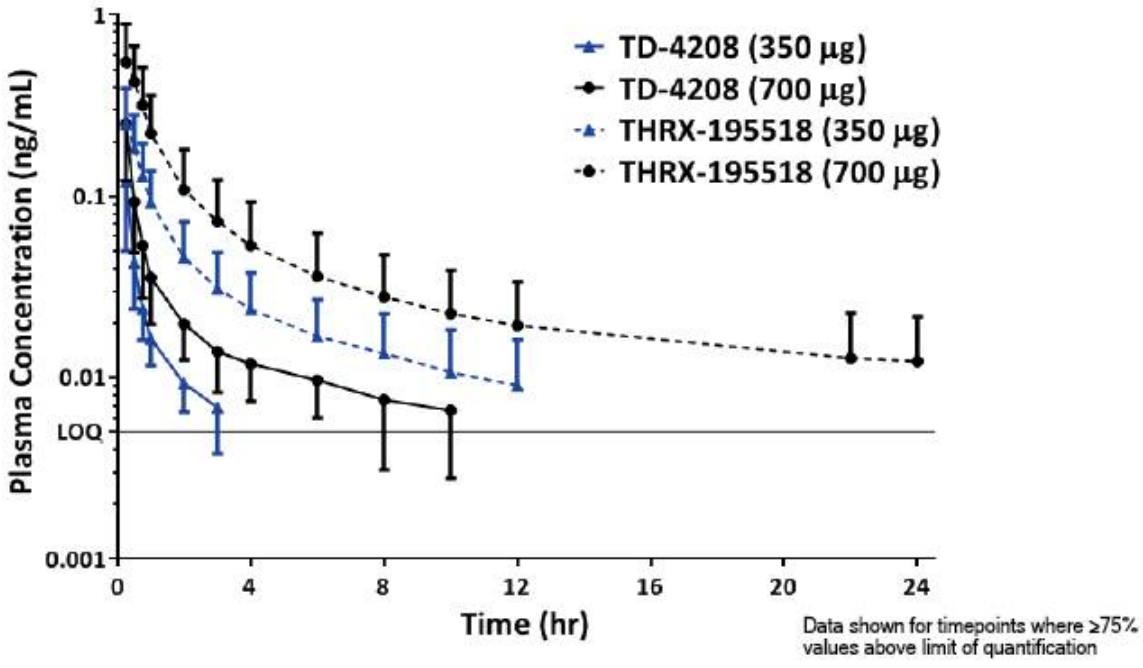


Table 2. Summary of Pharmacokinetic Values

	Dose (µg)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-12} (ng*hr/mL)	AE_{0-24}** (µg)	CL_{renal} (L/hr)
TD-4208	**350**	**0.12 ± 0.07**	**0.33 (0.20, 0.38)**	**0.096 ± 0.049**	**0.47 ± 0.21**	**6.0 ± 4.2**
	700	**0.25 ± 0.13**	**0.32 (0.18, 0.37)**	**0.23 ± 0.095**	**0.98 ± 0.40**	**4.3 ± 3.1**
THRX-195518	**350**	**0.25 ± 0.14**	**0.33 (0.20, 0.58)**	**0.41 ± 0.22**	**0.95 ± 0.61**	**2.1 ± 0.81**
	700	**0.56 ± 0.33**	**0.33 (0.18, 0.58)**	**0.93 ± 0.58**	**2.0 ± 1.3**	**1.9 ± 0.87**
M:P ratio (molar)*	**350**	**2.9 ± 2.1**	**—**	**5.3 ± 4.1**	**—**	**—**
	700	**2.6 ± 1.7**	**—**	**4.2 ± 2.3**	**—**	**—**

Mean values ± standard deviation, median (min, max) presented for T_{max}
***Molar ratio of metabolite to parent**
****Cumulative amount excreted in urine from time 0 to 24 hours**

Table 3. In Vitro Binding Constants

	Fraction Unbound (%)	hM_R receptor Ki(nM)	$C_{avg0-24}$** (ng/mL) 350 µg TD-4208	$C_{avg0-24}$** (ng/mL) 700 µg TD-4208	Predicted Average M_3 Receptor Occupancy*** 350 µg TD-4208	Predicted Average M_3 Receptor Occupancy*** 700 µg TD-4208
TD-4208	26	0.18*	0.0044	0.0124	2.2%	5.6%
THRX-195518	64	1.8*	0.0206	0.0467		

***Data taken from Steinfeld et al. 2009 (4)**
CHO-K1 cells stably expressing human recombinant muscarinic receptors
TD-4208 or THRX-195518 were incubated with cell membranes and [^{3}H]NMS (1 nM) for six hours at 37ºC
****Average plasma concentration of total drug or metabolite from time 0 to 24 hours**
*****Predicted average total M3 receptor occupancy based on unbound concentrations and in vitro hM3 receptor binding affinities for both TD-4208 and THRX-195518**

- The predicted average systemic M3 receptor occupancies were less than 6%.
- Adverse events generally mild with frequencies similar to the placebo treated arm. Most common were headache and dyspnea (5).
- No dry mouth was reported for either TD-4208 dose level.

CONCLUSIONS

- Single doses of nebulized TD-4208 at the active dose levels of 350 µg and 700 µg result in low systemic exposures.
- TD-4208 is rapidly cleared and extensively converted to the pharmacologically less-active metabolite, THRX-195518.
- Parent and metabolite combined have minimal projected systemic M_3 receptor occupancy and negligible renal elimination.
- TD-4208 is suitable for development as a once daily inhaled agent for COPD and asthma.

REFERENCES

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