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 7, 2014**

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)

951 Gateway Boulevard
South San Francisco, California 94080
(650) 238-9600
(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 7, 2014 at the European Respiratory Society (ERS) Annual Congress, Munich, Germany, GlaxoSmithKline plc (GSK) presented posters containing information from Phase 3 studies of umeclidinium/vilanterol (UMEC/VI) and Phase 1 studies of the 'closed triple' combination fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI). ANORO® ELLIPTA® is a once-daily combination treatment comprising two bronchodilators, UMEC, a long-acting muscarinic antagonist (LAMA), and VI, a long-acting beta$_2$ agonist (LABA), in a single inhaler, the ELLIPTA®. FF/UMEC/VI is being investigated as a once-daily 'closed triple' combination treatment of an inhaled corticosteroid, a LAMA and a LABA in patients with COPD. A Phase 3 study of FF/UMEC/VI is currently ongoing. FF/UMEC/VI is not approved anywhere in the world. UMEC/VI has been developed and UMEC/FF/VI is being developed under the 2002 LABA collaboration between Glaxo Group Limited and Theravance, Inc. The posters are filed as Exhibits 99.1 to 99.5 to this report and are incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit	Description
Exhibit 99.1	Umeclidinium/vilanterol (UMEC/VI) once daily (OD) vs fluticasone/salmeterol combination (FSC) twice daily (BD) in patients with moderate-to-severe COPD and infrequent COPD exacerbations
Exhibit 99.2	Evaluating lung function response to umeclidinium/vilanterol (UMEC/VI) 62.5/25mcg, UMEC 62.5mcg and VI 25mcg in

	COPD patients
Exhibit 99.3	Effect of the once-daily long-acting bronchodilator combination umeclidinium/vilanterol (UMEC/VI) and bronchodilator monotherapy on dyspnoea as measured by the transitional dyspnoea index (TDI) in COPD
Exhibit 99.4	Pharmacokinetic (PK) analysis of fluticasone furoate (FF), umeclidinium (UMEC) and vilanterol (VI) following triple therapy in healthy subjects
Exhibit 99.5	Pharmacokinetic (PK) analysis of fluticasone furoate (FF), umeclidinium (UMEC) and vilanterol (VI) following triple therapy at two UMEC doses in healthy subjects

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 7, 2014

By: /s/ Michael W. Aguiar
Michael W. Aguiar
Chief Executive Officer

EXHIBIT INDEX

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Exhibit 99.1

Umeclidinium/vilanterol (UMEC/VI) once daily (OD) vs fluticasone/salmeterol combination (FSC) twice daily (BD) in patients with moderate-to-severe COPD and infrequent COPD exacerbations

Poster No. P290

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Aims

- Umeclidinium/vilanterol (UMEC/VI), a long-acting muscarinic antagonist (LAMA)/long-acting beta(2) agonist (LABA) combination(1) is an approved COPD maintenance treatment in the EU(2) and USA(3) and several other countries. The inhaled corticosteroid (ICS)/LABA combination fluticasone propionate/salmeterol(4) (FSC) is also approved for COPD in the EU (500/50mcg twice daily).
- Guidelines recommend treatment with an ICS/LABA combination in COPD patients with moderate-to-very-severe lung function impairment and/or a history of exacerbations (GOLD C and D).(5) A LAMA/LABA combination is one treatment recommendation for GOLD B patients.(5) In clinical practice, treatment of patients in various GOLD categories diverges from current recommendations based on clinical judgement.
- For COPD patients with dyspnoea and without frequent exacerbations (i.e. GOLD B and a subset of GOLD D), a key clinical question is whether non-ICS combinations are more efficacious than ICS-containing treatments.
- The objective of this study was to compare the efficacy and safety of once-daily UMEC/VI 62.5/25mcg with twice-daily FSC 500/50mcg over 12 weeks in patients with moderate-to-severe COPD with a history of infrequent COPD exacerbations.

Methods

Study design and population

- Phase IIIb, multicentre, randomised, double-blind, double-dummy, parallel-group study (GSK study code: DB2116134; clinicaltrials.gov: NCT01822899).
- Inclusion criteria were: males or females ≥40 years old; pre- and post-salbutamol forced expiratory volume in 1s (FEV_1)/forced vital capacity (FVC) ratio <0.70 and post-salbutamol FEV_1 ≥30% and ≥70% of predicted normal values; dyspnoea score ≥2 (modified Medical Research Council [mMRC] Dyspnoea Scale); current or former smokers (history of cigarette smoking ≥10 pack-years).
- Key exclusion criteria were: other respiratory disorders; hospitalisation for pneumonia; a documented history of ≥1 COPD exacerbation requiring oral corticosteroids, antibiotics and/or hospitalisation in the previous 12 months.

Treatment

- After a 7–14 day run-in, patients were randomised 1:1 to receive 12 weeks of treatment
  - once-daily UMEC/VI 62.5/25mcg (delivered doses 55/22mcg; via ELLIPTA® dry powder inhaler [DPI]) + twice-daily placebo (via DISKUS®)
  - twice-daily FSC 500/50mcg (via DISKUS®) + once-daily placebo (via ELLIPTA® DPI).

Endpoints and analyses

- Lung-function endpoints included: 0–24h weighted mean (wm) FEV_1 (day 84, primary); trough FEV_1 (day 85, secondary); other (selected) endpoints are listed in the Results.
- Symptomatic endpoints and health outcomes: rescue medication use; dyspnoea (Transition Dyspnoea Index [TDI] focal score); St George's Respiratory Questionnaire for COPD patients (SGRQ-C); EuroQoL-5D (EQ-5D) questionnaire and the COPD Assessment Test (CAT).
- Safety assessments included adverse events (AEs) and COPD exacerbations.
- Primary endpoint was analysed using analysis of covariance (covariates: baseline [BL] FEV_1, smoking status, treatment). Secondary endpoint was analysed using a mixed model for repeated measures analysis (covariates: BL FEV_1, smoking status, day, treatment, day by BL interaction, day by treatment). Multiplicity across primary and secondary endpoints was accounted for by a step-down statistical hierarchy.

Results

Baseline characteristics

- Of 1009 patients enrolled, 870 were screened, 717 were randomised, 716 were included in the ITT population and 674 completed the study (UMEC/VI: 334; FSC: 340).
- All patients were of White race. At BL, patient demographics and characteristics were similar between groups (Table 1) and 55% and 45% of patients overall had percent-predicted FEV_1 ≥50% (moderate COPD) and <50% (severe COPD), respectively.
- Mean (SD) treatment compliance was 100.4% (28.3%) UMEC/VI and 99.3% (3.7%) FSC.

Table 1. Baseline and disease characteristics (ITT population)

	UMEC/VI 62.5/25mcg (N=358)	FSC 500/50mcg (N=358)
Age, mean ± SD, years	61.8 ± 7.94	61.4 ± 8.06
Sex: male, n (%)	261 (73)	254 (71)
Current smoker, n (%)	204 (57)	217 (61)
Screening lung function: pre-salbutamol FEV_1, mean ± SD, L	1.423 ± 0.4573	1.457 ± 0.4555
GOLD stage (percent predicted FEV_1) and reversibility, n (%)		
Stage II (³50% to <80%) = moderate	193 (54)	201 (56)
Stage III (³30% to <50%) = severe	165 (46)	157 (44)
Reversible to salbutamol	100 (28)	108 (30)
mMRC dyspnoea scale, mean (SD)	2.2 (0.41)	2.2 (0.42)

Efficacy – lung function

- UMEC/VI resulted in statistically significant improvements in 0–24h wmFEV1 and trough FEV1 (both p<0.001, Table 2, Figs. 1 and 2), and all other lung function measures (Table 2) compared with FSC
  - UMEC/VI also significantly improved forced vital capacity endpoints versus FSC (data not shown).
- In a descriptive summary, UMEC/VI improved lung function versus FSC for each GOLD stage for the primary endpoint (see below) and trough FEV1 (day 85; data not shown). The mean (SD) change from BL in 0–24h wmFEV1 (day 84) was
  - GOLD stage II: 0.181 (0.2476) L (UMEC/VI) and 0.096 (0.2230) L (FSC)
  - GOLD stage III: 0.152 (0.2111) L (UMEC/VI) and 0.071 (0.2038) L (FSC).

Symptomatic endpoints and health outcomes

- No treatment differences in rescue salbutamol use were seen either in terms of mean number of puffs taken daily or in percentage of rescue-free days over 12 weeks.
- Both UMEC/VI and FSC demonstrated clinically meaningful improvements in dyspnoea (TDI focal score >1 unit increase) and health outcomes (SGRQ-C Total score >4 unit decrease from baseline) over 12 weeks
  - Least squares (LS) mean (SE) changes from BL in TDI focal score (day 84) were 2.0 (0.14) for UMEC/VI and 2.1 (0.13) for FSC; difference (95% CI): –0.1 (–0.4, 0.3), p=0.702
  - LS mean (SE) changes from BL in SGRQ-C Total score (day 84) were –5.10 (0.626) for UMEC/VI and –5.64 (0.619) for FSC; difference (95% CI): 0.53 (–1.20, 2.26), p=0.545.

- Mean change from BL in EQ-5D utility score was 0.03 on day 84 for both treatments.
- On day 84, no treatment differences were seen in mean change from BL CAT scores.

Table 2. Analyses of lung function endpoints (ITT population)

Endpoint	UMEC/VI 62.5/25mcg (N=358)	FSC 500/50mcg (N=358)	Difference
0–24h wmFEV_1 on day 84, L(a)	0.166 (0.0122)(b)	0.087 (0.0121)(c)	0.080 (0.046, 0.113)(d) **p<0.001**
Trough FEV_1 on day 85, L(a)	0.151 (0.0126)(e)	0.062 (0.0125)(f)	0.090 (0.055, 0.125)(d) **p<0.001**
Peak FEV_1 0–6h, L, on day 1(a)	0.266 (0.0083)	0.231 (0.0083)	0.034 (0.011, 0.057)(d) **p=0.003**
Peak FEV_1 0–6h, L, on day 84(a)	0.327 (0.0131)(g)	0.229 (0.0130)(h)	0.097 (0.061, 0.134)(d) **p<0.001**
Median time to onset on day 1, min (FEV_1 increase ³100mL vs BL)	17	60	1.3 (1.1, 1.5)(i) **p=0.002**
Patients with FEV_1 increase ³100mL vs BL at 5-min post-dose on day 1, n (%)	137 (39)	104 (30)	1.50 (1.10, 2.06)(j) **p=0.011**
Patients with FEV_1 increase ³12% and ³200mL on day 1 vs BL, n (%)	211 (59)	177 (49)	1.47 (1.09, 1.97)(j) **p=0.011**
Patients with trough FEV_1 increase ³100mL on day 85 vs BL, n (%)	192 (58)(e)	139 (41)(f)	1.94 (1.42, 2.64)(j) **p<0.001**

(a)values are LS mean (SE) change from BL; (b)n=332; (c)n=337; (d)treatment difference (95% CI); (e)n=333; (f)n=338; (g)n=335; (h)n=340; (i)hazard ratio (95% CI); (j)odds ratio (95% CI); BL: baseline

Figure 1. Least squares mean (95% CI) change from baseline in FEV_1 (L) over 0–24h post-dose on day 84 (ITT population)

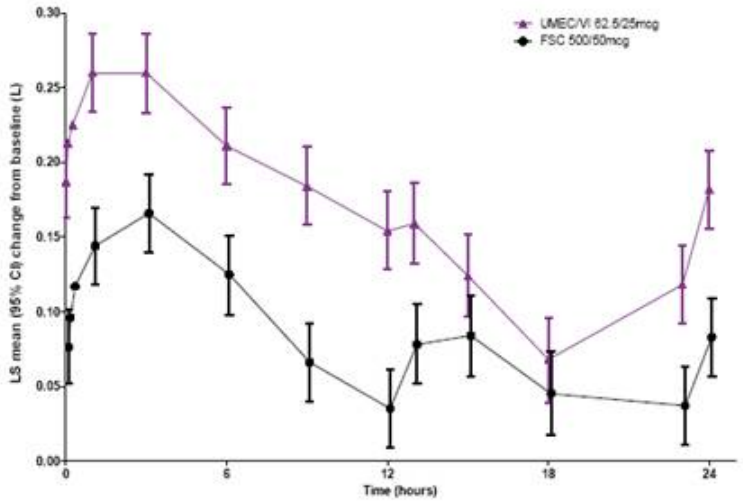
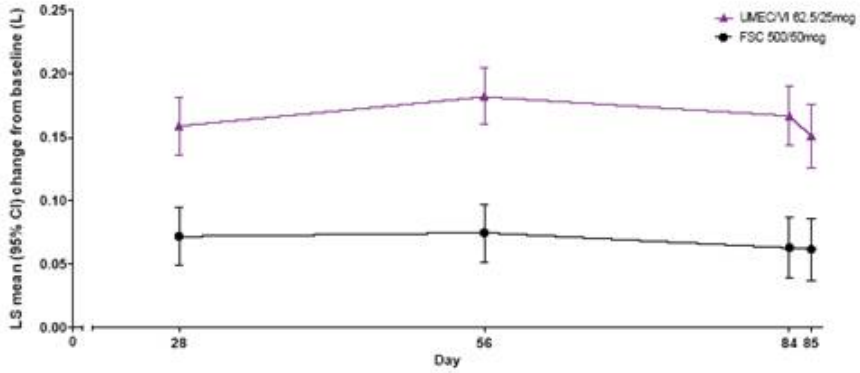


Figure 2. Least squares mean (95% CI) change from baseline in trough FEV_1 (L) on days 28, 56, 84 and 85 (ITT population)



Safety and tolerability

- The AE incidence was similar between UMEC/VI (28%) and FSC (29%). The incidence of fatal on-treatment AEs was 1% (UMEC/VI) and 0% (FSC).
- Headache, nasopharyngitis, back pain and dysphonia were the most common AEs reported in both groups. The incidence of drug-related AEs was lower with UMEC/VI (2%) than with FSC (4%).
- The incidence of cardiac disorders was low (2% UMEC/VI; <1% FSC). Pneumonia was reported by 1 patient in the FSC group and none in the UMEC/VI group. The incidence of on-treatment COPD exacerbations was higher with UMEC/VI (2%) than with FSC (<1%).

Conclusions

- Once-daily UMEC/VI 62.5/25mcg over 12 weeks resulted in significant, sustained and clinically meaningful improvements in lung function versus twice-daily FSC 500/50mcg in moderate-to-severe COPD patients with infrequent COPD exacerbations.
- Both UMEC/VI and FSC demonstrated clinically meaningful improvements in dyspnoea and QoL over 12 weeks, with no treatment differences.
- The safety and tolerability of UMEC/VI was consistent with previous studies and no difference was observed in AEs between UMEC/VI and FSC.
- For GOLD B and D patients with dyspnoea and infrequent exacerbations, our findings suggest that the LAMA/LABA combination UMEC/VI could provide greater lung function benefits than the ICS/LABA combination FSC.

References

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(4) Calverley PM, et al. *N Engl J Med* 2007;356:775–89.

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Acknowledgements

· The presenting author, D Singh, declares the following real or perceived conflicts of interest during the last 3 years in relation to this presentation: has served as consultant to Almirall, AstraZeneca, Boehringer Ingleheim, Chiesi, Cipla, GSK, Novartis, Nycomed and Roche; has received research grants from AstraZeneca, Almirall, Boehringer Ingleheim, Chiesi, Cipla, GSK, Novartis, Nycomed and Roche; has received payment for lectures including service on speakers bureaus from AstraZeneca, Almirall, Boehringer Ingleheim, Chiesi, Cipla, GSK, Novartis, Nycomed, Roche and Takeda. S Worsley, C-Q Zhu, L Hardaker and A Church are employed by and hold stock in GSK.
· This study was funded by GSK (GSK study code: DB2116134; clinicaltrials.gov: NCT01822899).
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Presented at the European Respiratory Society (ERS) International Congress, Munich, Germany, 6–10 September 2014

Evaluating lung function response to umeclidinium/vilanterol (UMEC/VI) 62.5/25mcg, UMEC 62.5mcg and VI 25mcg in COPD patients

Poster No. 291

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Aims

- The long-acting muscarinic antagonist (LAMA), umeclidinium (UMEC), and the combination of UMEC with the long-acting beta$_2$ agonist (LABA) vilanterol (VI) are approved maintenance treatments for chronic obstructive pulmonary disease (COPD) in the USA,(1) EU(2) and several other countries.
- UMEC/VI significantly improved lung function vs placebo(3),(4) and vs each monotherapy in parallel group studies.(3–5)
- A key point of interest for use of UMEC/VI (and other LAMA/LABA combinations) in clinical practice is to identify patient subgroups who will gain the most benefit from this dual therapy.
- The objective of these studies was to determine whether once-daily UMEC/VI provides additional benefit in patients with moderate-to-very severe COPD classified as responders ($\geq$12% and $\geq$200mL increase in FEV$_1$ from baseline [BL]) or non-responders to UMEC or VI monotherapy.

Methods

Study design and population

- Two phase IIIb, multicentre, randomised, double-blind, three-way, complete block, cross-over trials evaluating lung function response in COPD patients (GSK study codes: DB2116132; DB2116133; clinicaltrials.gov numbers: NCT02014480; NCT01716520).
- Inclusion criteria were: males or females ^{3}40 years old; pre- and post-salbutamol forced expiratory volume in 1s (FEV$_1$)/forced vital capacity (FVC) ratio <0.70 and FEV$_1$ $\leq$70% predicted normal; current or former (stopped smoking for ^{3}6 months) smokers with a history of ^{3}10 pack-years.
- Key exclusion criteria were: asthma/other known respiratory disorders; hospitalisation for COPD or pneumonia within 12 weeks of screening.

Treatment

- After a 5–7 day run-in period, patients were randomised to receive each of three treatments: UMEC 62.5mcg (delivered dose 55mcg); VI 25mcg (delivered dose 22mcg); UMEC/VI 62.5/25mcg (delivered dose 55/22mcg). Treatments were administered once daily via the ELLIPTA® dry powder inhaler for 14 days with a 10–14 day washout between each treatment period.

Endpoints and analyses

- Responder types to each monotherapy were identified on Day 1; a responder had an FEV$_1$ increase from BL of ^{3}12% and ^{3}200mL at any time 0–6h post-dose on Day 1.
- Several endpoints were evaluated in these studies, not all of which are shown.
- Efficacy endpoints evaluated in the individual studies and the pooled (post-hoc) analyses and reported herein
  - weighted mean (wm) FEV$_1$ over 0–6h post-dose on Day 14 of each treatment period (primary endpoint)
  - trough FEV$_1$ on Day 15 (a secondary endpoint).
- Safety endpoints (adverse events [AEs]; COPD exacerbations; vital signs) were assessed.
- The primary analysis, change from BL in 0–6h wmFEV$_1$ on Day 14 was by an analysis of covariance model.
- Analyses compared UMEC/VI vs UMEC in UMEC responders, UMEC/VI vs VI in VI responders, and UMEC/VI vs UMEC and VI in non-responders.

Results

Baseline characteristics

- In DB2116132, 238 patients enrolled, 207 randomised and 192 (93%) completed the study. In DB2116133, 207 patients enrolled, 182 randomised and 159 (87%) completed the study.

- Patient demographics and BL characteristics were similar between studies

  - COPD severity was marginally worse and less patients were reversible to salbutamol and salbutamol/ipratropium in DB2116132 vs DB2116133 (Table 1).

Table 1. Baseline and disease characteristics (ITT populations)

	DB2116132 (N=207)	DB2116133 (N=182)	Pooled (N=389)
Age, mean ± SD, years	60.5 ± 7.99	63.2 ± 8.19	61.8 ± 8.18
Sex: male, n (%)	169 (82)	127 (70)	296 (76)
White race, n (%)	207 (100)	182 (100)	389 (100)
Current smoker, n (%)	115 (56)	100 (55)	215 (55)
Screening lung function: pre-bronchodilator FEV_1, mean ± SD, L	1.354 (0.4732)	1.297 (0.4054)	1.328 (0.4431)
GOLD stage (percent predicted FEV_1) and reversibility, n (%)			
Stage II (³50% to <80%) = moderate	83 (40)	80 (44)	163 (42)
Stage III (³30% to <50%) = severe	95 (46)	91 (50)	186 (48)
Stage IV (<30%) = very severe	29 (14)	11 (6)	40 (10)
Reversible to salbutamol	32 (15)	71 (39)	103 (26)
Reversible to salbutamol and ipratropium	73 (36)*	105 (58)	178 (46)

*n=205

Treatment response (Day 1)

- In the pooled analysis (N=389), there were 67 (17%) responders to UMEC only, 79 (20%) responders to VI only, 106 (27%) responders to both UMEC and VI, 118 (30%) non-responders to UMEC and VI, and 19 (5%) patients had missing data (defined as a patient either missing both monotherapy treatments or a non-responder to one monotherapy treatment and missing the other).

Efficacy – lung function (pooled analysis)

- In responders to UMEC and VI, UMEC/VI significantly increased the least squares (LS) mean change from BL in $wmFEV_1$ 0–6h and trough FEV_1 compared with each monotherapy (Table 2, Figure 1).

- In non-responders to UMEC and VI, UMEC/VI significantly improved $wmFEV_1$ 0–6h and trough FEV_1 compared with monotherapy (Table 3, Figure 1).

Efficacy – additive and synergistic effects

LS mean change from BL in $wmFEV_1$ 0–6h on Day 14 by response type

- In the pooled analysis, in UMEC and VI non-responders, response to UMEC/VI was more than additive, possibly synergistic (+114mL compared with +44mL for UMEC and +52mL for VI monotherapies).

- The treatment effect was synergistic in DB2116132 (+92mL vs +14mL and +35mL) and additive in DB2116133 (+130mL vs +77mL and +57mL), respectively.

LS mean change from BL in trough FEV_1 on Day 15 by response type

- In the pooled analysis, in UMEC and VI non-responders, response to UMEC/VI on Day 15 was synergistic: +81mL compared with +39mL for UMEC and +23mL for VI monotherapies.

- The treatment effect was synergistic in DB2116132 (+62mL vs +16mL and +4mL) and additive in DB2116133 (+92mL vs +60mL and +35mL), respectively.

Table 2. Analysis of 0–6h $wmFEV_1$ on Day 14 and trough FEV_1 on Day 15 by response type on Day 1 (ITT populations)

Endpoint	DB2116132	DB2116133	Pooled analysis
UMEC/VI vs UMEC in responders to UMEC			
Difference in wmFEV1, L	0.108	0.121	0.114
(95% CI)	(0.065,0.151)	(0.085,0.157)	(0.086,0.142)
p-value	<0.001	<0.001	<0.001
n	79	90	169
Difference in trough FEV1, L	0.065	0.083	0.077
(95% CI)	(0.018,0.111)	(0.043,0.124)	(0.046,0.107)
p-value	0.007	<0.001	<0.001
n	79	90	169

UMEC/VI vs VI in responders to VI			
Difference in wmFEV1, L	0.082	0.098	0.092
(95% CI)	(0.040,0.125)	(0.067,0.130)	(0.066,0.118)
p-value	<0.001	<0.001	<0.001
n	77	102	179
Difference in trough FEV1, L	0.060	0.107	0.086
(95% CI)	(0.014,0.106)	(0.071,0.142)	(0.057,0.115)
p-value	0.011	<0.001	<0.001
n	78	101	179

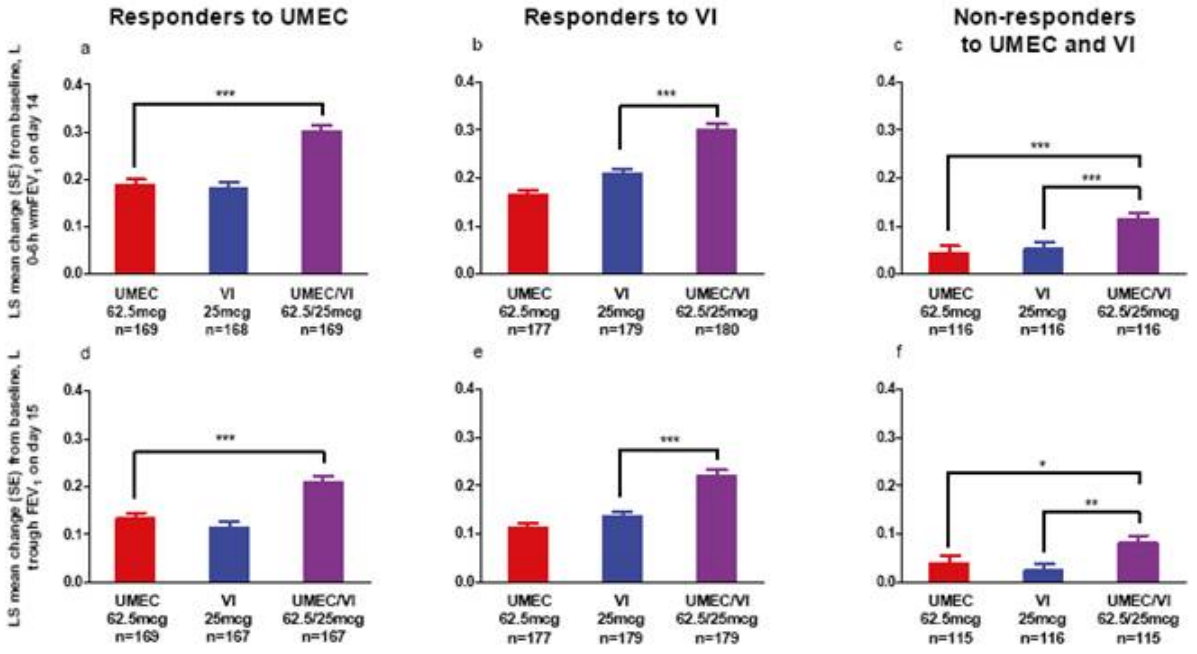
Table 3. Analysis of 0–6h wmFEV$_1$ on Day 14 and trough FEV$_1$ on Day 15 in non-responders to UMEC and VI monotherapy on Day 1 (ITT populations)

	DB2116132		DB2116133		Pooled analysis	
Endpoint	**vs UMEC**	**vs VI**	**vs UMEC**	**vs VI**	**vs UMEC**	**vs VI**
0–6h wmFEV1, L						
UMEC/VI vs monotherapy						
Difference	0.078	0.057	0.052	0.073	0.070	0.062
(95% CI)	(0.036,0.120)	(0.015,0.099)	(0.001,0.104)	(0.021,0.124)	0.038,0.103)	(0.030,0.094)
p-value	<0.001	0.008	0.047	0.006	<0.001	<0.001
n	80	79	36	37	116	116
Trough FEV1, L						
UMEC/VI vs monotherapy						
Difference	0.046	0.058	0.031	0.057	0.042	0.058
(95% CI)	(0.000,0.092)	(0.013,0.104)	(–0.027,0.090)	(–0.001,0.114)	(0.007,0.078)	(0.023,0.094)
p-value	0.049	0.012	0.293	0.055	0.020	0.001
n	80	79	35	37	115	116

Safety assessments

- The safety profiles of UMEC/VI, UMEC and VI were consistent with the known safety profile of LAMA/LABA and there was no evidence of an additive effect with UMEC/VI compared with UMEC or VI monotherapy.
- The incidence of AEs was similar across treatment groups in both studies: 18% UMEC/VI; 12–16% UMEC; 15–18% VI. The most common AEs (³3% patients in any treatment group) were nasopharyngitis and headache. One fatality was reported in DB2116133 (oesophageal carcinoma/pancreatic carcinoma).
- The incidence of serious AEs was <1% (1 patient) across all treatment arms with the exception of the UMEC/VI and UMEC arms in the DB2116133 study (both 2% [3 patients]).
- Two patients in DB2116132 (1 receiving UMEC; 1 receiving UMEC/VI), and 3 patients in DB2116133 (2 receiving UMEC; 1 receiving VI) had COPD exacerbations leading to withdrawal.
- Mean changes from BL in vital signs (blood pressure, heart rate) were similar across treatments within each study.

Figure 1. Analysis of 0–6h wmFEV$_1$ on Day 14 and trough FEV$_1$ on Day 15 by response type on Day 1 (ITT populations)



*p=0.020 for UMEC/VI versus UMEC in non-responders to UMEC and VI (panel f)
**p=0.001 for UMEC/VI versus VI in non-responders to UMEC and VI (panel f)
***p<0.001 for: UMEC/VI versus UMEC in UMEC responders (panels a and d); UMEC/VI versus VI in VI responders (panels b and e); UMEC/VI versus UMEC and versus VI in non-responders to UMEC and VI (panel c)

Conclusions

- Once-daily UMEC/VI improved lung function in patients with moderate-to-very severe COPD identified as responders to UMEC and VI monotherapy, and in those identified as non-responders to UMEC and VI monotherapy, without additional safety findings for combined therapy over monotherapy.

- These results suggest that dual bronchodilation with the fixed-dose, once-daily UMEC/VI combination is a potential treatment option for patients with moderate-to-very severe COPD and may offer additional benefits over its mono components.

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Presented at the European Respiratory Society (ERS) International Congress, Munich, Germany, 6–10 September 2014

Exhibit 99.3

Effect of the once-daily long-acting bronchodilator combination umeclidinium/vilanterol (UMEC/VI) and bronchodilator monotherapy on dyspnoea as measured by the transitional dyspnoea index (TDI) in COPD

Poster No. P921

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Aims

- Current guidelines recommend treatment with one or more long-acting bronchodilators for patients with moderate-to-very severe chronic obstructive pulmonary disease (COPD).(1)
- The long-acting muscarinic antagonist umeclidinium (UMEC, GSK573719) and the combination of UMEC with the long-acting β_2-agonist vilanterol (UMEC/VI) are approved maintenance treatments for COPD in the US and EU.(2),(3) They are not indicated for treatment of asthma.
- This study evaluated the effect of fixed-dose combinations of UMEC/VI (125/25 mcg and 62.5/25 mcg) and long-acting bronchodilator monotherapy on dyspnoea in patients with COPD.

Methods

Study design and treatments

- Data were pooled from two 24-week, randomised, blinded, double-dummy parallel-group studies (DB2113360, NCT01316900; DB2113374, NCT01316913).
- Key eligibility criteria: ≥40 years of age with a history of COPD; a post-bronchodilator forced expiratory volume in 1 second (FEV1) ≤70% of predicted; an FEV1/forced vital capacity (FVC) ratio <0.70; and a modified Medical Research Council Dyspnoea Scale (mMRC) score ≥2.
- Following a 7–10 day run-in period, patients in both studies were randomised in a 1:1:1:1 ratio to once-daily UMEC/VI 125/25 mcg (delivering 113/22 mcg), UMEC/VI 62.5/25 mcg (delivering 55/22 mcg), tiotropium (TIO) 18 mcg (delivering 10 mcg) and either VI 25 mcg (delivering 22 mcg; Study DB2113360) or UMEC 125 mcg (delivering 113 mcg; Study DB2113374). All patients received two inhalers for inhalation each morning, one containing placebo and one containing active treatment.
- UMEC/VI 125/25 and 62.5/25 mcg, UMEC 125 mcg, VI 25 mcg and corresponding placebo were delivered via ELLIPTA™ dry powder inhaler (DPI). TIO 18 mcg and corresponding placebo capsules were delivered via HandiHaler® DPI. Blinding of TIO was imperfect, as TIO capsules had trade markings and placebo capsules, although closely colour-matched, did not. For each study, there was a total of nine clinic visits.
- All patients provided written, informed consent prior to study participation, and studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Endpoints

- The primary endpoint was transitional dyspnoea index (TDI) focal score at Day 168, which measures changes in dyspnoea from baseline (possible scores: -9 [major deterioration] to 9 [major improvement]). Baseline dyspnoea index (BDI) scores were assessed at randomisation (Day 1; possible scores: 0 [severe] to 12 [unimpaired]).
- Other endpoints included TDI focal score on Days 28 and 84, and the proportion of responders (defined as patients with a TDI score ≥1) on Days 28, 84 and 168.

Statistical analysis

- The primary endpoint was analysed using mixed-model repeated measures analysis and categorical endpoints (e.g. TDI responder) were analysed by visit using logistic regression. The primary treatment comparisons of interest were UMEC/VI doses vs TIO for TDI focal score at Day 168.

Results

Patient demographics and baseline characteristics

- A total of 1,692 patients were included in the intent-to-treat population, and 1,351 patients (80%) completed the studies (subjects recruited by Investigator 040688 in Study DB2113360 were excluded because of significant deviations from good clinical practice standards [N=20]).
- Patient demographics and baseline characteristics were similar across treatment groups (Table 1).

Table 1. Patient demographics and baseline characteristics

	UMEC/VI 125/25 (N=423)	UMEC/VI 62.5/25 (N=424)	UMEC 125 (N=222)	VI 25 (N=205)	TIO 18 (N=418)
Age, years	63.4 (8.71)	64.1 (8.61)	64.5 (8.33)	63.3 (9.05)	64.1 (8.87)
Males, n (%)	294 (70)	286 (67)	148 (67)	140 (68)	291 (70)

White, n (%)	335 (79)	341 (80)	170 (77)	181 (88)	336 (80)
ICS users, n (%)(a)	213 (50)	196 (46)	124 (56)	82 (40)	208 (50)
mMRC dyspnoea score	2.5 (0.57)	2.4 (0.58)	2.5 (0.66)	2.4 (0.53)	2.4 (0.56)
Pre-bronchodilator FEV_1, L(b)	1.227 (0.4554)	1.236 (0.4738)	1.140 (0.4479)	1.324 (0.4907)	1.231 (0.4693)
Post-salbutamol FEV_1, L(c)	1.371 (0.4477)	1.378 (0.4832)	1.294 (0.4679)	1.450 (0.4833)	1.367 (0.4694)
Post-salbutamol % predicted FEV_1, L(c)	47.1 (12.85)	47.8 (13.20)	46.2 (13.03)	47.8 (12.70)	47.5 (13.22)
Reversible to salbutamol(d), (e) n (%)	139 (33)	119 (28)	75 (34)	51 (25)	106 (26)
Current smokers, n (%)	215 (51)	187 (44)	98 (44)	102 (50)	196 (47)
Smoking pack-years	44.7 (24.60)	46.1 (26.73)	47.6 (27.58)	40.4 (23.35)	47.9 (28.93)
GOLD Stage, n (%)(c)					
II	185 (44)	208 (49)	86 (39)	94 (47)	195 (47)
III	186 (44)	165 (39)	106 (48)	87 (43)	169 (41)
IV	49 (12)	49 (12)	29 (13)	21 (10)	51 (12)

All data presented as mean (SD) unless otherwise indicated.
(a)Patients taking ICS medications at screening; (b)UMEC 125/25, n=422; UMEC 62.5/25, n=424; UMEC 125, n=219; VI 25, n=204; TIO, n=413; (c)UMEC 125/25, n=420; UMEC 62.5/25, n=422; UMEC 125, n=221; VI 25, n=202; TIO, n= 415; (d)UMEC 125/25, n=420; UMEC 62.5/25, n=422; UMEC 125, n=219; VI 25, n=202; TIO, n= 412; (e)defined as an increase in FEV_1 of $\geq$12% and $\geq$0.200 L following administration of salbutamol.
GOLD, Global initiative for chronic obstructive lung disease; ICS, inhaled corticosteroid; SD, standard deviation.

BDI scores

· Mean BDI scores were similar across the treatment groups (Table 2).

Table 2. Mean BDI scores

	UMEC/VI 125/25 (N=423)	UMEC/VI 62.5/25 (N=424)	UMEC 125 (N=222)	VI 25 (N=205)	TIO 18 (N=418)
n	418	420	219	202	414
Mean BDI score (SD)	6.0 (1.94)	6.1 (2.00)	6.0 (2.17)	6.3 (2.03)	6.0 (2.07)

TDI scores

· Clinically-meaningful least squares (LS) mean TDI scores ($\geq$1 unit, demonstrating an improvement in dyspnoea from baseline) were observed for all treatment groups at all assessment visits (Days 28, 84 and 168), with the exception of UMEC 125 on Day 28 (Table 3; Figure 1).

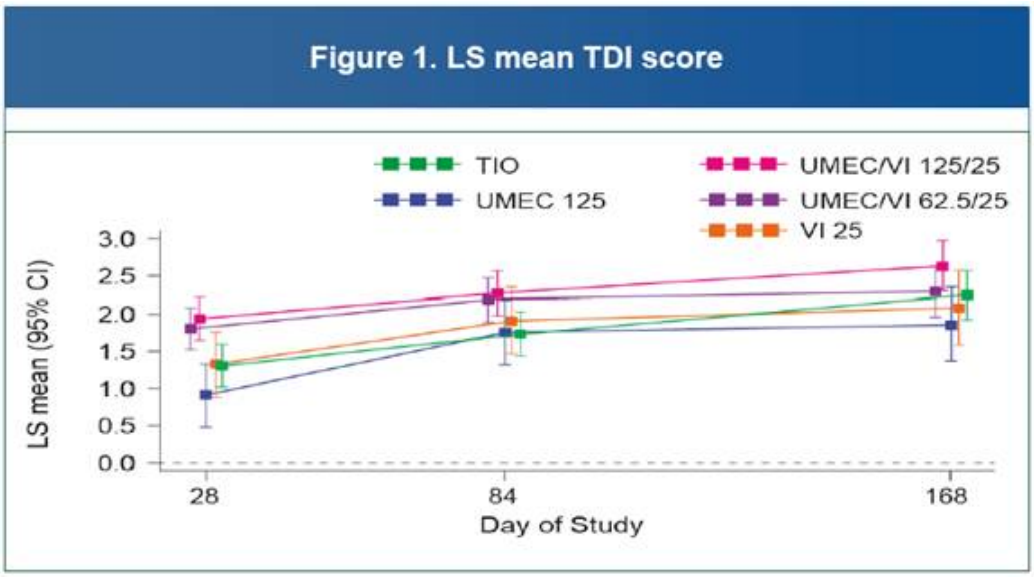
· There were no statistically significant differences for either dose of UMEC/VI compared with TIO for TDI score at Day 168 (both doses $p\geq0.05$).

· Treatment differences for LS mean TDI score favouring both doses of UMEC/VI over TIO were observed at Days 28 and 84 (0.5–0.6 units; $p<0.05$, nominal; Table 3).

Table 3. Mean TDI score(a) on days 28, 84 and 168

	UMEC/VI 125/25 (N=423)	UMEC/VI 62.5/25 (N=424)	UMEC 125 (N=222)	VI 25 (N=205)	TIO 18 (N=418)
Day 28	n=387	n=391	n=202	n=189	n=381
LS mean TDI score (SE)	1.9 (0.15)	1.8 (0.14)	0.9 (0.21)	1.3 (0.22)	1.3 (0.15)
UMEC/VI 125/25 vs column difference, OR (95% CI)			1.0 (0.5, 1.5)***	0.6 (0.1, 1.1)*	0.6 (0.2, 1.0)**
UMEC/VI 62.5/25 vs column difference, OR (95% CI)			0.9 (0.4, 1.4)***	0.5 (0.0, 1.0)	0.5 (0.1, 0.9)*
Day 84	n=363	n=371	n=183	n=179	n=365
LS mean TDI score (SE)	2.3 (0.15)	2.2 (0.15)	1.8 (0.22)	1.9 (0.23)	1.7 (0.15)
UMEC/VI 125/25 vs column difference, OR (95% CI)			0.5 (0.0, 1.0)	0.4 (-0.2, 0.9)	0.5 (0.1, 1.0)*
UMEC/VI 62.5/25 vs column difference, OR (95% CI)			0.4 (-0.1, 1.0)	0.3 (-0.2, 0.8)	0.5 (0.0, 0.9)*
Day 168	n=331	n=339	n=163	n=159	n=346
LS mean TDI score (SE)	2.6 (0.17)	2.3 (0.17)	1.9 (0.25)	2.1 (0.26)	2.2 (0.17)
UMEC/VI 125/25 vs column difference, OR (95% CI)			0.8 (0.2, 1.4)*	0.6 (0.0, 1.2)	0.4 (-0.1, 0.9)
UMEC/VI 62.5/25 vs column difference, OR (95% CI)			0.4 (-0.2, 1.0)	0.2 (-0.4, 0.8)	0.1 (-0.4, 0.5)

(a)A mean TDI score $\geq$1 unit is considered clinically meaningful; *p<0.05; **p<0.01; ***p<0.001 (p-values are nominal and provided for descriptive purposes).
CI, confidence interval; OR, odds ratio; SE, standard error.



Proportion of responders according to TDI score

- On Day 168, the odds of being a responder (vs non-responder) were not significantly different for either UMEC/VI 125/25 or UMEC/VI 62.5/25 compared with TIO (Table 4).

- However, patients in both UMEC/VI groups had higher odds of being responders compared with TIO at Days 28 and 84 (all p≤0.022, nominal).

Table 4. Proportion of responders according to TDI score

	UMEC/VI 125/25 (N=423)	UMEC/VI 62.5/25 (N=424)	UMEC 125 (N=222)	VI 25 (N=205)	TIO 18 (N=418)
Day 28	n=387	n=391	n=202	n=189	n=381
Responder, n (%)(a)	247 (64)	239 (61)	101 (50)	100 (53)	197 (52)
UMEC/VI 125/25 vs column difference, OR (95% CI)			2.0 (1.4, 2.8)***	1.4 (1.0, 2.1)	1.6 (1.2, 2.2)***
UMEC/VI 62.5/25 vs column difference, OR (95% CI)			1.8 (1.2, 2.5)**	1.3 (0.9, 1.9)	1.5 (1.1, 2.0)**
Day 84	n=390	n=393	n=203	n=191	n=381
Responder, n (%)(a)	233 (60)	235 (60)	111 (55)	114 (60)	195 (51)
UMEC/VI 125/25 vs column difference, OR (95% CI)			1.2 (0.8, 1.7)	1.0 (0.7, 1.5)	1.4 (1.0, 1.9)*
UMEC/VI 62.5/25 vs column difference, OR (95% CI)			1.2 (0.8, 1.8)	1.1 (0.7, 1.5)	1.4 (1.1, 1.9)*
Day 168	n=390	n=393	n=203	n=193	n=382
Responder, n (%)(a)	229 (59)	221 (56)	102 (50)	95 (49)	210 (55)
UMEC/VI 125/25 vs column difference, OR (95% CI)			1.3 (0.9, 1.9)	1.7 (1.1, 2.4)**	1.2 (0.9, 1.5)
UMEC/VI 62.5/25 vs column difference, OR (95% CI)			1.2 (0.8, 1.7)	1.5 (1.0, 2.2)*	1.1 (0.8, 1.4)

(a)Responder: TDI focal score ≥1 unit at that visit; non-responder: TDI focal score <1 unit or a missing TDI focal score with no subsequent non-missing TDI assessments; *p<0.05; **p<0.01; ***p<0.001 (p-values are nominal and provided for descriptive purposes).

Conclusions

- All treatments resulted in clinically-meaningful TDI scores at all study visits (Days 28, 84 and 168), except for UMEC 125 on Day 28.

- The primary comparisons of UMEC/VI 125/25 and 62.5/25 mcg with TIO for TDI focal score at Day 168 were not statistically significant.

- The odds of being a responder vs a non-responder based on TDI score was higher for patients receiving UMEC/VI compared with TIO at Days 28 and 84, but not at Day 168.

- The once-daily combination of UMEC/VI provides an additional treatment option to long-acting bronchodilator monotherapy for management of dyspnoea in COPD.

Reference

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Pharmacokinetic (PK) analysis of fluticasone furoate (FF), umeclidinium (UMEC) and vilanterol (VI) following triple therapy in healthy subjects

Poster No. P895

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Aims

- FF/UMEC/VI is a novel inhaled corticosteroid/long-acting muscarinic antagonist/long-acting beta$_2$ agonist (ICS/LAMA/LABA) therapy.
- Dual therapies of FF/VI and UMEC/VI were recently approved for treatment of moderate-to-severe COPD.
- The aim of this study was to assess the systemic exposure of FF, UMEC and VI, systemic pharmacodynamics (PD) (heart rate, serum potassium and blood glucose) and safety and tolerability following single inhaled doses of FF/UMEC/VI compared with the dual therapies FF/VI, UMEC/VI and FF/UMEC (all administered by ELLIPTA™ dry powder inhaler).

Methods

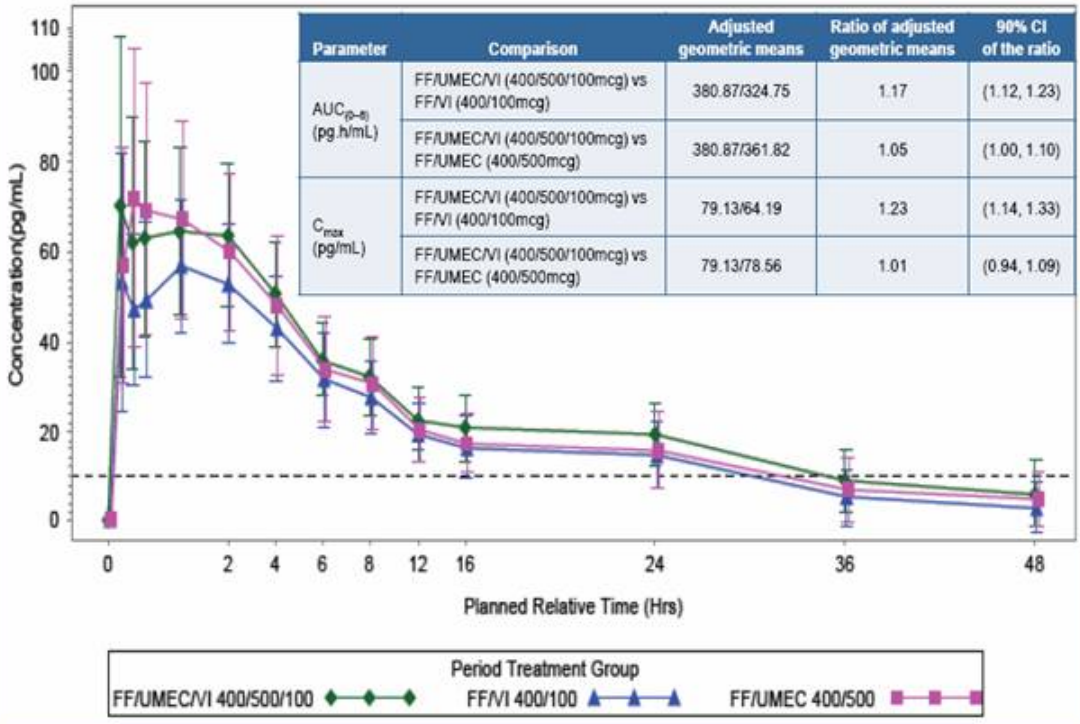
- Randomised, open-label, single-centre, single-dose (four inhalations), four-way crossover study in 44 healthy male and female subjects.
- Four inhalations of each of the following treatments were administered to achieve adequate plasma concentrations: FF/UMEC/VI (100/125/25mcg), FF/UMEC/VI (100/62.5/25mcg), FF/VI (100/25mcg) and UMEC/VI (125/25mcg) in a randomised fashion.
- Each subject received a single dose of FF/UMEC/VI (400/500/100mcg), FF/UMEC/VI (400/250/100mcg), FF/VI (400/100mcg) and UMEC/VI (250/100mcg).
- It was not possible to determine area under the curve (AUC)(0–∞) for all profiles, therefore AUC to last common quantifiable time-point for each analyte was used for statistical analysis.
- Systemic PD effects of FF (0–24h serum cortisol) and VI (0–4h heart rate and serum potassium) were assessed.
- This study was designed to estimate the effects of each treatment on primary and secondary parameters of interest. No formal hypotheses were tested.
- Point estimates and corresponding 90% confidence intervals (CI) were calculated to provide a range of plausible values for the comparisons of interest.

Results

Fluticasone furoate (FF) pharmacokinetics

- The estimates of total systemic exposure and drug delivery to the airways for FF $AUC_{(0–8)}$ were similar* when administered as the triple therapy (FF/UMEC/VI) compared to FF/VI (Figure 1).
- The maximum observed plasma concentration (C_{max}) was slightly higher for FF administered as the triple combination FF/UMEC/VI product compared with FF/VI (Figure 1)
  - this difference was attributed to small differences in absorption kinetics from the airways since the T_{max} occurred earlier (0.23h) for the triple therapy (FF/UMEC/VI) vs 1.0h and 0.5h for FF/VI and FF/UMEC, respectively
  - this small difference was not considered to be clinically significant.

Figure 1. Mean plasma FF concentration-time profiles and statistical results after single-dose administration of FF/UMEC/VI, FF/VI and FF/UMEC to healthy subjects

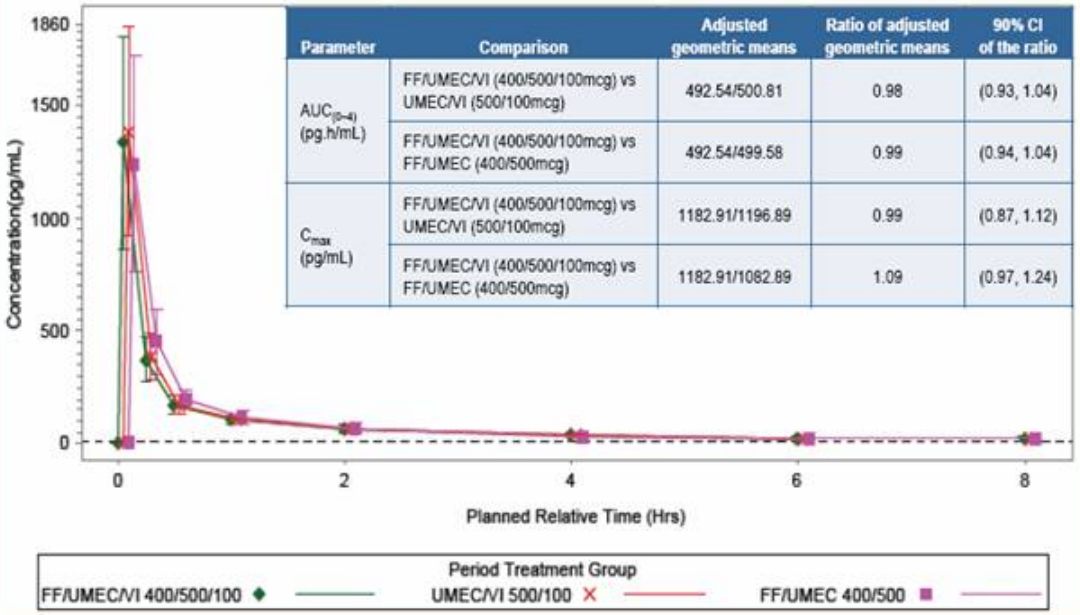


Parameter	Comparison	Adjusted geometric means	Ratio of adjusted geometric means	90% CI of the ratio
$AUC_{(0-6)}$ (pg.h/mL)	FF/UMEC/VI (400/500/100mcg) vs FF/VI (400/100mcg)	380.87/324.75	1.17	(1.12, 1.23)
	FF/UMEC/VI (400/500/100mcg) vs FF/UMEC (400/500mcg)	380.87/361.82	1.05	(1.00, 1.10)
C_{max} (pg/mL)	FF/UMEC/VI (400/500/100mcg) vs FF/VI (400/100mcg)	79.13/64.19	1.23	(1.14, 1.33)
	FF/UMEC/VI (400/500/100mcg) vs FF/UMEC (400/500mcg)	79.13/78.56	1.01	(0.94, 1.09)

Umeclidinium (UMEC) pharmacokinetics

· The estimates of total systemic exposure and drug delivery to the airways for UMEC ($AUC_{(0-4)}$ and C_{max}) were similar* when administered as the triple (FF/UMEC/VI) therapy compared with UMEC/VI (Figure 2).

Figure 2. Mean UMEC plasma concentration-time profiles and statistical results after single-dose administration of FF/UMEC/VI, UMEC/VI and FF/UMEC to healthy subjects



Parameter	Comparison	Adjusted geometric means	Ratio of adjusted geometric means	90% CI of the ratio
$AUC_{(0-4)}$ (pg.h/mL)	FF/UMEC/VI (400/500/100mcg) vs UMEC/VI (500/100mcg)	492.54/500.81	0.98	(0.93, 1.04)
	FF/UMEC/VI (400/500/100mcg) vs FF/UMEC (400/500mcg)	492.54/499.58	0.99	(0.94, 1.04)
C_{max} (pg/mL)	FF/UMEC/VI (400/500/100mcg) vs UMEC/VI (500/100mcg)	1182.91/1196.89	0.99	(0.87, 1.12)
	FF/UMEC/VI (400/500/100mcg) vs FF/UMEC (400/500mcg)	1182.91/1082.89	1.09	(0.97, 1.24)

Vilanterol (VI) pharmacokinetics

· The estimates of total systemic exposure and drug delivery to the airways for VI $AUC_{(0-2)}$ were similar* when administered as the triple (FF/UMEC/VI) vs FF/VI and UMEC/VI (Figure 3).

· C_{max} was slightly higher for VI administered as the triple (FF/UMEC/VI) compared with FF/VI (Figure 3).

- The PK profile of VI has consistently been described by a rapid absorption phase, with peak VI concentrations generally observed at 5 minutes post-dose in healthy subjects, followed by a rapid decline.

- The differences observed for VI C_{max} were considered to be a consequence of inadequate definition of the maximum observed concentration for VI that may have occurred between 5 and 15 minutes post-dose as

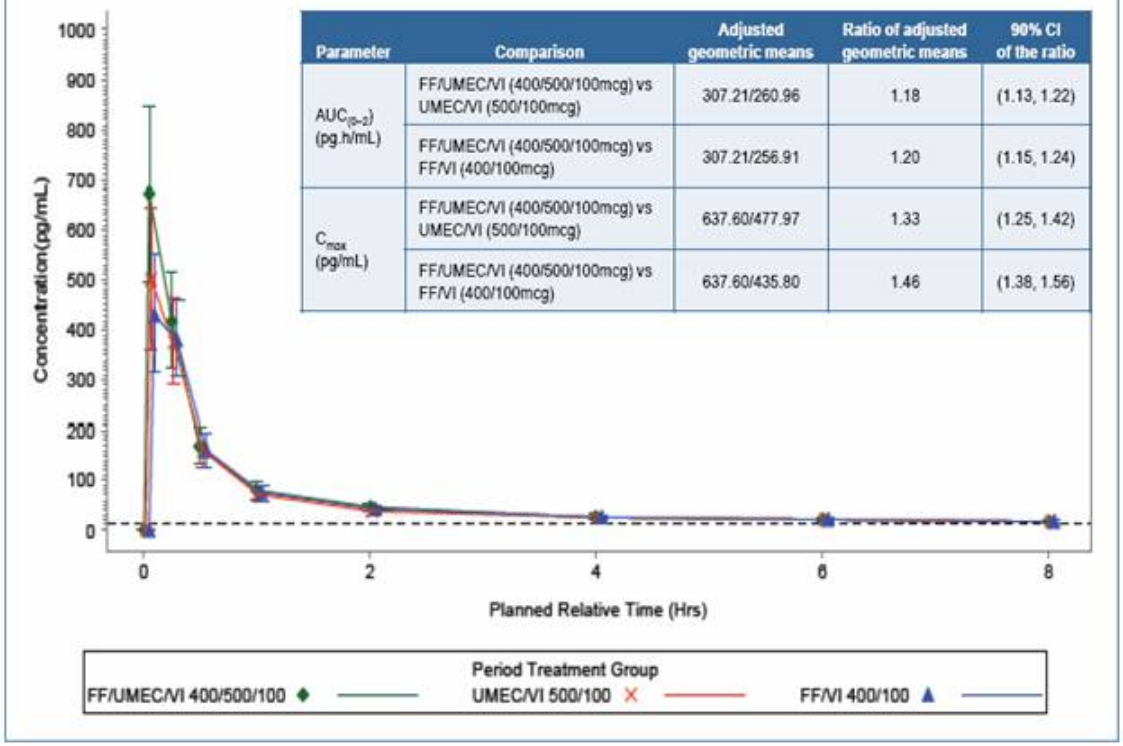
  - only two plasma samples were taken in the first 15 minutes post dose (at 5 minutes and 15 minutes)

  - the presence of an atypical 'plateau' between 5 and 15 minutes in some subjects was more common for the dual treatments FF/VI (52%) and UMEC/VI (33%) compared with the triple (FF/UMEC/VI) (12%).

- A second study (200587; see poster P938)(1) was conducted to evaluate different doses of the triple combination. Additional time-points were included in study 200587 to better characterise the PK profile of VI. There was no evidence of 'atypical' VI concentration-time profiles in study 200587.

- The small difference in VI C_{max} was not considered to be clinically significant.

Figure 3. Mean VI plasma concentration-time profiles and statistical results after single-dose administration of FF/UMEC/VI, FF/VI and UMEC/VI to healthy subjects



Parameter	Comparison	Adjusted geometric means	Ratio of adjusted geometric means	90% CI of the ratio
$AUC_{(0-2)}$ (pg.h/mL)	FF/UMEC/VI (400/500/100mcg) vs UMEC/VI (500/100mcg)	307.21/260.96	1.18	(1.13, 1.22)
	FF/UMEC/VI (400/500/100mcg) vs FF/VI (400/100mcg)	307.21/256.91	1.20	(1.15, 1.24)
C_{max} (pg/mL)	FF/UMEC/VI (400/500/100mcg) vs UMEC/VI (500/100mcg)	637.60/477.97	1.33	(1.25, 1.42)
	FF/UMEC/VI (400/500/100mcg) vs FF/VI (400/100mcg)	637.60/435.80	1.46	(1.38, 1.56)

Pharmacodynamics

- There were no differences in heart rate for FF/UMEC/VI compared with either UMEC/VI or FF/VI. The heart rate effects seen for FF/UMEC/VI compared with FF/UMEC – maximum and weighted mean change from baseline HR were increased by ~14 and ~6 beats/min, respectively – can be attributed to the VI component. These increases are similar to those seen in previous studies with FF/VI (800/100mcg) and UMEC/VI (500/100mcg).

- On average both minimum and weighted mean change from baseline serum potassium were comparable when FF/UMEC/VI was compared with UMEC/VI, FF/VI and FF/UMEC.

- Small increases in blood glucose were seen following FF/UMEC/VI compared with FF/UMEC: maximum and weighted mean change from baseline glucose were increased by approximately 0.5 and 0.15 mmol/L, respectively. These changes can also be attributed to the VI component and the magnitude of these increases are similar to those seen in previous studies with FF/VI (800/100mcg). There were no differences in blood glucose for FF/UMEC/VI compared with either UMEC/VI or FF/VI.

Safety

- There was a low incidence of adverse events (AEs), with no notable difference in the incidence of AEs reported for each treatment group. All AEs were mild-to-moderate in intensity.

- One subject reported an SAE of diabetes mellitus that led to withdrawal from the study. This event was not considered causally related to the study drug and it was subsequently identified that this subject was suffering from undiagnosed type 2 diabetes mellitus at study entry.

Conclusions

- FF/UMEC/VI delivered in a single inhaler achieved similar exposure to that seen with the dual therapies investigated.

· The safety and delivered lung dose of all three agents in a single inhaler are expected to be similar to corresponding dual therapies.

Reference

(1) Henderson A et al. Pharmacokinetic (PK) analysis of fluticasone furoate (FF), umeclidinium (UMEC) and vilanterol (VI) following triple therapy at two UMEC doses in healthy subjects. ERS 2014; poster P938, abstract 2826 (855608).

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*Although the study was not conducted as a formal bioequivalence study, the 90% CIs were within standard bioequivalence acceptance limits (0.8–1.25).

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Pharmacokinetic (PK) analysis of fluticasone furoate (FF), umeclidinium (UMEC) and vilanterol (VI) following triple therapy at two UMEC doses in healthy subjects

Poster No. P938

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Aims

- FF/UMEC/VI is a novel inhaled corticosteroid/long-acting muscarinic antagonist/long-acting beta$_2$ agonist (ICS/LAMA/LABA therapy). Dual therapies of FF/VI and UMEC/VI were recently approved for treatment of moderate-to-severe COPD.
- We compared the systemic exposure of FF, UMEC and VI after co-administration of FF, UMEC and VI in a single device at two UMEC doses (62.5mcg or 125mcg), and versus the dual therapies FF/VI and UMEC/VI (all in ELLIPTA™ dry powder inhaler).
- The evaluation at low-dose UMEC strength (62.5mcg) was included to support the proposed dose for Phase III studies with FF/UMEC/VI (100/62.5/25mcg).
- In this study, additional time-points were included to better characterise the PK profile of VI. Results from a previous study (CTT116415; see poster P895)(1), suggested that the conclusions for VI may have been confounded by inadequate estimates of C_{max}.

Methods

- Randomised, open-label, single-centre, single-dose (four inhalations), four-way crossover study in 44 healthy male and female subjects.
- Four inhalations of each of the following treatments were administered to achieve adequate plasma concentrations: FF/UMEC/VI (100/125/25mcg), FF/UMEC/VI (100/62.5/25mcg), FF/VI (100/25mcg) and UMEC/VI (125/25mcg) in a randomised fashion.
- Each subject received a single dose of FF/UMEC/VI (400/500/100mcg), FF/UMEC/VI (400/250/100mcg), FF/VI (400/100mcg) and UMEC/VI (250/100mcg).
- It was not possible to determine area under the curve (AUC)(0-∞) for all profiles therefore AUC to last common quantifiable time-point for each analyte was used for statistical analysis.
- This study was designed to estimate the effects of each treatment on primary and secondary parameters of interest. No formal hypotheses were tested.
- Point estimates and corresponding 90% confidence intervals (CI) were calculated to provide a range of plausible values for the comparisons of interest.

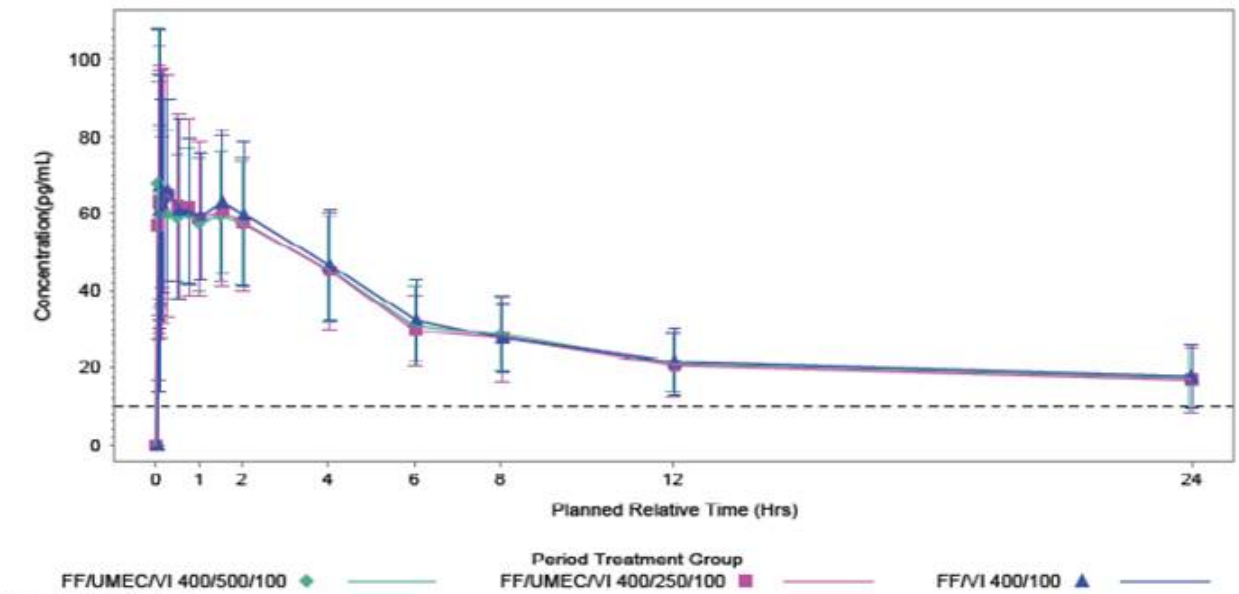
Results

Table 1. Statistical comparison of FF pharmacokinetic parameters

Parameter	Comparison	Adjusted geometric means	Ratio of adjusted geometric means	90% CI of the ratio
$AUC_{(0–4)}$ (pg.h/mL)	FF/UMEC/VI (400/500/100mcg) vs FF/UMEC/VI (400/250/100mcg)	211.92/211.22	1.00	(0.95, 1.06)
	FF/UMEC/VI (400/250/100mcg) vs FF/VI (400/100mcg)	211.22/218.49	0.97	(0.92, 1.02)
C_{max} (pg/mL)	FF/UMEC/VI (400/500/100mcg) vs FF/UMEC/VI 400/250/100mcg	81.45/80.96	1.01	(0.93, 1.09)
	FF/UMEC/VI (400/250/100mcg) vs FF/VI (400/100mcg)	80.96/85.59	0.95	(0.87, 1.03)

- There was no evidence for a difference* in the systemic exposure and drug delivery to the airways for FF (AUC and C_{max}, Table 1) following
  - administration of FF/UMEC/VI (400/250/100mcg) compared with FF/VI (400/100mcg)
  - administration of FF/UMEC/VI at two UMEC dose strengths (62.5 and 125mcg).

Figure 1. Mean FF plasma concentration-time profiles after single dose administration of FF/UMEC/VI at two UMEC doses and FF/VI



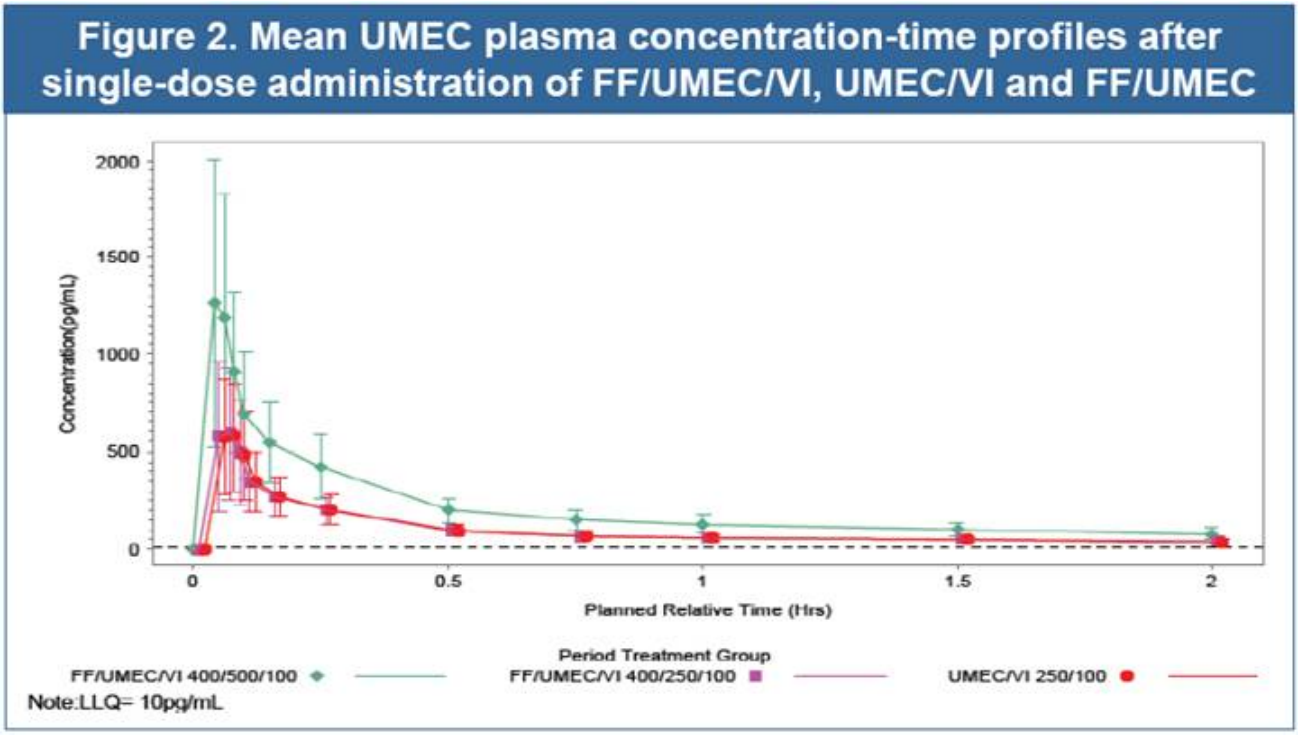
Umeclidinium (UMEC) pharmacokinetics

- There was no evidence for a difference* in the systemic exposure and drug delivery to the airways for UMEC (AUC and C_{max}; Table 2) following administration of FF/UMEC/VI (400/250/100mcg) compared with UMEC/VI (250/100mcg).

- Following administration of FF/UMEC/VI, at two UMEC dose strengths (62.5 and 125mcg), the systemic exposure for UMEC (C_{max} and AUC; Table 2) increased in proportion to the increase in dose.

Table 2. Statistical comparison of dose-normalised UMEC pharmacokinetic parameters

Parameter	Comparison	Adjusted geometric means	Ratio of adjusted geometric means	90% CI of the ratio
$AUC_{(0–2)}$ (pg.h/mL)	FF/UMEC/VI (400/500/100mcg) vs FF/UMEC/VI (400/250/100mcg)	0.85/0.81	1.04	(0.99, 1.10)
	FF/UMEC/VI (400/250/100mcg) vs UMEC/VI (250/100mcg)	0.81/0.81	1.00	(0.95, 1.06)
C_{max} (pg/mL)	FF/UMEC/VI (400/500/100mcg) vs FF/UMEC/VI (400/250/100mcg)	2.20/2.11	1.04	(0.96, 1.13)
	FF/UMEC/VI (400/250/100mcg) vs UMEC/VI (250/100mcg)	2.11/2.15	0.98	(0.91, 1.07)



Vilanterol (VI) Pharmacokinetics

- There was no evidence for a difference* in the systemic exposure and drug delivery to the airways (Table 3) for
  - VI AUC and C_{max} following administration of FF/UMEC/VI (400/250/100mcg) compared with FF/VI (400/100mcg)
  - VI AUC following administration of FF/UMEC/VI (400/250/100mcg) compared with UMEC/VI (250/100mcg)
  - VI AUC and C_{max} following administration of FF/UMEC/VI at two different dose strengths of UMEC (62.5 and 125mcg).
- The maximum observed plasma concentration (C_{max}) was slightly higher for VI administered as the triple FF/UMEC/VI (100/62.5/25mcg), compared with UMEC/VI (62.5/25mcg). This small PK difference is not considered to be of clinical significance.

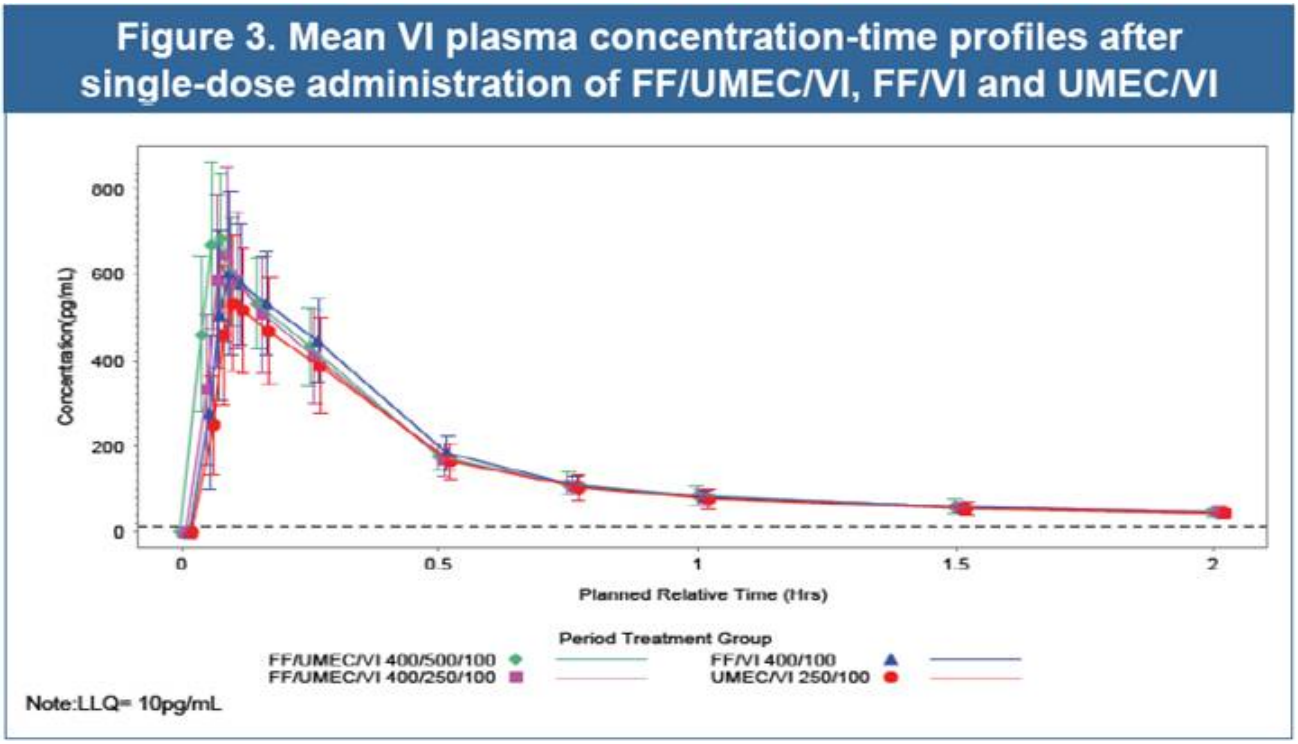


Table 3. Statistical comparison of VI pharmacokinetic parameters

Parameter	Comparison	Adjusted geometric means	Ratio of adjusted geometric means	90% CI of the ratio
$AUC_{(0-6)}$ (pg.h/mL)	FF/UMEC/VI (400/500/100mcg) vs FF/UMEC/VI (400/250/100mcg)	422.95/402.50	1.05	(1.01, 1.10)
	FF/UMEC/VI (400/250/100mcg) vs FF/VI	402.50/407.56	0.99	(0.95, 1.03)

	(400/100mcg)			
	FF/UMEC/VI (400/250/100mcg) vs UMEC/VI (250/100mcg)	402.50/370.76	1.09	(1.04, 1.13)
C_{max} (pg/mL)	FF/UMEC/VI (400/500/100mcg) vs FF/UMEC/VI (400/250/100mcg)	695.83/635.51	1.10	(1.04, 1.16)
	FF/UMEC/VI (400/250/100mcg) vs FF/VI (400/100mcg)	635.51/598.70	1.06	(1.01, 1.12)
	FF/UMEC/VI (400/250/100mcg) vs UMEC/VI (250/100mcg)	635.51/527.52	1.21	(1.14, 1.27)

- In this study there was no evidence for 'atypical' VI concentration time profiles, as seen in study CTT116415.(1) This supports the hypothesis that the VI C_{max} results reported in the CTT116415 study were due to insufficient characterisation of VI.

Safety

- There was a low incidence of adverse events (AEs), with no notable difference in the incidence of AEs reported for each treatment group. No serious AEs were reported. No subjects were withdrawn due to an AE.

Conclusions

- FF/UMEC/VI achieved similar exposure to dual therapies (FF/VI and UMEC/VI).

- FF/UMEC/VI in a single inhaler, at UMEC 250mcg or 500mcg, achieved dose-proportional systemic exposure for UMEC and similar FF or VI exposure between doses.

- The safety and delivered lung dose of all three agents in a single inhaler are expected to be similar to those in approved dual therapies.

References

(1) Allen A et al. Pharmacokinetic (PK) analysis of fluticasone furoate (FF), umeclidinium (UMEC) and vilanterol (VI) following triple therapy in healthy subjects. ERS 2014; poster P895; abstract 2950 (855739)

Acknowledgements

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