

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203975Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA	203975
Submission Date	12/18/2012
Proposed Brand Name	ANORO ELLIPTA
Generic Name	Umeclidinium Bromide/Vilanterol Inhalation Powder
Clinical Pharmacology Reviewer	Jianmeng Chen, M.D., Ph.D. and Ping Ji Ph.D.
Clinical Pharmacology Team Leader	Satjit Brar, Pharm. D., Ph.D.
Pharmacometrics Reviewer	Hongshan Li Ph.D.
Pharmacometrics Team Leader	Atul Bhattaram, Ph.D.
Pharmacogenomics Reviewer	Sarah Dorff, Ph.D.
Pharmacogenomics Team Leader	Michael Pacanowski, Pharm. D., MPH
OCP Division	Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor/Authorized Applicant	GSK
Submission Type; Code	505(b)(1); standard review
Formulation; Strength(s)	Inhalation powder administered from NDPI
Indication	COPD
Dosage Regimen	UMEC/VI (62.5/25) QD

1.	Executive Summary	4
1.1	Recommendations	4
1.2	Phase IV Commitments	4
1.3	Summary of Clinical Pharmacology and Biopharmaceutics Findings	4
2.	Question Based Review	11
2.1	List the <i>in vitro</i> and <i>in vivo</i> Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA. 11	
2.2	General Attributes of the Drug	20
2.2.1	What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?.....	20
2.2.2	What are the proposed mechanism of action and therapeutic indications?	21
2.2.3	What are the proposed dosages and routes of administration?	21

2.2.4	What drugs (substances, products) indicated for the same indication are approved in the US?.....	21
2.3	General Clinical Pharmacology.....	21
2.3.1	What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?..	21
2.3.2	What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?.....	23
2.3.3	Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?	23
2.4	Exposure-Response.....	23
2.4.1	Are the two dose regimens selected for the Phase 3 clinical trials, UMEC/VI 62.5 mcg/25 mcg once daily (QD) and 125 mcg/25 mcg QD, based on sufficient efficacy and safety data of Phase 2 clinical trials?	23
2.4.2	Are the two dose regimens, UMEC/VI 62.5 mcg/25 mcg QD and UMEC/VI 125 mcg/25 mcg QD proposed by the sponsor, appropriate for COPD patients?	28
2.4.3	Are there any covariates that influence the systemic exposure of UMEC and VI that need dose adjustment?	32
2.4.4	Does this drug prolong QT/QTc Interval?.....	33
2.5	What are the PK characteristics of the drug?.....	33
2.5.1	What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?.....	33
2.5.2	How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?.....	38
2.5.3	What are the characteristics of drug absorption?.....	39
2.5.4	What are the characteristics of drug distribution?	40
2.5.5	Does the mass balance study suggest renal or hepatic as the major route of elimination?.....	41
2.5.7	What are the characteristics of drug metabolism?	41
2.5.8	Is there evidence for excretion of parent drug and/or metabolites into bile?.	43
2.5.9	Is there evidence for enterohepatic recirculation for parent and/or metabolites?	43
2.5.10	What are the characteristics of drug excretion in urine?.....	43
2.5.11	Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?	44
2.5.12	How do the PK parameters change with time following chronic dosing?.....	45
2.6	Intrinsic Factors	46
2.6.1	What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?.....	46
2.6.2	Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?	47
2.6.3	Does genetic variation impact exposure and/or response?	52

2.7	Extrinsic Factors	52
2.7.2	Is the drug a substrate of CYP enzymes?.....	53
2.7.3	Is the drug an inhibitor and/or an inducer of enzymes/transporters?.....	53
2.7.4	Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?	53
2.7.5	Are there other metabolic/transporter pathways that may be important?	53
2.7.6	What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?	53
2.7.7	Is there any drug-drug and/or formulation interaction between the UMEC and VI when delivered via the NDPI device?	53
2.7.8	What are the drug-drug interactions?.....	54
2.7.9	Does the label specify co-administration of another drug?	56
2.7.10	What other co-medications are likely to be administered to the target population?.....	56
2.7.11	Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?	56
2.8	General Biopharmaceutics.....	57
2.8.1	Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?.....	57
2.8.2	How is the proposed to-be-marketed formulation linked to the clinical service formulation?.....	57
2.8.3	What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?	57
2.8.4	Was the bioequivalence of the different strengths of the to-be-marketed formulation tested? If so were they bioequivalent or not?.....	57
2.9	Analytical Section.....	57
2.9.1	How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?.....	57
2.9.2	Which metabolites have been selected for analysis and why?	62
2.9.3	For all moieties measured, is free, bound, or total measured?.....	62
2.9.4	What bioanalytical methods are used to assess concentrations of the measured moieties?	62
2.9.5	What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?.....	62
3.	Detailed Labeling Recommendations	64
4.	Appendix.....	68
4.1	PM Review.....	68
4.2.	Pharmacogenomics Review	91
4.3.	Individual Study Review.....	97

1. **Executive Summary**

1.1 Recommendations

From the viewpoint of the Office of Clinical Pharmacology, NDA 203975 is acceptable.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

GSK has submitted NDA 203975 seeking the marketing approval for Umeclidinium bromide/Vilanterol Inhalation Powder (UMEC/VI) (ANORO ELLIPTA) for the treatment of chronic obstructive pulmonary disease (COPD). UMEC/VI is a long-acting anticholinergic/long-acting beta2 agonist combination for oral inhalation to be administered from a Novel Dry Powder Inhaler (NDPI).

This submission includes 7 Phase 3 studies to evaluate the efficacy and safety of UMEC/VI combination, 3 Phase 2b studies to support dose selection of UMEC, 3 Phase 2b studies to support dose selection of VI and 37 Phase 1 and Phase 2a studies for the UMEC/VI combination and/or the monotherapy components including several studies of fluticasone furoate/VI (FF/VI) combination. One additional Phase 3 study to support the efficacy and safety of UMEC monotherapy (AC4115408) is also included.

Dose selection

Rationale for Dose and Dosing Frequency Selection

The proposed dose of UMEC/VI is 62.5/25 mcg once daily. Two dosing regimens, once daily doses of UMEC/VI 62.5/25 and 125/25 (mcg/mcg), were tested in Phase 3 studies in COPD patients. The dosing regimen, including the selection of dose, dosing frequency and timing of the dose, was established in dose-ranging studies in the COPD population as well as in asthma patients.

Dose Selection

VI

The 25 mcg daily dose of VI was selected on the basis of results from a Phase 2 dose-ranging study in subjects with COPD (Study B2C111045), which tested a range of VI doses (3, 6.25, 12.5, 25 and 50 mcg once daily). Based upon the primary endpoint of

Following selection of doses for the individual components of UMEC and VI, the sponsor evaluated the efficacy of UMEC/VI 62.5/25 and 125/25 mcg in Phase 3 studies in COPD patients.

Dosing Frequency

Study AC4115321 evaluated once and twice daily dosing for UMEC in subjects with COPD. The improvement of weighted mean FEV₁ (0-24h) was similar with UMEC 31.25 mcg twice daily and UMEC 62.5 mcg once daily dosing (Figure 2). For VI, Study HZA113310 investigated once-daily vs. twice daily administration in subjects with persistent asthma. The improvement of weighted mean FEV₁ (0-24h) was similar with VI 6.25 mcg twice daily and VI 12.5 mcg once daily dosing (Figure 3).

Figure 2: COPD; Change from Baseline FEV₁ (L) on Day 7; Study AC4115321

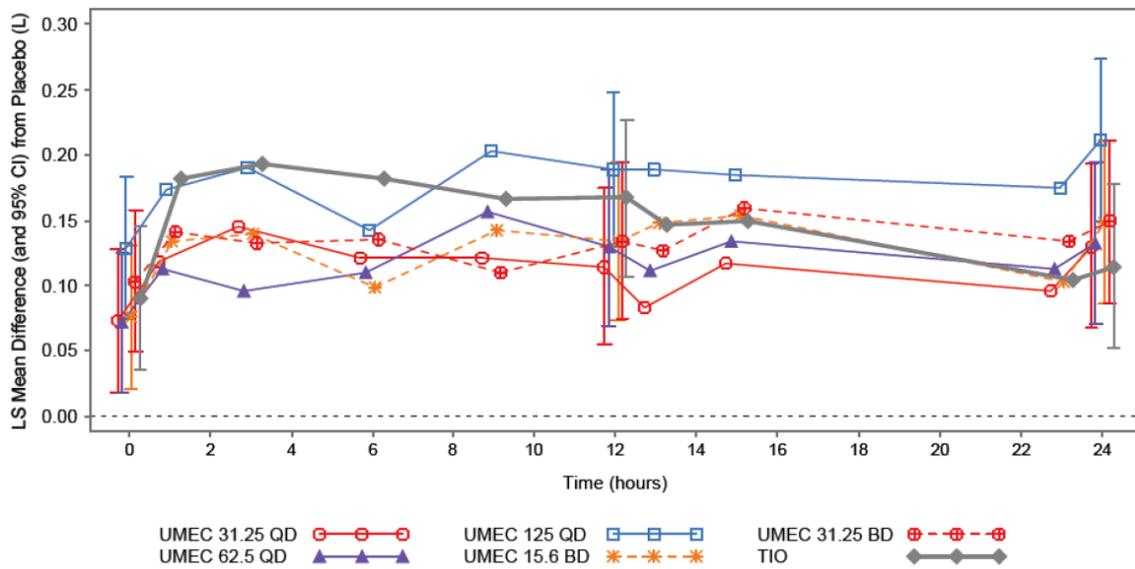
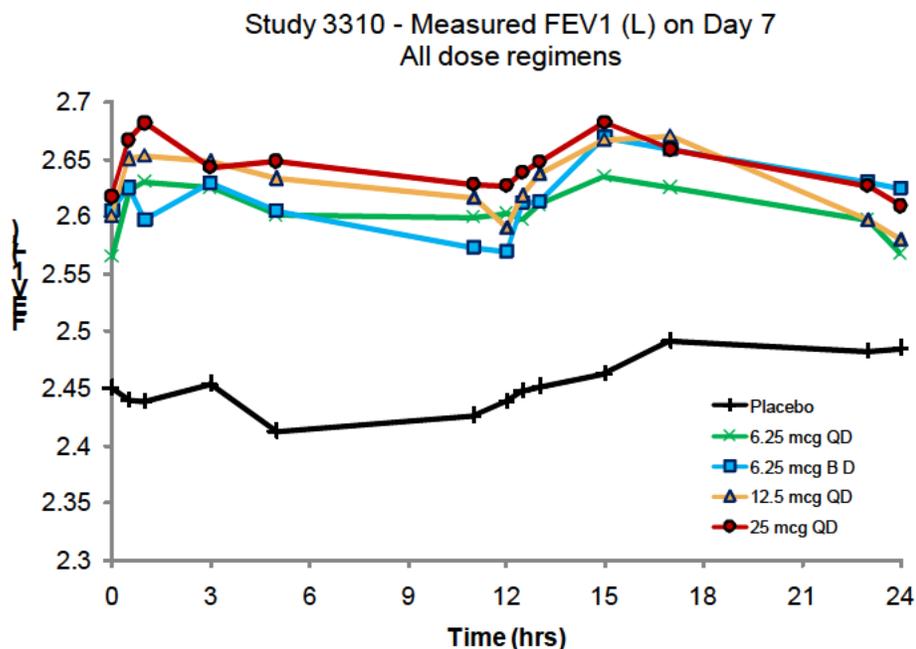


Fig 3: Effect of VI Dosing on FEV₁ in Subjects with Persistent Asthma (Study HZA113310)



Morning vs. evening dosing

All Phase 2 and 3 studies used morning dosing. The timing of dosing is not specified in the proposed label.

Dose selection based on Phase 3 trials

The efficacy and safety data collected from 6 Phase 3 clinical trials demonstrated that UMEC/VI 62.5 mcg/25 mcg QD is appropriate for COPD patients. However, UMEC/VI 125 mcg/25 mcg QD did not demonstrate additional benefit to UMEC/VI 62.5 mcg/25 mcg QD.

Trough FEV₁ change from baseline data on Day 169 of the four Phase 3 clinical trials (DB2113360, DB2113361, DB2113373 and DB2113374) demonstrated that UMEC/VI 62.5/25 and 125/25 improved lung function. The following conclusions can be deduced from the acquired Phase 3 information:

- The combination of UMEC/VI 62.5 mcg/25 mcg QD demonstrated added benefit to individual treatment of VI 25 mcg or UMEC 62.5 mcg, and both VI 25 mcg and UMEC 62.5 demonstrated higher efficacy than the placebo while safety profiles were comparable amongst the 4 treatments.
- The combination of UMEC/VI 125 mcg/25 mcg QD demonstrated added benefit to individual treatment of VI 25 mcg or UMEC 125 mcg, and both VI 25 mcg and UMEC 125 demonstrated higher efficacy than the placebo while safety profiles were comparable amongst the 4 treatments.
- The efficacy and safety profiles were comparable between the two combinations UMEC/VI 62.5 mcg/25 mcg and 125 mcg/25 mcg while they are numerically better than tiotropium 18 mcg QD. Similar FEV₁ results were obtained in other two Phase 3 studies (DB2114417 and DB2114418).

The safety profiles were comparable between different treatments of the 6 Phase 3

studies. Out of all 4647 patients of the 6 studies, 1502 patients reported AEs. Moderate or severe AEs totaled 1155 cases, including the following most frequent ones: 155 cases of headache, 81 cases of common cold, 78 exacerbations of COPD, 50 cases of upper respiratory infection, 49 cases of cough, 46 cases of toothache, 43 cases of back pains and 32 cases of pneumonia.

In summary, the efficacy and safety data collected from 6 Phase 3 clinical trials demonstrated that UMEC/VI 62.5 mcg/25 mcg QD is appropriate for COPD patients. However, UMEC/VI 125 mcg/25 mcg QD did not demonstrate additional benefit to UMEC/VI 62.5 mcg/25 mcg QD.

PHARMACOKINETICS

Absorption

- The absolute systemic bioavailability for UMEC and VI was about 12.8% (based on earlier clinical formulation) and 26%, respectively. However, the systemic bioavailability of both UMEC and VI was low after oral administration, on average <1% and <2%, respectively. Therefore, systemic exposures for both inhaled UMEC and VI are primarily due to absorption of the inhaled portion of the dose delivered to the lung.
- T_{max} was reached by approximately 0.08-1 hours for both UMEC and VI following oral inhalation administration.
- The accumulation of C_{max} after once-daily dosing of UMEC/VI 125/25 μ g was 1.3 for UMEC and up to 2.4 fold for VI at Day 7. The assessment of accumulation of AUC is limited by low assay sensitivity.
- Systemic exposure for UMEC/VI increased in proportion to the dose in the dose range of 125 to 500 μ g for UMEC (AUC_{tau} , C_{max}), and 25 to 100 mcg for VI (C_{max}).

Distribution

- The *in vitro* plasma protein binding of UMEC and VI is independent of concentration with average values of 89% and 97%, respectively.

Metabolism and Transporters

- *In vitro* metabolism of UMEC is mediated primarily by CYP2D6. However, no clinically meaningful difference in systemic exposure to UMEC was observed following repeat daily inhaled dosing of 500 mcg to normal and CYP2D6 poor metabolizer subjects (Study AC4110106). No dose adjustment is needed in patients using concomitant CYP2D6 inhibitors or subjects with genetic polymorphisms of CYP2D6.
- VI is a substrate of CYP3A4.
- Both VI and UMEC are substrates of P-glycoprotein (P-gp).
- Based on *in vitro* studies, the potential for UMEC and VI to inhibit and induce metabolic enzymes is negligible at low inhalation doses.

Elimination

- In humans, UMEC is eliminated by a combination of biliary and renal elimination of unchanged UMEC and metabolism. VI is primarily eliminated by metabolism with metabolites excreting both in urine and feces.
- The effective half-lives of UMEC and VI following oral inhalation administration of UMEC/VI were about 11 h.

COPD vs. Healthy

- UMEC C_{max} in COPD patients was <50% lower as compared to C_{max} in healthy subjects.
- VI C_{max} in COPD patients was 62% lower while AUC(0-24) was 43% higher compared to that in healthy subjects.

POPULATION PHARMACOKINETIC ANALYSIS

Population PK models were developed to describe the UMEC and VI systemic exposure in subjects with COPD in Phase 3 studies DB2113361 and DB2113373. There were no covariates found in the population PK of UMEC and VI that warrant any dose adjustment of either component.

SPECIAL POPULATIONS

Renal Impairment

The effect of renal function on the PK of UMEC was evaluated in Studies DB2114636 (UMEC and UMEC/VI) and HZA113970 (VI).

- Following administration of UMEC 125 µg IH, UMEC plasma exposure for subjects with severe renal impairment was comparable with healthy controls. There was no difference in the *in vitro* plasma protein binding of UMEC in healthy vs. severe renal impaired subjects.
- Systemic VI exposure is higher in severe renal impairment patients. At day 7, subjects with severe renal impairment had a mean (90%CI) increase in VI AUC by 56% (27%, 92%) and had similar VI C_{max} compared to subjects with normal renal function. The increased PK exposure of VI did not result in significant heart rate increase or serum potassium decrease in severe renal impairment patients compared to healthy subjects.
- No dose adjustment is needed for subjects with renal impairment.

Hepatic Impairment

The effect of hepatic function on the PK of UMEC was evaluated in Study DB2114637 (UMEC and UMEC/VI) and Study HZA111789 (VI).

- Systemic UMEC and VI exposure in moderate hepatic impairment patients is comparable to that in healthy subjects. There was no evidence for reduced plasma

protein binding of either UMEC or VI in plasma from subjects with varying degrees of hepatic impairment.

- No dose adjustment is needed for subjects with hepatic impairment.

DRUG-DRUG INTERACTIONS (DDI)

Drug-Drug and Formulation Interactions

There were no clinically relevant differences (<20% difference between the geometric means) in the pharmacokinetics of either UMEC or VI when administered in combination compared with administration alone.

During review, we noted that the exposure of VI is 2-3 fold higher after administration of UMEC/VI compared to FF/VI in both healthy subjects and COPD patients as summarized in the following table (Table 2). The exposure difference in the two submissions was communicated to the clinical team, as UMEC/VI is administered by oral inhalation and the systemic exposure is associated with safety rather than efficacy. An information request (IR) was also sent to the Sponsor for clarification. Although the Sponsor agreed with our observation, they did not provide plausible explanation. Therefore, the VI PK characteristics (ADME) derived from FF/VI studies are not used for labeling. For VI PK in special population and drug-drug interaction, we consider all studies done with VI, UMEC/VI, and FF/VI, and use the worst case scenario (largest observed change in AUC or C_{max}) in the labeling.

Table 2: Exposure Comparison between UMEC/VI and FF/VI Programs.

Study	Subjects	Treatment	Days of dosing	Geometric mean	
				AUC ₍₀₋₂₄₎ (pg*h/ml)	C _{max} (pg/ml)
DB2114635	Healthy	UMEC/VI 125/25 mcg	10	429	340
DB2113361, DB2113373	COPD	UMEC/VI 125/25 mcg, VI 25 mcg	Phase 3, steady state	614.7	127.9
HZA102936, HZA105548, HZA113970, HZA111789	Healthy	FF/VI 200/25 mcg VI 25mcg	7	213.9	130.5
HZC111348, HCZ110946, HZC112206, HZC112207	COPD	FF/VI 50/25, 100/25, 200/25, 400/25 mcg	Phase 3, steady state	265.7	43.2

Source: Table 11, Table 26, Table 78 and Table 79, 2.7.2, Summary of Clinical Pharmacology

Effect of co-administered drugs on UMEC/VI exposure

- Co-administration with strong CYP3A4 and potent P-gp inhibitor ketoconazole,

resulted in higher VI AUC_(0-t) (increase by 90%). Caution should be exercised when co-administer UMEC/VI with ketoconazole.

- Co-administration with potent P-glycoprotein and moderate CYP3A4 inhibitor verapamil did not affect the VI C_{max} or AUC. No dose adjustment is needed for UMEC/VI when co-administered with verapamil.
- There was no clinically significant difference in the systemic exposure to UMEC following 7 days of repeat dosing with IH doses up to 1000 mcg between normal metabolizer and CYP2D6 poor metabolizer. No dose adjustment is needed in patients using concomitant CYP2D6 inhibitors or subjects with genetic polymorphisms of CYP2D6.

Effect of UMEC/VI on exposure of co-administered drugs

- With low systemic exposures for both UMEC and VI after oral inhalation administration, potential for inhibition and induction of metabolic enzymes is negligible.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS FOR SAFETY

UMEC/VI is administered by oral inhalation and efficacy is presumed to be driven by local effects in the lung. Systemic exposures of UMEC and VI are considered more relevant for safety.

Effect of UMEC/VI on QTc

QT effect for UMEC/VI was evaluated in a randomized, placebo-controlled, incomplete block, four-period crossover, repeat dose study (DB2114635). In this study, subjects were given dry powder inhaler once daily for 10 days as placebo, UMEC 500 mcg, UMEC/VI 125/25 mcg, UMEC/VI 500/100 mcg. The active control was single oral dose of moxifloxacin 400 mg on Day 10. No significant QTc prolongation effects of a therapeutic dose of UMEC/VI 125/25 mcg and suprathreshold dose of UMEC 500 mcg were detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between UMEC/VI 125/25 mcg and placebo, and between UMEC 500 mcg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. However, the largest upper bounds of the 2-sided 90% CI for the mean difference between UMEC/VI 500/100 mcg and placebo was 10.7 which is higher than the threshold for regulatory concern as described in ICH E14 guidelines.

2. Question Based Review

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA.

In vitro studies using human biomaterials were conducted and are listed Table 2.1a.

Table 2.1a: <i>In Vitro</i> Studies for UMEC and VI Using Human Biomaterials.			
Drug	ADME	Objective	Study/Report name
Umeclidinium bromide (GSK573719)	Absorption	In vitro substrate of P-gp	WD2006/02657
	Distribution	In vitro inhibition of P-gp	WD2006/02596
		In vitro substrate of OCT1,2,3, OCTN1,2	WD2010/00669
		In vitro protein binding	WD2008/00503
		Protein binding in renal and hepatic impairment patients	2012N144582
	Metabolism	In vitro inhibition of CYP450 enzymes	CH200500950
		In vitro metabolism profiling in human	05DMW039
		In vitro investigation of human Oxidative enzymology	06DMW086
In vitro metabolism in human hepatocytes		06DMW136	
Vilanterol (GW642444)	Absorption	VI as P-gp substrate	WD2004/00106/00
	Distribution	Blood cell association	WD2006/02044/01
		Human plasma protein binding Human albumin, α 1-acid glycoprotein, or gamma-globulin binding	2011N118910_00
	Metabolism	Metabolism of VI in human liver and lung microsomes	2011N21880_00
		Identify CYP450 isoforms responsible for VI metabolism	WD2006/02720/00 WD2006/02574/00 SH2003/00040/00
		Potential of VI to inhibit CYPs	SH2003/00040/00
		Potential for VI to inhibit P-gp	WD2007/01087/00
UMEC/VI	Distribution	Healthy, hepatic impairment and renal impairment human plasma, protein binding for UMEC and VI	2011N118910_00

The clinical pharmacology studies in healthy subjects are summarized in Table 2.1b (UMEC) and Table 2.1c (VI). The PK profile of UMEC in healthy subjects was evaluated in 9 Phase 1 studies (Studies AC4105209, AC4106889, AC4113377, DB2113208, DB2114636, DB2114637, DB2114635, AC4110106, DB2113950), and in COPD in one Phase 1 study (Study AC4108123), one Phase IIa study (Study AC4105211), three Phase 2b studies (Studies AC4115321, AC4113073, AC4113589), and three Phase 3 studies (Studies AC4115408, DB2113361, DB2113373).

The PK profile of VI in healthy subjects was evaluated in 11 Phase 1 studies (Studies HZA102934, B2C108784, DB1111509, DB1112146, DB2113208, DB1112017, HZA111789, HZA113970, B2C112205, HZA105548, and HZA102936) and in COPD patients in one Phase 1 study (Study B2C110165), one Phase 2a study (Study HZC111348), one Phase 3 study (Study HZC110946), and two Phase 3 studies (Study DB2113361 and Study DB2113373).

The PK of UMEC/VI after the administration following routes other than inhalation was evaluated in Studies HZA102934, B2C106181, B2C106180, AC4112008, AC4112014. The PD of UMEC/VI was evaluated in Studies DB2113120, AC4115487, P2C1001, DB1111509, HZA102940, B2C104604. All clinical studies by treatment are summarized briefly in Table 2.1d.

Table 2.1b: Summary of Clinical Studies with UMEC PK Assessments.

Protocol	Design	No. of Subjects Treated	Treatments	Formulation and Device
DB2114635	Phase 1, R, DB ^a , PC, 4-way XO, RD, TQT Study	Healthy subjects aged 19-63 years N=103	UMEC 500 mcg QD (N=76) UMEC/VI 125/25 mcg QD (N=78) UMEC/VI 500/100 mcg QD (N=76) Moxifloxacin 400 mg QD (N=74) Placebo (N=77)	Lactose/MgSt via Novel DPI
DB2113208	Phase 1, R, DB, PC, 4-way XO, SD	Healthy Japanese subjects aged 21-58 years N=16	UMEC 500 mcg QD (N=15) VI 50 mcg QD (N=16) UMEC/VI 500/50 mcg QD (N=15) Placebo (N=14)	Lactose/MgSt via Novel DPI
DB2113950	Phase 1, R, PG, OL, RD	Healthy subjects aged 20-65 years N=32	UMEC 500 mcg QD (N=16) UMEC 500 mcg QD+V 240 mg QD (N=15) UMEC/VI 500/25 mcg QD (N=16) UMEC/VI 500/25 mcg+ V 240 mg QD (N=15)	Lactose/MgSt via Novel DPI
DB2114636 ^b	Phase 1, SB, NR, SD, 2-Period	Healthy subjects and subjects with renal impairment aged 36-63 years N=9 (healthy subjects only)	UMEC 125 mcg QD (N=9) UMEC/VI 125/25 mcg QD (N=9)	Lactose/MgSt via Novel DPI
DB2114637 ^c	Phase 1, OL, NR, SD, RD, 2-Period	Healthy subjects and subjects with hepatic impairment aged 31-70 years N=9 (healthy subjects only)	UMEC 125 mcg QD (SD and RD) (N=9) UMEC/VI 125/25 mcg (SD only) (N=9)	Lactose/MgSt via Novel DPI
AC4105209	Phase 1, R, DB, PC, 5-way XO, SD, Dose-ascending	Healthy subjects aged 21-50 years N=20	UMEC 10 mcg QD (N=10) UMEC 20 mcg QD (N=10) UMEC 60 mcg QD (N=10) UMEC 100 mcg QD (N=9) UMEC 250 mcg QD (N=10) UMEC 350 mcg QD (N=9) TIO (N=19) Placebo (N=19)	Lactose/ (b) (4) (b) (4), ia DISKUS
AC4106889 ^d	Phase 1, R, DB, PC, PG, SD, RD, Dose-ascending	Healthy subjects aged 20-53 years N=36	UMEC 250 mcg QD (N=9) UMEC 750 mcg QD (N=9) UMEC 1000 mcg QD (N=9) Placebo QD (N=9)	Lactose/ (b) (4) (b) (4) via DISKUS

AC4110106	Phase 1, R, DB, PC, SD, RD, 2-Part, Dose-ascending	Healthy subjects and in a healthy population of cytochrome P450 isoenzyme 2D6 poor metabolizers aged 18-64 years N=20 (Part 1) N=16 (Part 2)	<u>Part 1/Single-dose</u> UMEC 100 mcg QD (N=16) UMEC 500 mcg (N=16) UMEC 1000 mcg (N=16) Placebo (N=4) <u>Part 1/Repeat-dose</u> UMEC 500 mcg (N=8) UMEC 1000 mcg (N=8) Placebo (N=4) <u>Part 2/Single-dose</u> UMEC 100 mcg QD (N=6) UMEC 500 mcg (N=12) UMEC 1000 mcg (N=6) Placebo (N=4) <u>Part 2/Repeat-dose</u> UMEC 500 mcg (N=6) UMEC 1000 mcg (N=11) Placebo (N=4)	Lactose/MgSt via Novel DPI
AC4113377	Phase 1,R, DB, PC, SD, RD, Dose-ascending	Healthy Japanese subjects aged 21-38 years N=48	UMEC 250 mcg (N=12) UMEC 500 mcg (N=12) UMEC 1000 mcg (N=12) Placebo (N=12)	Lactose/MgSt via Novel DPI

Protocol	Design	Diagnosis/No. of Subjects Treated	Treatments	Formulation and Device
AC4105211	Phase 2a, R, DB, PC, PG, 7-Day, Dose-ascending, RD	Subjects with COPD aged 48-75 years N=38	UMEC 250 mcg QD (Cohort 1; N=10) UMEC 250 mcg QD (Cohort 2; N=10) UMEC 1000 mcg QD (Cohort 3; N=9) Placebo (N=9)	Lactose/MgSt via Novel DPI
DB2113361	Phase 3a, R, DB, PG, PC, 24-week; RD	Subjects with COPD aged 40-86 years N=1489	UMEC 125 mcg QD (N=407) VI 25 mcg QD (N=404) UMEC/VI 125/25 mcg QD (N=403) Placebo (N=275)	Lactose/MgSt via Novel DPI
DB2113373	Phase 3a, R, DB, PG, PC, 24-week; RD	Subjects with COPD aged 40-93 years N=1532	UMEC 62.5 mcg QD (N=418) VI 25 mcg QD (N=421) UMEC/VI 62.5/25 mcg QD (N=413) Placebo (N=280)	Lactose/MgSt via Novel DPI
AC4108123	Phase 1, R, DB, PC, 4-way XO, Dose-ascending; SD	Subjects with COPD aged 48-67 years N=24	UMEC 250 mcg QD (N=22) UMEC 500 mcg QD (N=21) UMEC 1000 mcg QD (N=13) TIO 18 mcg QD (N=8) Placebo (N=21)	Lactose/ (b) (4) via DISKUS/ACCUHALER
AC4113589	Phase 2b, R, DB, PC, PG, 28-Day, Dose-ranging, RD	Subjects with COPD aged 40-79 years N=285	UMEC 125 mcg QD (N=71) UMEC 250 mcg QD (N=72) UMEC 500 mcg QD (N=71) placebo (N=71)	Lactose/MgSt via Novel DPI
AC4115321	Phase 2b, R, DB, PC, 3-way XO, 7-day, Dose-ranging, RD	Subjects with COPD aged 41-80 years N=163	UMEC 15.6 mcg QD (N=60) UMEC 31.25 mcg QD (N=57) UMEC 62.5 mcg QD (N=59) UMEC 125 mcg QD (N=60) UMEC 15.6 mcg BD (N=56) UMEC 31.25 mcg BD (N=58) TIO 18 mcg QD (N=56) Placebo (N=60)	Lactose/MgSt via Novel DPI
AC4113073	Phase 2b, R, DB, PC, 3-way XO, 14-day, Dose-ranging, RD	Subjects with COPD aged 42-79 years N=176	UMEC 62.5 mcg QD (N=35) UMEC 125 mcg QD (N=34) UMEC 250 mcg QD (N=36) UMEC 500 mcg QD (N=38) UMEC 1000 mcg QD (N=32) UMEC 62.5 mcg BD (N=34) UMEC 125 mcg BD (N=37) UMEC 250 mcg BD (N=33) TIO 18 mcg QD (N=35) Placebo (N=158)	Lactose/MgSt via Novel DPI
AC4115408	Phase 3a, R, DB, PG, PC, 12-week; RD	Subjects with COPD aged 41-86 years N=206	UMEC 62.5 mcg QD (N=69) UMEC 125 mcg QD (N=69) Placebo (N=68)	Lactose/MgSt via Novel DPI

Source: Table 3, Summary of Clinical Pharmacology

Table 2.1c: Summary of Clinical Studies with VI PK Assessments.

Protocol	Design	No. of Subjects Treated	Treatments	Formulation and Device
HZA102936	Phase 1, R, DB ^a , PC, 4-way XO, RD, TQT Study	Healthy subjects aged 18-65 years N=85	FF/VI 200/25 mcg (N=81) FF/VI 800/100 mcg (N=80) Moxifloxacin (N=79) Placebo (84)	Lactose/MgSt via Novel DPI
HZA102934	Phase 1, NR, OL, 3-period XO, SD	Healthy subjects aged 21-40 years N=16	FF/VI 800/100 mcg IH (N=16) FF 250 mcg IV (N=16) VI 55 mcg IV (N=16)	Lactose/MgSt via Novel DPI
HZA105548	Phase 1, R, DB, PC, 2-way XO, RD	Healthy subjects aged 22-39 years N=18	FF/VI 200/25 mcg + KETO 200 mg (N=18) FF/VI 200/25 mcg + Placebo (N=18) KETO 200 mg (N=18) Placebo (N=18)	Lactose/MgSt via Novel DPI
HZA111789 ^b	Phase 1, NR, OL, RD,	Healthy subjects and subjects with hepatic impairment aged 33-61 years N=9 (healthy subjects only)	FF/VI 200/25 mcg (N=9)	Lactose/MgSt via Novel DPI
HZA113970 ^c	Phase 1, NR, OL, RD	Healthy subjects and subjects with severe renal impairment aged 33-66 years N=9 (healthy subjects only)	FF/VI 200/25 mcg (N=9)	Lactose/MgSt via Novel DPI
B2C108784	Phase 1, R, DB, PC, PG, RD	Healthy subjects aged 19-53 years N=36	VI 25 mcg (N=9) VI 50 mcg (N=9) VI 100 mcg (N=9) Placebo (N=9)	Lactose/MgSt powder via DISKUS
B2C112205	Phase 1, R, DB, PC, 2-way XO, SD ^d	Healthy subjects aged 18-52 years N=20	VI 25 mcg + KETO 400 mg (N=19) VI 25 mcg + Placebo (N=18) KETO 400 mg (N=20) Placebo (N=19)	MgSt via Novel DPI
DB1111509 ^e	Phase 1, R, DB, PC, 4-way XO, SD	Healthy subjects aged 23-65 years N=16	GSK233705 200 mcg (N=16) VI 50 mcg (N=16) GSK233705/VI 200/50 mcg (N=16) Placebo (N=16)	Lactose/MgSt via Novel DPI
DB1112017	Phase 1, R, DB, PC, PG, RD	Healthy Japanese subjects aged 20-28 years N=32	VI 12.5 mcg (N=12) VI 25 mcg (N=12) Placebo (N=8)	Lactose/MgSt via Novel DPI
DB1112146 ^e	Phase 1, R, DB, PC, 4-way XO, SD	Healthy Japanese subjects aged 22-48 years N=16	GSK233705 200 mcg (N=16) VI 50 mcg (N=16) GSK233705/VI 200/50 mcg (N=16) Placebo (N=16)	Lactose/MgSt via Novel DPI
DB2113208	Phase 1, R, DB, PC, 4-way XO, SD	Healthy Japanese subjects aged 21-58 years N=16	UMEC 500 mcg QD (N=15) VI 50 mcg QD (N=16) UMEC/VI 500/50 mcg QD (N=15) Placebo (N=14)	Lactose/MgSt via Novel DPI

Protocol	Design	Diagnosis/No. of Subjects Treated	Treatments	Formulation and Device
DB2113361	Phase 3a, R, DB, PG, PC, 24-week, RD	Subjects with COPD aged 40-86 years N=1489	UMEC 125 mcg QD (N=407) VI 25 mcg QD (N=404) UMEC/VI 125/25 mcg QD (N=403) Placebo (N=275)	Lactose/MgSt via Novel DPI
DB2113373	Phase 3a, R, DB, PG, PC, 24-week, RD	Subjects with COPD aged 40-93 years N=1532	UMEC 62.5 mcg QD (N=418) VI 25 mcg QD (N=421) UMEC/VI 62.5/25 mcg QD (N=413) placebo (N=280)	Lactose/MgSt via Novel DPI
HZC111348	Phase 2a, R, DB, PC, PG, 28-day, RD	Subjects with COPD aged 42-77 years N=60	FF/VI 400/25 mcg QD (N=40) placebo (N=20)	Lactose/MgSt via Novel DPI
B2C110165	Phase 1, R, DB, PC, 4-way XO, Dose-ascending, SD	Subjects with COPD aged 48-75 years N=20	VI 25 mcg QD (N=20) VI 50 mcg QD (N=19) VI 100 mcg QD (N=8) GW642444H 100mcg QD (N=12) placebo (N=19)	Lactose/MgSt via DISKUS/ACCUHALER
HZC110946	Phase 3, R, DB, PC, 3-way XO, 28-day, RD	Subjects with COPD aged 44-82 years N=54	FF/VI 50/25 mcg QD (N=34) FF/VI 100/25 mcg QD (N=33) FF/VI 200/25 mcg QD (N=31) placebo (N=51)	Lactose/MgSt via Novel DPI

Source: Table 5, Summary of Clinical Pharmacology

Table 2.1d: All Clinical Studies by Treatment.

Type of Study	Number of Studies	Studies
All Clinical Pharmacology Studies (40 studies total)		
UMEC/VI ^a	8	DB2113208, DB2113950, DB2114635, DB2114636, DB2114637, DB2113120, DB2113361, DB2113373
UMEC	13	AC4105209, AC4105211, AC4110106, AC4106889, AC4108123, AC4112008, AC4113377, AC4115487, AC4112014, AC4113589, AC4115321, AC4113073, AC4115408
VI (including GW642444H) ^b	19	B2C10001, B2C106180, B2C106181, B2C108784, B2C110165, B2C112205, DB1112146, DB1111509/AC2111509, DB1112017, HZA102934, HZA102936, HZA102940, HZA105548, HZA105871, HZA111789, HZA113970, HZC111348, HZC110946, B2C104604

Source: Table 1, Summary of Clinical Pharmacology

The UMEC formulation and VI formulation were developed separately and subsequently combined as a single inhaler. The proposed to-be-marketed product contains 2 double-foil blister strips. Each blister on one strip contains a white powder mix of micronized umeclidinium bromide (74.2 mcg equivalent to 62.5 mcg of umeclidinium), magnesium stearate (75 mcg), and lactose monohydrate (to 12.5 mg), and each blister on the other strip contains a white powder mix of micronized vilanterol trifenate (40 mcg equivalent to 25 mcg of vilanterol), magnesium stearate (125 mcg), and lactose monohydrate (to 12.5 mg). For UMEC, the formulations used in early clinical studies and the to-be-marketed formulation were different. However, as Phase 3 formulation was same as

commercial formulation, no relative bioavailability study was conducted. Because the earlier clinical formulation and Phase 3 formulation was not bridged, the PK results from earlier clinical formulation will not be included the labeling, although the results will be presented briefly in this review.

A summary of formulations for UMEC or UMEC/VI used in the clinical studies is shown in the table 2.1e.

Study	Design	Formulation	Formulation source	Comments
AC4105211	safety tolerability and PK	Earlier clinical formulation	P22 table 16	PK results will not be in the labeling
AC4113589	dose-ranging	Earlier clinical formulation	P22 Table 16	PK results will not be in the labeling
AC4113073	dose-ranging and dose interval	Earlier clinical formulation	P22 Table 16	PK results will not be in the labeling
AC4105209	FTIM, safety, tolerability, PK, PD	Earlier clinical formulation	P22 Table 16	PK results will not be in the labeling
AC4108123	safety, tolerability, PK, PD	Earlier clinical formulation	P22 Table 16	PK results will not be in the labeling
AC4106889	safety, tolerability, PK, PD	Earlier clinical formulation	P22 Table 16	PK results will not be in the labeling
AC4110106	safety, tolerability, PK, PD	Earlier clinical formulation	P22 Table 16	PK results will not be in the labeling
AC4112008	safety and tolerability	Earlier clinical formulation	P22 Tables 16, 18, 18	PK results will not be in the labeling
DB2113950	safety, tolerability, PK, PD	Earlier clinical formulation	P22 Tables 16, 23	PK results will not be in the labeling
AC4115321	dose-ranging	Earlier clinical formulation	P22 Table 17	PK results will not be in the labeling
AC4113377	safety, tolerability, PK, PD	Earlier clinical formulation	P22 Table 17	PK results will not be in the labeling
AC4112014	safety, tolerability, mass balance	solution	P22 Table 18	PK results will be in the labeling
B2113208	safety, tolerability, PK, PD	Earlier clinical formulation	P22 Tables 21, 22	PK results will not be in the labeling
DB2114635	QT	Earlier clinical formulation	P22 Tables 21, 24, 23	PK results will be in the labeling
DB2113120	safety tolerability 28 days	Earlier clinical formulation	P22 Table 23	PK results will not be in the labeling
DB2114636	renal impairment study	Commercial and phase 3 formulation	p22 Tables 24, 25	PK results will be in the labeling
DB2114637	hepatic impairment study	Commercial and Phase 3 formulation	P22 Tables 24, 25	PK results will be in the labeling
DB2113361	efficacy and safety over 24 weeks	Commercial and Phase 3 formulation	P22 Tables 24, 25, 26	PK results will be in the labeling
DB2113373	efficacy and safety over 24 weeks	Commercial and Phase 3 formulation	P22 Tables 24, 25, 26	PK results will be in the labeling

AC4115408	safety and efficacy and dose selection	Commercial and phase 3 formulation	P22 Tables 25	PK results will be in the labeling
AC4115487	PD	Commercial and phase 3 formulation	P22 Tables 25, 27	PK results will be in the labeling

The formulation for VI or FF/VI used in clinical trials in this submission was the to-be-marketed formulation. Therefore, the PK data from these studies (B2C10001, B2C110165, DB1111509/AC2111509, HZA102936, HZA111789, B2C104604, B2C106180, B2C112205, DB1112017, HZA102940, HZA113970, B2C106181, DB1112146, HZA102934, HZA105548, HZC111348, B2C108784, HZA105871, HCZ110946) are reviewed for UMEC/VI labeling.

During review, we noted that the exposure of VI is 2-3-fold higher after administration of UMEC/VI compared to FF/VI in both healthy subjects and COPD patients, as summarized in the following table (Table 2.1.f). The exposure difference in the two submissions was communicated to the clinical team, as UMEC/VI is administered by oral inhalation and the systemic exposure is associated with safety rather than efficacy. An information request (IR) was also sent to the Sponsor for clarification. Although the Sponsor agreed with our observation, they did not provide plausible explanation. Therefore, the VI PK characteristics (ADME) derived from FF/VI studies are not used for labeling. For VI PK in special population and drug-drug interaction, we consider all studies done with VI, UMEC/VI, and FF/VI, and use the worst case scenario (largest observed change in AUC or C_{max}) in the labeling.

Table 2.1f: Comparison of VI exposure in FF/VI and UMEC/VI.

Study	Subjects	Treatment	Days of dosing	Geometric mean	
				AUC ₍₀₋₂₄₎ (pg*h/ml)	C _{max} (pg/ml)
DB2114635	Healthy	UMEC/VI 125/25 mcg	10	429	340
DB2113361, DB2113373	COPD	UMEC/VI 125/25 mcg, VI 25 mcg	Phase 3, steady state	614.7	127.9
HZA102936, HZA105548, HZA113970, HZA111789	Healthy	FF/VI 200/25 mcg, VI 25mcg	7	213.9	130.5
HZC111348, HCZ110946, HZC112206, HZC112207	COPD	FF/VI 50/25, 100/25, 200/25, 400/25 mcg	Phase 3, steady state	265.7	43.2

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Umeclidinium bromide and vilanterol are both small molecule drugs. Umeclidinium bromide is a white powder with a molecular weight of 508.49, and the empirical formula is $C_{29}H_{34}BrNO_2$ or $C_{29}H_{34}NO_2.Br$. Vilanterol trifenate is a white powder with a molecular weight of 774.8, and the empirical formula is $C_{24}H_{33}Cl_2NO_5 \cdot C_{20}H_{16}O_2$. UMEC is slightly soluble in water. VI is practically insoluble in water.

Drug Product

Umeclidinium/Vilanterol Inhalation Powder 62.5/25 microgram is available as 30 and 7 dose packs. Each dose contains 62.5 micrograms of umeclidinium (as bromide) and 25 micrograms of vilanterol (as trifenate) per inhalation.



Table 2.2.1: Composition of Umeclidinium/Vilanterol Inhalation Powder 62.5/25 µg.

Component	Quantity per 12.5 mg Blister ³	Function	Reference to Standard
Umeclidinium Blister Strip			
Umeclidinium bromide micronised	74.2 mcg ⁴	Active	GlaxoSmithKline ¹
Magnesium Stearate	75 mcg	(b) (4)	JP, Ph. Eur and USP/NF ⁶
Lactose Monohydrate	to 12.5 mg	(b) (4)	JP, Ph. Eur and USP/NF ⁶
Vilanterol Blister Strip			
Vilanterol trifenate micronised	40 mcg ⁵	Active	GlaxoSmithKline ²
Magnesium Stearate	125 mcg	(b) (4)	JP, Ph. Eur and USP/NF ⁶
Lactose Monohydrate	to 12.5 mg	(b) (4)	JP, Ph. Eur and USP/NF ⁶

Note:

mcg: microgram

1. Details of the specification of the active ingredient are provided in [m3.2.S.4.1. Specification_Umeclidinium Bromide](#)
2. Details of the specification of the active ingredient are provided in [m3.2.S.4.1. Specification_Vilanterol Trifenate](#)
3. A manufacturing overage (b) (4) may be included.
4. 74.2 micrograms of umeclidinium bromide is equivalent to 62.5 micrograms of umeclidinium (b) (4)
5. 40 micrograms of vilanterol trifenate is equivalent to 25 micrograms of vilanterol. (b) (4)
6. Excipients comply with JP, Ph. Eur and USP/NF and additional tests to ensure the quality for inhaled use. Details of the specification are provided in Section 4.

Source : Table 1, P.2., Description and Composition of the Drug Product

2.2.2 What are the proposed mechanism of action and therapeutic indications?

Umeclidinium bromide (UMEC)/vilanterol (VI) Inhalation Powder is an orally inhaled long-acting muscarinic antagonist [LAMA, UMEC] and an orally inhaled, selective long-acting beta2 agonist [LABA, VI] combination for oral inhalation.

The proposed indication is “*indicated for the long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.*” UMEC/VI is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

2.2.3 What are the proposed dosages and routes of administration?

The recommended dose is 1 inhalation of ANORO ELLIPTA 62.5/25 mcg/mcg once daily.

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

The drugs which are approved for treatment of COPD in the US can be classified into the following classes:

(a) Bronchodilators

- β_2 agonist:
 - long acting: salmeterol, formoterol, arformoterol, indacaterol etc.
 - short acting: salbutamol, albuterol, terbutaline etc.
- Anticholinergics:
 - long acting: tiotropium, aclidinium
 - short acting: ipratropium
- Methylxanthine: theophylline
- Combination: albuterol+ipratropium (Combivent, Duoneb)

(b) Corticosteroids

- Oral corticosteroids
- ICS
- Combination:
 - salmeterol+fluticasone (Advair)
 - formoterol+budesonide (Symbicort)

(c) Other medications

- Long acting PDE-4 inhibitor: roflumilast (Daliresp)
- Antibiotics

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

This development program includes full characterization (dose-ranging) of the individual

components (UMEC and VI) to establish the appropriate dose for each component, before proceeding to studies with the combination product in the Phase 3 studies. The key studies supporting choice of dose and dosing interval are shown in Table 2.3.1.

Table 2.3.1: Studies to Support Doses and Dosing Interval of UMEC and VI Used in the UMEC/VI Phase 3 COPD Studies.

Study Number	Study Objective(s)	Study Design	Duration	Relevant Treatment Arms (mcg) (once-daily unless otherwise specified)	Population
UMEC Dose Selection					
AC4113589, m5.3.5.1	Dose-ranging	R, DB, PG, PC	28 days	UMEC 125 UMEC 250 UMEC 500 PLA	COPD
AC4113073, m5.3.5.1	Dose-ranging, dosing-interval, and PK	R, DB, XO, PC Incomplete block	3 periods per subject, 14 days per period	Once-daily: UMEC 62.5 UMEC 125 UMEC 250 UMEC 500 UMEC 1000 TIO 18 OL PLA Twice-daily: UMEC 62.5 UMEC 125 UMEC 250 PLA	COPD
AC4115321, m5.3.5.1	Dose-ranging and dosing-interval	R, DB, XO, PC Incomplete block	3 periods per subject, 7 days per period	Once-daily: UMEC 15.6 UMEC 31.25 UMEC 62.5 UMEC 125 TIO 18 OL PLA Twice-daily: UMEC 15.6 UMEC 31.25 PLA	COPD
AC4115408, m5.3.5.1	Efficacy and safety	R, DB, PG, PC	12 weeks	UMEC 125 UMEC 62.5 PLA	COPD
VI Dose Selection					
B2C111045, m5.3.5.1	Dose-ranging	R, DB, PG, PC Stratified a	28 days	VI 3 VI 6.25 VI 12.5 VI 25 VI 50 PLA	COPD

Study Number	Study Objective(s)	Study Design	Duration	Relevant Treatment Arms (mcg) (once-daily unless otherwise specified)	Population
HZA113310, m5.3.5.1	Dose-ranging and dosing-interval	R, DB, XO, PC	5 periods per subject, 7 days per period	Once-daily: VI 6.25 VI 12.5 VI 25 Twice-daily: VI 6.25 PLA	Asthma
B2C109575, m 5.3.5.1	Dose-ranging	R, DB, PG, PC Stratified b	28 days	VI 3 VI 6.25 VI 12.5 VI 25 VI 50 PLA	Asthma

The clinical pharmacology and biopharmaceutics studies supporting this NDA and their design features are listed under section 2.1.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Sponsor has used trough FEV₁ as the primary endpoint in all Phase 2 dose-ranging/regimen selection studies. Trough FEV₁ is the primary endpoints for the primary Phase 3 studies (DB2113361, DB2113373, DB2113360 and DB2113374).

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

In all relevant studies only UMEC/VI concentrations were measured. No metabolites were quantified because the metabolites of UMEC and VI are not active and are not associated with efficacy or safety.

2.4 Exposure-Response

2.4.1 Are the two dose regimens selected for the Phase 3 clinical trials appropriate regarding dosing amounts and dosing frequency?

UMEC/VI 62.5 mcg/25 mcg QD and 125 mcg/25 mcg QD were selected for Phase 3 trials based on sufficient efficacy and safety data from Phase 2 clinical trials. Dose ranging studies for each individual component was explored in Phase 2 trials. No dose-ranging studies of UMEC/VI combinations had been executed prior to the Phase 3 clinical trials.

- For UMEC, the drug development program includes dose-ranging information of four Phase 2 studies in COPD patients.
- For VI, the drug development program includes dose-ranging information of one Phase 2 study in asthma patients and one Phase 2 study in COPD patients.
- As a result, two dosing regimens, UMEC/VI 62.5 mcg/25 mcg and 125 mcg/25 mcg, were agreed upon by the FDA for Phase 3 trials in COPD patients.

For the UMEC component, four dose-ranging trials were conducted in COPD patients exploring daily doses from 15.6 mcg to 1000 mcg. An overall dose response relationship was observed for UMEC QD doses ranging from UMEC 15.6 mcg to 125 mcg, with no consistent additive benefit for UMEC doses above 125 mcg. The results of these four trials in COPD were the basis for the selection of UMEC 62.5 and 125 mcg for further evaluation in confirmatory trials. Of all 1204 patients, 118 patients reported AEs. Total 107 moderate or severe AEs were reported. The most frequently reported moderate or severe AEs are 24 headaches, 8 cases of common cold, 8 coughs, 5 cases of COPD exacerbation, 4 cases of hoarseness, 4 cases of sore throat, and 4 cases of sinusitis.

Figure 2.4.1a: Change from Baseline in trough FEV₁ in COPD Patients for Umeclidinium Daily Doses Ranging from 15.6 to 1000 mcg QD or BID and the Comparison to Tiotropium and Placebo.

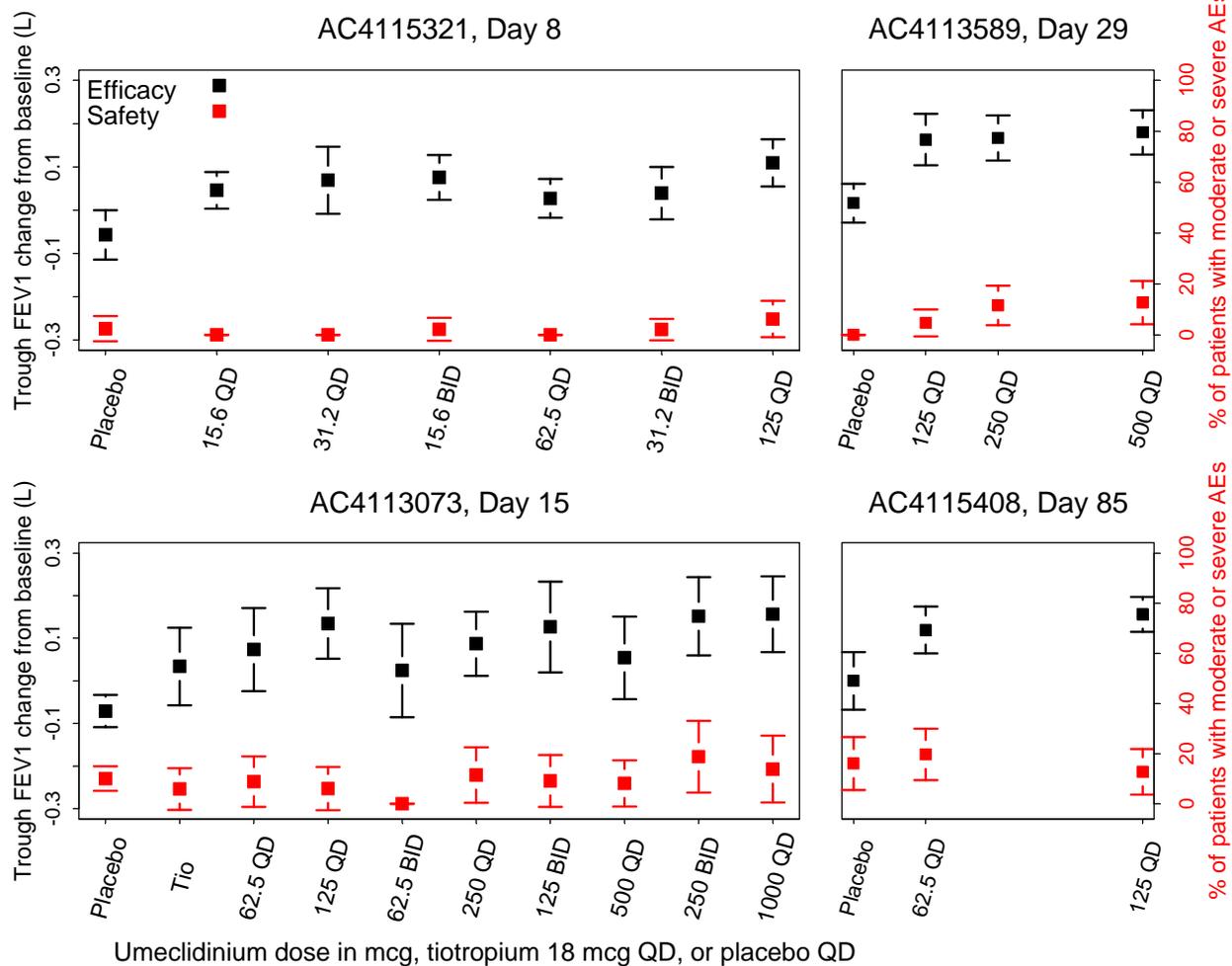


Table 2.4.1a: Mean Change from Baseline in trough FEV₁ (L) for Umeclidinium Once or Twice Daily Doses.								
	AC4115321 on Day 8		AC4113073 on Day 15		AC4113589 on Day 29		AC4115408 on Day 85	
Treatment	FEV1TRC (CI _{95_lo} , CI _{95_hi})	N	FEV1TRC (CI _{95_lo} , CI _{95_hi})	N	FEV1TRC (CI _{95_lo} , CI _{95_hi})	N	FEV1TRC (CI _{95_lo} , CI _{95_hi})	N
Placebo	-0.057 (-0.114, 0.000)	41	-0.071 (-0.109, -0.033)	150	0.016 (-0.029, 0.061)	67	0.000 (-0.068, 0.068)	50
Tio			0.034 (-0.057, 0.125)	34				
15.6 QD	0.046 (0.004, 0.088)	51						
31.2 QD	0.069 (0.009, 0.147)	46						
15.6 BID	0.076 (0.024, 0.127)	45						
62.5 QD	0.027 (-0.018, 0.072)	48	0.073 (-0.024, 0.171)	34			0.119 (0.064, 0.174)	61
31.2 BID	0.039 (-0.021, 0.100)	48						
125 QD	0.109 (0.054, 0.164)	48	0.135 (0.052, 0.217)	33	0.163 (0.104, 0.223)	64	0.156 (0.115, 0.197)	55
62.5 BID			0.024 (-0.085, 0.134)	31				
250 QD			0.087 (0.012, 0.163)	35	0.167 (0.115, 0.219)	69		
125 BID			0.126 (0.020, 0.233)	33				
500 QD			0.054 (-0.043, 0.151)	37	0.180 (0.128, 0.231)	63		
250 BID			0.152 (0.059, 0.244)	32				
1000 QD			0.157 (0.068, 0.246)	29				

FEV1TRC: change from baseline in trough FEV1 at the end of Day 28; CI_{95_lo}: the lower boundary of 95% confidence interval; CI_{95_up}: the upper boundary of 95% confidence interval; N: number of patients in the group; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; Tio: tiotropium 18 mcg once daily dose; 15.6 QD: umeclidinium 15.6 mcg once daily dosing, other numbers followed by QD have the similar explanation; 15.6 BID: umeclidinium 15.6 mcg twice daily dosing, other numbers followed by BID have the similar explanation

Dosing frequency with UMEC, QD versus BID (twice daily), was explored in patients with COPD. In the randomized, double-blind, placebo-controlled, cross-over trial (AC4115321) in patients with COPD, the efficacy and safety was compared between UMEC 31.2 mcg BID, UMEC 62.5 mcg QD, and UMEC 125 mcg QD. Based on trough FEV₁, 62.5 mcg QD and 31.2 mcg BID appeared similar, whereas 125 mcg QD resulted in the highest trough FEV₁, numerically. These results supported the selection of the QD regimen of 62.5 and 125 mcg of UMEC for further evaluation. Another study in COPD patients (AC4113073) demonstrated the efficacy profile of 125 mcg QD was numerically better than 62.5 mcg BID, and the safety profile of 125 mcg QD was comparable to 62.5 mcg BID.

For VI, a range of doses were explored in both COPD patients (Study B2C111045) and persistent asthma patients (B2C109575). In each patient population, a randomized, double-blind, placebo-controlled, parallel group, 28-day trials evaluated five doses of VI (3, 6.25, 12.5, 25, and 50 mcg) administered once daily. Trough FEV₁ results demonstrated a shallow dose-response relationship between the lowest and highest doses for both studies. The 25 mcg dose was identified as optimal dose in asthma study. In the COPD study, 25 mcg also demonstrated comparable efficacy/safety profile to 50 mcg QD, the best regimen based on efficacy and safety data.

Out of all 537 COPD patients of Study B2C111045, 67 patients reported AEs. Moderate or severe AEs totaled 71 cases, including the following most frequently reported cases: 6 cases of headache, 5 cases of intensified back pain, 3 cases of common cold, and 3 cases of sinusitis.

Figure 2.4.1b: Effect of Vilanterol on Lung Function (trough FEV₁) across Doses Ranging from 3 mcg to 50 mcg QD (COPD Left, Asthma Right).

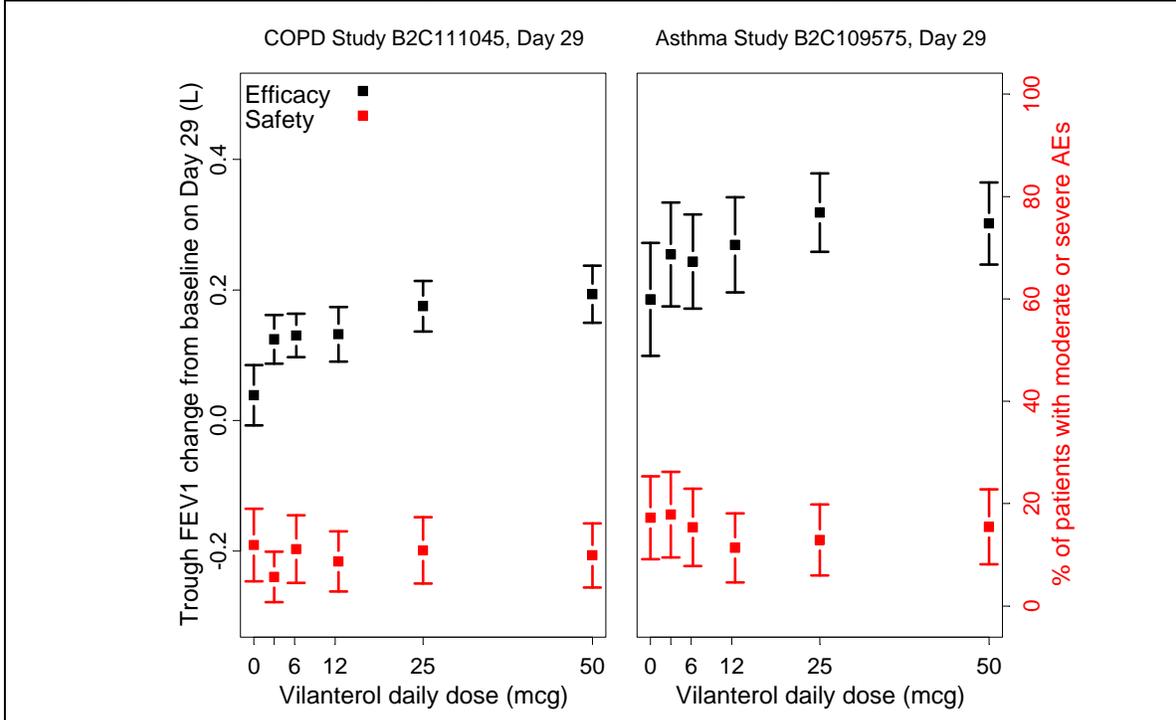


Table 2.4.1b: Mean Change from Baseline in Trough FEV1 in L for Vilanterol Once Daily Doses.

Dose (µg)	Study B2C111045 in COPD Patients		Study B2C109575 in Asthma Patients	
	FEV1TRC (CI _{95_lo} , CI _{95_up})	N	FEV1TRC (CI _{95_lo} , CI _{95_up})	N
0	0.039 (-0.008, 0.085)	84	0.186 (0.099, 0.272)	87
3	0.124 (0.087, 0.162)	88	0.254 (0.175, 0.334)	84
6.25	0.130 (0.097, 0.164)	90	0.243 (0.171, 0.316)	91
12.5	0.132 (0.090, 0.174)	92	0.269 (0.196, 0.342)	88
25	0.175 (0.136, 0.214)	92	0.318 (0.258, 0.378)	93
50	0.193 (0.150, 0.237)	91	0.302 (0.239, 0.365)	97

FEV1TRC: change from baseline in trough FEV1 at the end of Day 28; CI_{95_lo}: the lower boundary of 95% confidence interval; CI_{95_up}: the upper boundary of 95% confidence interval; N: number of patients in the group; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second

Regarding dosing frequency of VI, a Phase 2 study (HZA113310) conducted in subjects with persistent asthma supported the comparability of once and twice daily dosing, where the improvement of mean FEV₁ (0-24h) was similar between VI 6.25 mcg twice daily and VI 12.5 mcg once daily dosing.

In summary, that UMEC 62.5 mcg QD and UMEC 125 mcg QD being carried forward for combination studies in the Phase 3 COPD program was supported by dose frequency and dose-ranging data of the UMEC component in COPD patients. In terms the selection of VI 25mcg QD for the Phase 3 COPD program, it was supported by the results of dose-ranging studies in both COPD and asthma patients and the dosing frequency study in asthma patients.

2.4.2 Do Phase III confirmatory study results support the approval of the two dose regimens, UMEC/VI 62.5 mcg/25 mcg QD and UMEC/VI 125 mcg/25 mcg QD for COPD patients?

The efficacy and safety data collected from 6 Phase 3 clinical trials demonstrated that UMEC/VI 62.5 mcg/25 mcg QD is appropriate for COPD patients. However, UMEC/VI 125 mcg/25 mcg QD didn't demonstrate additional benefit to UMEC/VI 62.5 mcg/25 mcg QD

Trough FEV₁ change from baseline data on Day 169 of the four Phase 3 clinical trials (DB2113360, DB2113361, DB2113373 and DB2113374) demonstrated that UMEC/VI 62.5/25 and 125/25 improved lung function. The following points can be made in regard to the results of the clinical trials:

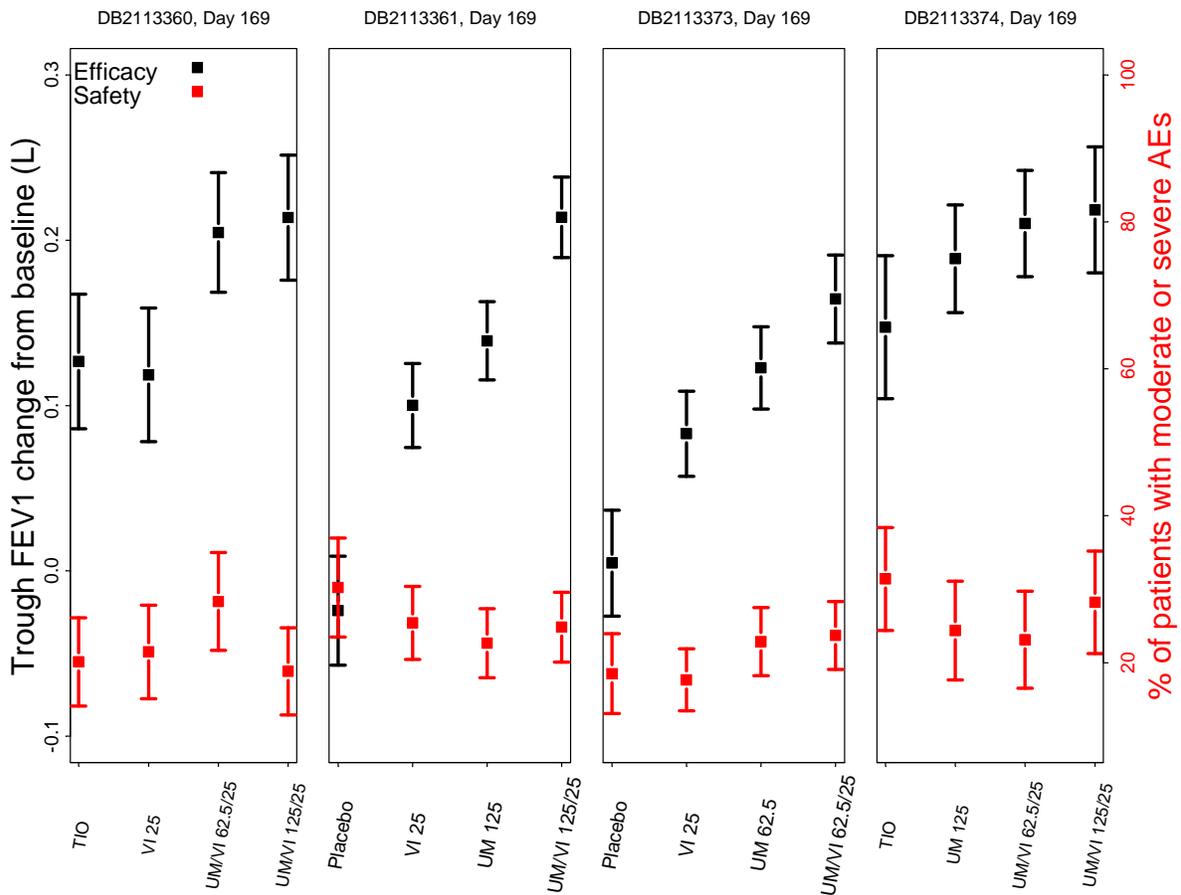
- The combination of UMEC/VI 62.5 mcg/25 mcg QD demonstrated added benefit to individual treatment of VI 25 mcg or UMEC 62.5 mcg, and both VI 25 mcg and UMEC 62.5 demonstrated higher efficacy than the placebo while safety profiles were comparable amongst the 4 treatments.
- The combination of UMEC/VI 125 mcg/25 mcg QD demonstrated added benefit to individual treatment of VI 25 mcg or UMEC 125 mcg, and both VI 25 mcg and

UMEC 125 demonstrated higher efficacy than the placebo while safety profiles were comparable amongst the 4 treatments.

- The efficacy and safety profiles were comparable between the two combinations UMEC/VI 62.5 mcg/25 mcg and 125 mcg/25 mcg while they are numerically better than tiotropium 18 mcg QD. Similar FEV1 results were obtained in another two Phase 3 studies (DB2114417 and DB2114418).

The safety profiles were comparable between different treatment arms of the 6 Phase 3 studies. Out of all 4647 patients of the 6 studies, 1502 patients reported AEs. Moderate or severe AEs totaled 1155 cases, including the following most frequent ones: 155 cases of headache, 81 cases of common cold, 78 exacerbations of COPD, 50 cases of upper respiratory infection, 49 cases of cough, 46 cases of toothache, 43 cases of back pain and 32 cases of pneumonia.

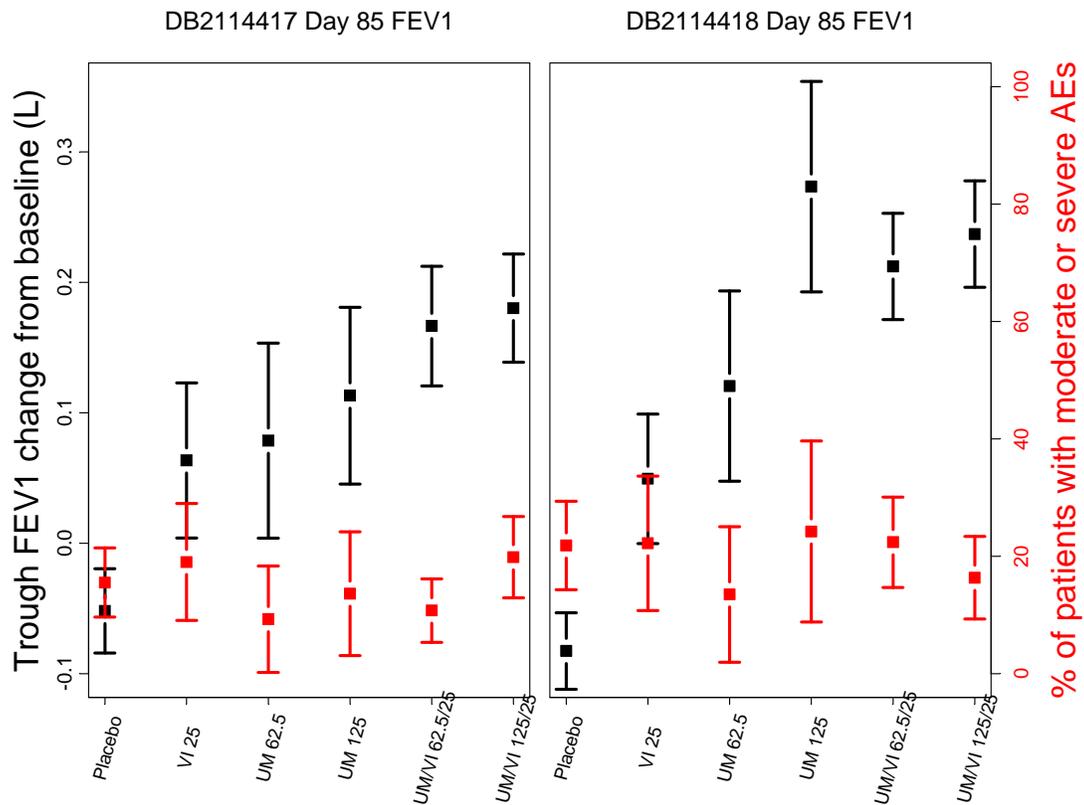
Figure 2.4.2a: Change from Baseline in Trough FEV1 in COPD Patients for Umeclidinium, Vilanterol, and Combination of them in Once Daily Doses and the Comparison to Tiotropium and Placebo.



Tio: tiotropium 18 mcg QD; VI 25: vilanterol 25 mcg QD, UM 62.5: umeclidinium 62.5 mcg QD; UM 125: umeclidinium 125 mcg QD; UM/VI 62.5/25: umeclidinium 62.5 mcg and vilanterol 25 mcg QD; UM/VI 125/25: umeclidinium 125 mcg and vilanterol 25 mcg QD

Table 2.4.2a: Mean Change from Baseline in Trough FEV1 (L) for Once Daily Treatments of Phase 3 Studies on Day 169.								
	DB2113360		DB2113361		DB2113373		DB2113374	
Treatment	FEV1TRC (CI95_lo,CI95_hi)	N	FEV1TRC (CI95_lo,CI95_hi)	N	FEV1TRC (CI95_lo,CI95_hi)	N	FEV1TRC (CI95_lo,CI95_hi)	N
Placebo			-0.024 (-0.057, 0.009)	182	0.005 (-0.027, 0.037)	200		
Tio	0.127 (0.086, 0.167)	174					0.147 (0.104, 0.191)	172
VI 25	0.119 (0.078, 0.159)	163	0.1 (0.075, 0.125)	299	0.083 (0.057, 0.109)	317		
UM 62.5					0.123 (0.098, 0.148)	319		
UM 125			0.139 (0.115, 0.163)	309			0.189 (0.156, 0.221)	160
UMEC/VI 62.5/25	0.205 (0.168, 0.241)	180			0.164 (0.138, 0.191)	329	0.21 (0.178, 0.242)	160
UMEC/VI 125/25	0.214 (0.176, 0.251)	170	0.214 (0.19, 0.238)	322			0.218 (0.18, 0.256)	163
FEV1TRC: change from baseline in trough FEV1 at the end of Day 84; CI95_lo: the lower boundary of 95% confidence interval; CI95_up: the upper boundary of 95% confidence interval; N: number of patients in the group; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; VI 25: vilanterol 25 mcg; UMEC 62.5 : umeclidinium 62.5 mcg; UMEC 125 : umeclidinium 125 mcg; UMEC/VI 62.5/25: the combination of umeclidinium 62.5 mcg and vilanterol 25 mcg; UMEC/VI 125/25: the combination of umeclidinium 125 mcg and vilanterol 25 mcg; Tio: tiotropium 18 mcg once daily								

Figure 2.4.2b: Change from Baseline in Trough FEV1 in COPD Patients for Umeclidinium, Vilanterol, and Combination of them in Once Daily Doses and the Comparison to Tiotropium and Placebo.



VI 25: vilanterol 25 mcg QD, Tio: tiotropium 18 mcg QD; UM 62.5: umeclidinium 62.5 mcg QD;

Treatment	Study DB2114417		Study DB2114418	
	FEV1TRC (CI95_lo,CI95_hi)	N	FEV1TRC (CI95_lo,CI95_hi)	N
Placebo	-0.052 (-0.084, -0.019)	148	-0.083 (-0.112, -0.053)	119
VI 25	0.063 (0.004, 0.123)	63	0.049 (0.000, 0.099)	54
UMEC 62.5	0.079 (0.004, 0.153)	43	0.121 (0.048, 0.193)	37
UMEC 125	0.113 (0.045, 0.181)	44	0.273 (0.193, 0.354)	33
UMEC/VI 62.5/25	0.167 (0.121, 0.212)	130	0.212 (0.171, 0.253)	116
UMEC/VI	0.18 (0.139, 0.222)	131	0.237 (0.196, 0.278)	110

125/25				
FEV1TRC: change from baseline in trough FEV1 at the end of Day 84; CI95_lo: the lower boundary of 95% confidence interval; CI95_up: the upper boundary of 95% confidence interval; N: number of patients in the group; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; VI 25: vilanterol 25 mcg; UMEC 62.5 : umeclidinium 62.5 mcg; UMEC 125 : umeclidinium 125 mcg; UMEC/VI 62.5/25: the combination of umeclidinium 62.5 mcg and vilanterol 25 mcg; UMEC/VI 125/25: the combination of umeclidinium 125 mcg and vilanterol 25 mcg				

In summary, the efficacy and safety data collected from 6 Phase 3 clinical trials demonstrated that UMEC/VI 62.5 mcg/25 mcg QD is appropriate for COPD patients. However, UMEC/VI 125 mcg/25 mcg QD didn't demonstrate additional benefit to UMEC/VI 62.5 mcg/25 mcg QD.

2.4.3 Are there any covariates that influence the systemic exposure of UMEC and VI that need dose adjustment?

There were no covariates found in the population PK of UMEC and VI that warrant any dose adjustment of either component. Based on pooled population PK data from Study DB2113361 and DB2113373, both UMEC and VI PK can be best described by a two-compartment model with first order absorption. The population PK parameters and associated inter-individual variability were adequately characterized. There was no apparent PK interaction with co-administration of UMEC with VI.

Weight, age and creatinine clearance were statistically significant covariates on apparent inhaled clearance (CL/F) of UMEC and weight was significant covariate on UMEC volume of distribution (V₂/F). For every 10% increase in weight the CL/F increased approximately by 2%. The apparent volume of distribution of central compartment V₂/F increased approximately 6% for every 10% increase in body weight from 70 kg. With 10% increase in age from 60 years of age, the CL/F decreased by approximately 7%. Regarding creatinine clearance, the CL/F decreased by approximately 3% with every 10% decrease in creatinine clearance from 110 mL/min. The changes in CL/F and V₂/F due to differences in age, weight and creatinine clearance are marginal and do not warrant any dose adjustments for UMEC based on these covariates in the population spanning the observed weight, age and creatinine clearance rang.

Weight and age were statistically significant covariates on VI apparent inhaled clearance (CL/F). For every 10% increase in weight the CL/F increased by about 2%. With a 10% increase in age from 60 years, the CL/F decreased by approximately 4%. The changes in CL/F due to age and weight are marginal and do not warrant any dose adjustments for VI based on these covariates in population spanning the observed weight and age range.

2.4.4 Does this drug prolong QT/QTc Interval?

QT effect for UMEC/VI was evaluated in a randomized, placebo-controlled, incomplete block, four-period crossover, repeat dose study (DB2114635). In this study, subjects were given dry powder inhaler once daily for 10 days as placebo, UMEC 500 mcg, UMEC/VI 125/25 mcg, UMEC/VI 500/100 mcg, or a single oral dose of placebo /moxifloxacin 400 mg on Day 10. No significant QTc prolongation effects of a therapeutic dose of UMEC/VI 125/25 mcg and suprathreshold dose of UMEC 500 mcg were detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between UMEC/VI 125/25 mcg and placebo, and between UMEC 500 mcg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. However, the largest upper bounds of the 2-sided 90% CI for the mean difference between UMEC/VI 500/100 mcg and placebo was 10.7 which is higher than the threshold for regulatory concern as described in ICH E14 guidelines.

For further details refer to QT/IRT review for this NDA.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Single dose PK

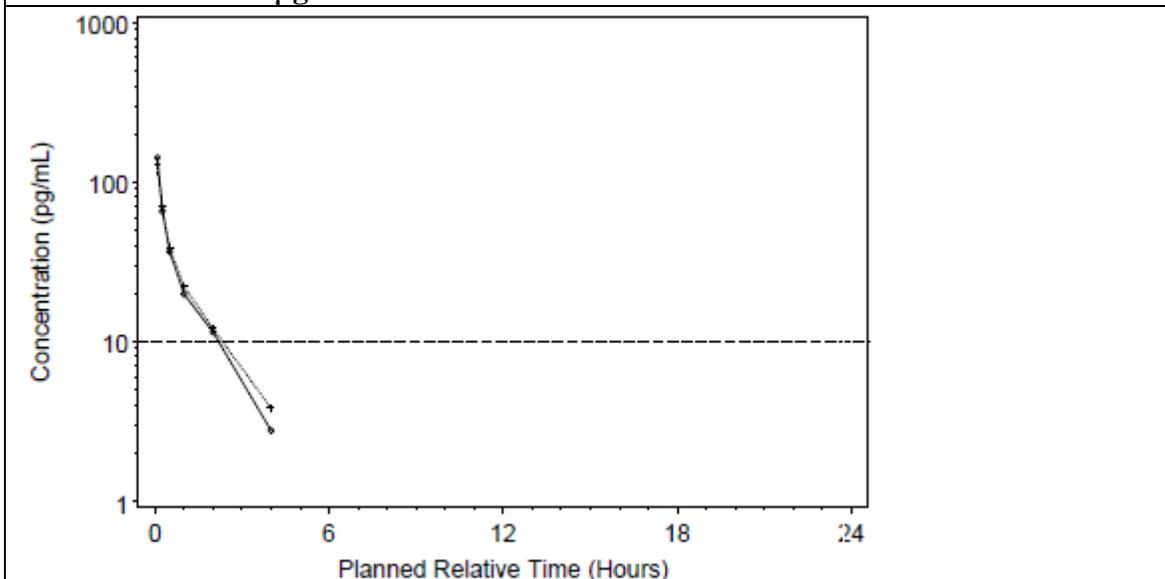
The single dose PK of UMEC and VI in healthy subjects with to-be-marketed formulation was characterized in study DB2114636. Study DB2114636A was a single-blind, non-randomized pharmacokinetic and safety study of single dose of UMEC and UMEC/VI combination in healthy subjects and in subjects with severe renal impairment.

UMEC

UMEC PK data from UMEC 125 µg in healthy subjects are summarized here. The bioanalytical method (LLQ of 10 pg/mL) was not sensitive enough to fully characterize the pharmacokinetic profile of UMEC due to low levels of UMEC present in plasma following a single dose administration of UMEC. After single dose UMEC 125 µg, 52.2% of post-dose samples (47 samples of a total of 90) were non-quantifiable (NQ). After inhalation of UMEC 125 µg, the absorption of UMEC is rapid. An average C_{max} of 127.6 pg/mL reached at the first sampling time of 5 min. UMEC concentration quickly declined to below LLQ (10 pg/mL). It is of note that there are no PK data after single

inhaled dose of UMEC 62.5 µg with the to-be-marketed formulation in healthy subjects.

Figure 2.5.1a: Semi-log Mean Plasma UMEC Concentration-Time plot after single dose of UMEC125 µg.



Source: Figure 10.3, db2114636 report

Table 2.5.1a: Summary Statistics of Plasma UMEC Pharmacokinetic Parameters after Single Dose of UMEC125 µg.

Parameter	Geo mean	cv%
AUC(0–0.25) (h·pg/mL)	20.3	53.0
AUC(0–2) (h·pg/mL)	56.5	69.7
Cmax (pg/mL)	127.6	57.1
Tlast (h)*	2.00	NA
Tmax (h)*	0.08	NA

Source: Table 8, db2114636 report

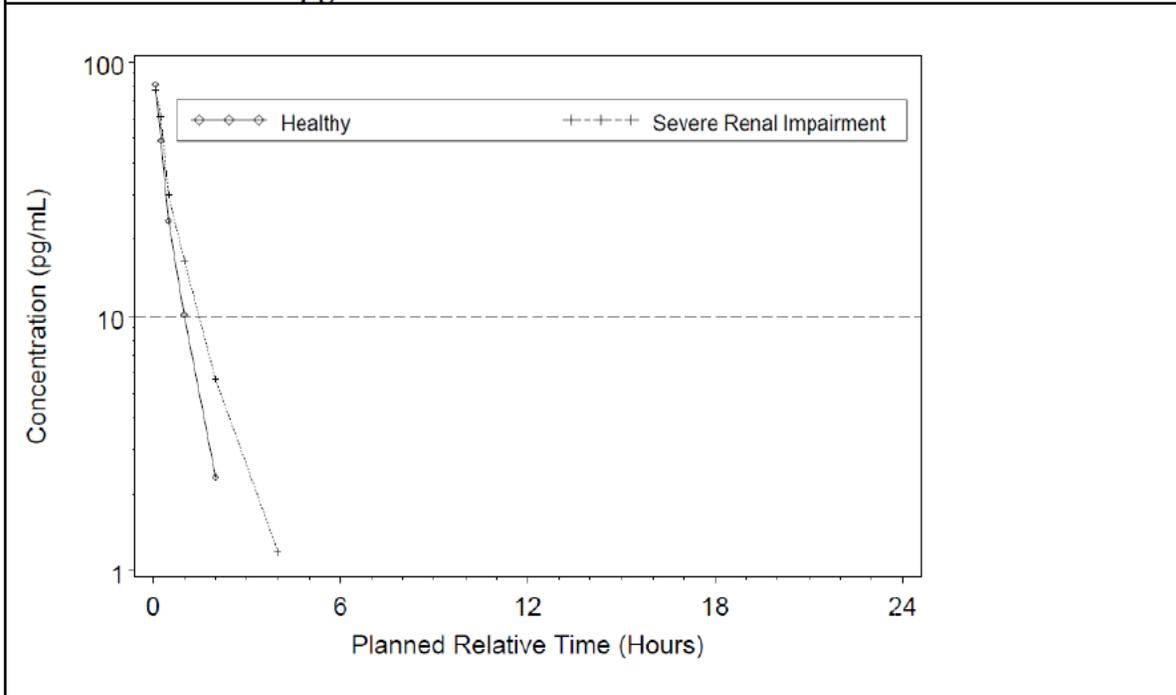
VI

VI PK data from UMEC/VI 125/25 µg in healthy subjects are summarized here.

The bioanalytical method (LLQ of 10 pg/mL) was not sensitive enough to fully characterize the pharmacokinetic profile of VI due to the low level of VI present in plasma following a single dose administration of UMEC/VI 125/25 mcg. Overall 61% of post-dose samples (55 samples of a total of 90) were NQ in healthy subjects.

Following oral inhalation, maximum plasma concentration of VI was reached by 6 min (i.e., T_{max}). VI concentration quickly declined to below LLQ (10 pg/mL) after 1 hour. PK parameters for VI are summarized in Table 2.5.1b.

Figure 2.5.1b: Semi-log Mean Plasma VI Concentration-Time Plot after Single Dose of UMEC/VI 125/25 µg.



Source: Figure 10.6, db2114636 report

Table 2.5.1b: Pharmacokinetic Parameters of VI Following Administration of a Single Dose of FF/VI by NDPI in Healthy Subjects.

Parameter	Geomean	cv%
AUC(0–0.25) (h·pg/mL)	12.8	46.6
AUC(0–1) (h·pg/mL)	28.7	45.3
C _{max} (pg/mL)	74.8	46.9
T _{last} (h)*	1.00	NA
T _{max} (h)*	0.10	NA

Source: Table 10.5, db2114636 report

Multiple dose PK

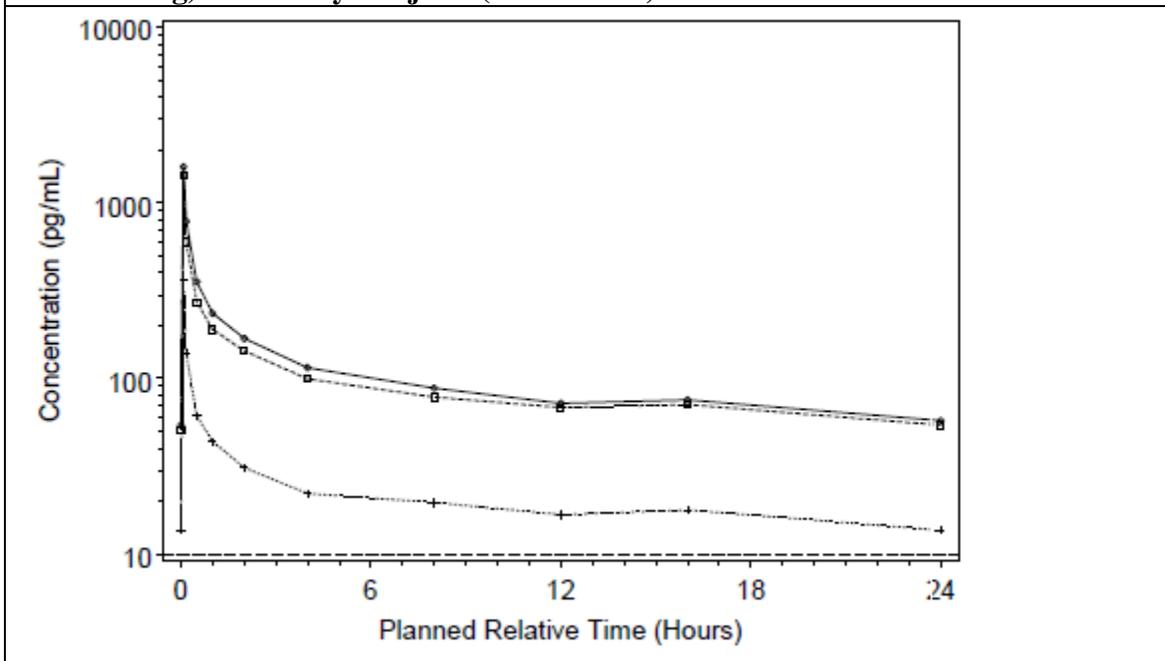
The PK profile of UMEC and VI in healthy subjects based on the repeat-dose of the to-be marketed formulation and doses administered was studied in study DB2114635. DB2114635 was a randomized, placebo-controlled, four-period crossover, repeat dose study to evaluate the effect of the inhaled GSK573719/vilanterol combination and GSK573719 monotherapy on electrocardiographic parameters, with moxifloxacin as a positive control, in healthy subjects.

UMEC

Following repeat-dose administration of UMEC in combination with VI, UMEC was rapidly absorbed with median t_{max} values occurring at 6 minutes post-dose. The terminal phase $t_{1/2}$ for all subjects was estimated to be on average approximately 19 to 25 hours. Systemic exposure of UMEC in terms of both $AUC(0-\infty)$ and C_{max} following UMEC/VI 500/100 mcg were approximately dose proportional (~4-fold higher) with systemic exposure of UMEC/VI 125/25 mcg.

The median UMEC PK profile at Day 10 following the administration of UMEC 500 mcg, UMEC/VI 125/25 mcg, and 500/125 mcg are presented below. Selected UMEC PK parameters at Day 10 for UMEC are shown in the table 2.5.1c.

Figure 2.5.1c: Median UMEC Semi-log Concentration-Time Profile at Day 10 Following Repeat-Dose of UMEC (500 mcg) and UMEC/VI (125/25 mcg and 500/100 mcg) in Healthy Subjects (DB2114635).



Source: Study DB2114635, Figure 11.2

Table 2.5.1c: Summary Statistics of Day 10 UMEC PK Parameters (DB2114635).

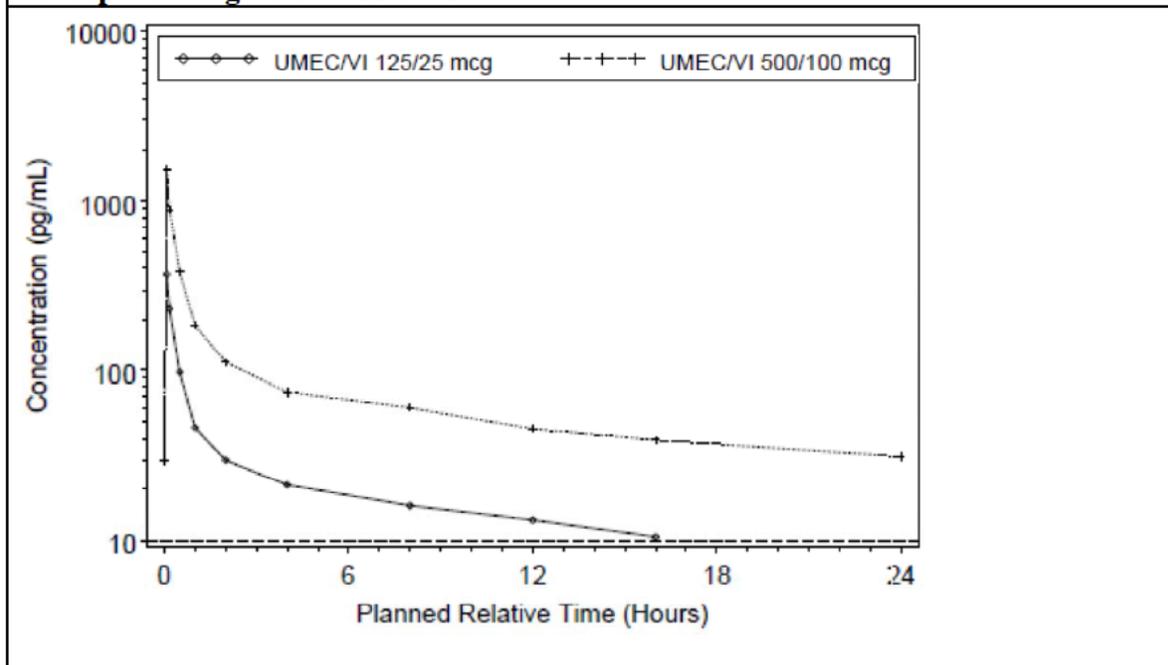
Parameter	Treatment	N	n	Geometric		
				Mean	95% CI	%CVb
AUC _(0-t) (h•pg/mL)	UMEC/VI 125/25 mcg	75	74	495	431, 569	65.6
	UMEC/VI 500/100 mcg	73	70	2145	1977, 2328	35.2
C _{max} (pg/mL)	UMEC/VI 125/25 mcg	75	74	334	294, 379	59.1
	UMEC/VI 500/100 mcg	73	70	1400	1285, 1525	37.1
t _{max} (h) ^a	UMEC/VI 125/25 mcg	75	74	0.10	0.08, 0.15	NA
	UMEC/VI 500/100 mcg	73	70	0.10	0.08, 0.12	NA

Source: Summary of Clinical Pharmacology.pdf. Table 10

VI

Mean plasma VI PK profiles are shown in Figure 2.5.1d and summary PK parameters are listed in Table 2.5.1c. VI PK after multiple doses was consistent with the single dose PK. T_{max} was reached within 6 min. The terminal half life is 11hrs (range: 8-13) for VI. From other studies, measurement of trough concentrations indicated that steady-state for VI was achieved by the 6th dose. Accumulation after multiple doses was 1.24 to 2.4 fold for VI.

Figure 2.5.1d: Mean Plasma Concentrations Versus Time on Day 10 Following Multiple Dosing with UMEC/VI.



Source: Figure 11.5, Study DB2114635

Table 2.5.1d: VI Pharmacokinetic Parameters on Days 10 Following Repeated Inhaled Administration of UMEC/VI in Healthy Volunteers.

Parameter	Treatment	N	n	Geometric Mean	95% CI	%CVb
AUC _(0-t) (h•pg/mL)	UMEC/VI 125/25 mcg	75	74	495	431, 569	65.6
AUC _(0-t) (h•pg/mL)	UMEC/VI 500/100 mcg	73	70	2145	1977, 2328	35.2
C _{max} (pg/mL)	UMEC/VI 125/25 mcg	75	74	334	294, 379	59.1
C _{max} (pg/mL)	UMEC/VI 500/100 mcg	73	70	1400	1285, 1525	37.1
t _{max} (h) ^a	UMEC/VI 125/25 mcg	75	74	0.10	0.08, 0.15	NA
t _{max} (h) ^a	UMEC/VI 500/100 mcg	73	70	0.10	0.08, 0.12	NA

Parameter	Treatment	N	n	Geometric		
				Mean	95% CI	%CVb
AUC _(0-τ) (h*pg/mL)	UMEC/VI 125/25 mcg	75	74	429	379, 486	57.6
	UMEC/VI 500/100 mcg	73	70	1824	1729, 1925	22.9
C _{max} (pg/mL)	UMEC/VI 125/25 mcg	75	74	340	307, 376	45.9
	UMEC/VI 500/100 mcg	73	70	1518	1416, 1627	29.8
t _{max} (h) ^a	UMEC/VI 125/25 mcg	75	74	0.10	0.08, 0.15	NA
	UMEC/VI 500/100 mcg	73	70	0.10	0.08, 0.22	NA
t _{last} (h) ^a	UMEC/VI 125/25 mcg	75	74	16.02	0.52, 24.25	NA
	UMEC/VI 500/100 mcg	73	70	24.08	24.08, 24.25	NA
t _{1/2} (h)	UMEC/VI 125/25 mcg	75	55	10.52	8.43, 13.12	97.8
	UMEC/VI 500/100 mcg	73	62	19.22	17.68, 20.90	33.9
CL/F (L/h)	UMEC/VI 125/25 mcg	75	74	58.2	51.4, 65.9	57.6
	UMEC/VI 500/100 mcg	73	70	54.8	52.0, 57.9	22.9
V/F (L)	UMEC/VI 125/25 mcg	75	55	890	783, 1010	49.8
	UMEC/VI 500/100 mcg	73	62	1526	1383, 1684	40.2
λ _z	UMEC/VI 125/25 mcg	75	55	0.066	0.053, 0.082	97.8
	UMEC/VI 500/100 mcg	73	62	0.036	0.033, 0.039	33.9

Source: Table 11.4, Study DB2114635

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

UMEC

The systemic exposure of UMEC in COPD patients was generally less than that in healthy subjects. In subjects with COPD, UMEC C_{max} was <50% lower compared to healthy subjects. AUC was not comparable between the two populations as sampling duration was different.

VI

VI C_{max} in COPD patients was 62% lower while AUC_(0-24hr) was 43% higher compared to that in healthy subjects (Table 2.5.2b).

Subject	Study	Treatment	N	C _{max} (CV%) (pg/mL)	T _{max} (h)	AUC (pg h/mL)
Healthy	DB2114637	UMEC 125 μg	9	283 (33%)	0.08	87 (AUC0-2 h)
COPD	AC4115408	UMEC 62.5 μg QD	56	48 (131%)	0.08	7 (AUC0-0.25 h)
		UMEC 125 μg QD	56	123 (80%)	0.10	18 (AUC0-0.25 h)

Source: Table 76, Summary of Clinical Pharmacology and DB2114637 report

Table 2.5.2b: Comparison of VI Systemic Exposure in Healthy Subjects vs. Subjects with COPD following Repeat Dosing with VI.					
Study	Subjects	Treatment	Days of dosing	Geometric mean	
				AUC ₍₀₋₂₄₎ (pg*h/ml)	C _{max} (pg/ml)
DB2114635	Healthy	UMEC/VI 125/25 mcg	10	429	340
DB2113361, DB2113373	COPD	UMEC/VI 125/25 mcg, VI 25 mcg	Phase 3, steady state	614.7	127.9

Source: Table 11 and Table 26, 2.7.2, Summary of Clinical Pharmacology

2.5.3 What are the characteristics of drug absorption?

UMEC absolute bioavailability following oral inhalation was ~12%. VI absolute bioavailability following oral inhalation was ~26%. The oral bioavailability of UMEC and VI was low, on average <1% and <2%, because of the extensive first pass metabolism.

UMEC

The absolute bioavailability of UMEC was evaluated in study AC4112014 and AC4112008.

AC4112014 was an open-label, two period study to determine the excretion and pharmacokinetics of [¹⁴C]-GSK573719, administered as a single dose of an oral solution (1000 µg) and an intravenous infusion (65 µg), to healthy male adults. Plasma UMEC PK parameters following oral administration could not be estimated due to all non-quantifiable data. Based on a lower limit of quantification of 20 pg/mL for GSK573719, maximal possible oral bioavailability was calculated as <1%.

AC4112008 was a single-center, open-label, sequential, cross-over study to examine the safety, tolerability and pharmacokinetics of three ascending single intravenous doses (20, 50, 65 µg), a single 1000 µg oral dose and a single 1000 µg inhaled dose of GSK573719 in healthy male volunteers. In this study, the formulation of 1000 µg inhaled dose was not the to-be-marketed formulation. There are no data available in this submission to calculate the absolute bioavailability with the to-be-marketed IH formulation.

Table 2.5.3: AUC and Absolute Bioavailability of UMEC in Study AC4112008.			
Parameter	Dose	Geomean (cv%)	Study
AUC _{0-inf} (ng h/mL)	20 µg IV	0.132 (64)	AC4112008
	50 µg IV	0.525 (28)	
	65 µg IV	0.543 (108)	
	1000 µg IH	1.33 (28)	
F	1000 µg IH	12.82 (44)	

Source: Table 7, AC4112008 study report

Following a single inhaled dose administration, UMEC was rapidly absorbed with the C_{max} values occurring at approximately 5 to 15 minutes post-dose. Absolute bioavailability following oral inhalation was ~12%. The oral bioavailability of UMEC was <1%, because of the extensive first pass metabolism. These data show that the systemic exposure of UMEC and VI is primarily due to absorption of the drugs in lung.

In vitro studies using transfected MDCK cells (WD2006/02657 and WD2006/02596), demonstrated that UMEC is a substrate of P-gp. However, because of low oral bioavailability, inhibition of P-gp is unlikely to have an impact on the overall bioavailability of UMEC.

VI

The absolute bioavailability of VI was evaluated in study HZA106180.

HZA106180 was an open-label, non-randomized, three-way crossover, single dose study to determine the absolute bioavailability of GW642444 inhalation powder in healthy subjects.

VI absolute bioavailability following oral inhalation was 25-30%. The oral bioavailability of VI was low, on average, <2%, because of the extensive first pass metabolism. The systemic exposure of VI is primarily due to absorption of the drugs in lung. In single- and multiple-dose studies, maximum plasma concentrations were reached within 6-9 min for VI after oral inhalation administration. *In vitro* studies using transfected MDCK cells (WD2004/00106/00), demonstrated that VI is substrate of P-gp. However, because of low oral bioavailability, inhibition of P-gp is unlikely to have an impact on the overall bioavailability of VI.

2.5.4 What are the characteristics of drug distribution?

Both UMEC and VI are widely distributed with V_{ss} greater than total body water.

UMEC

The distribution of UMEC after IV dosing was evaluated in study AC4112014.

Following intravenous dosing, the average steady-state volume of distribution (V_{ss}) of UMEC was estimated to be 86 L. *In vitro* studies determined low blood cell association for UMEC with an in vitro blood-to-plasma ratio of 0.67. Plasma protein binding was 89% regardless of concentration.

VI

The distribution of VI after IV dosing was evaluated in study B2C106180.

Following intravenous dosing, the average steady-state volume of distribution (V_{ss}) of VI was estimated to be 167 L, suggesting distribution into tissues. *In vitro* studies

determined low blood cell association for VI with an in vitro blood-to-plasma ratio of 0.8. Plasma protein binding was moderate (93.9%) regardless of concentration.

2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Both hepatic and renal play a role in eliminating UMEC after IV dosing, while hepatic route plays a major role in eliminating VI after IV dosing.

UMEC

The mass balance study (AC4112014) showed that urine and feces were predominant routes of excretion following IV administration. Approximately 81% of the administered dose was recovered, with fecal excretion and urinary excretion accounting for approximately 58% and 22%, respectively. Total radioactivity was eliminated primarily in feces following oral administration of [¹⁴C]-GSK573719, accounting for approximately 92% of the orally administered dose. Less than 1% of the oral administered dose was excreted in urine suggesting negligible absorption following oral dose.

VI

Following oral administration of [¹⁴C]VI, 70% of the recovered radioactivity was excreted in urine and 30% of the recovered radioactivity was in feces. However, most radioactivity recovered in the urine was in form of metabolites. Therefore, hepatic metabolism is the major route of elimination for VI.

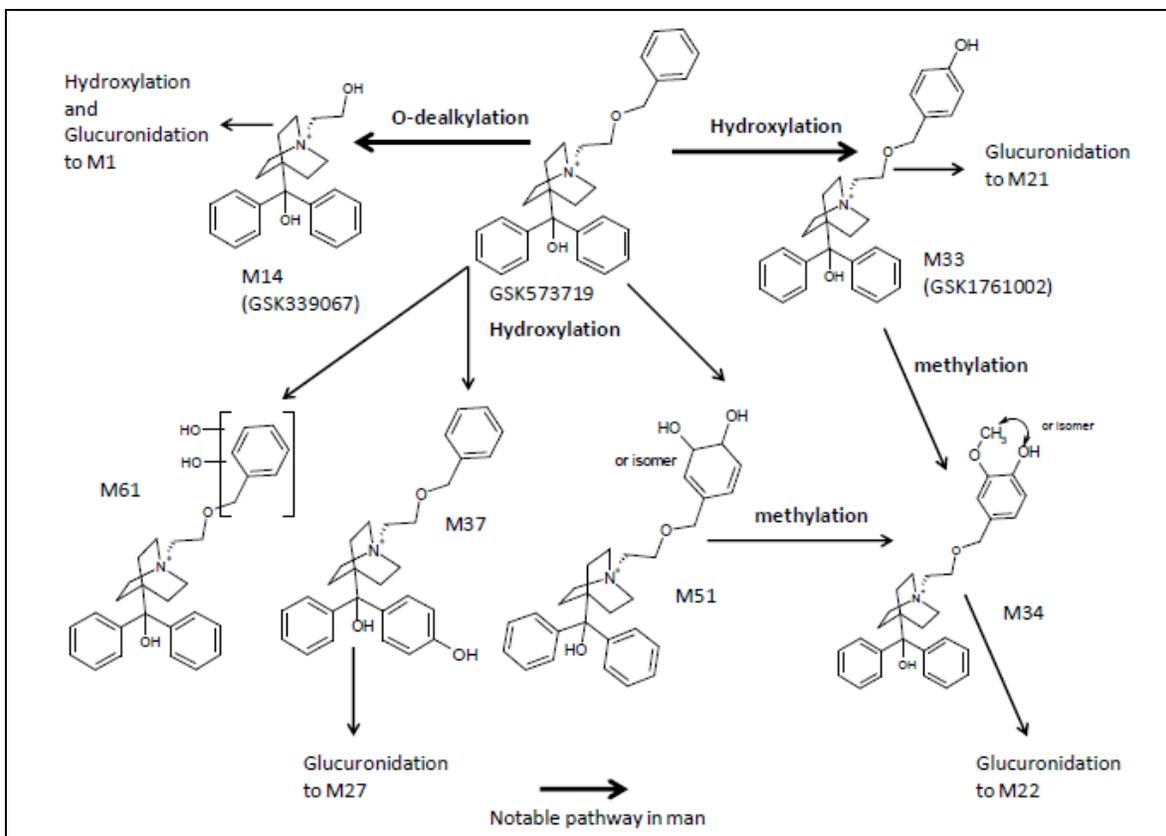
2.5.7 What are the characteristics of drug metabolism?

Both UMEC and VI are extensively metabolized. The main routes of metabolism in human for UMEC are O-dealkylation and hydroxylation. The major route of metabolism for VI is O-dealkylation.

UMEC

The proposed metabolic pathway for UMEC is shown in Figure 2.5.7a. Both in vitro and in vivo studies indicate that UMEC is extensively metabolized. The data suggest the main routes of metabolism in human are likely to be O-dealkylation (20% of the total metabolism via M14, GSK339067) and hydroxylation (23% of the total metabolism via M33, GSK1761002 and M34, which co-eluted). Other routes are conjugation with glutathione and methylation and/or glucuronidation of the hydroxylated metabolites.

Figure 2.5.7a. Metabolic Scheme for the Major in vivo Metabolites of GSK573719.

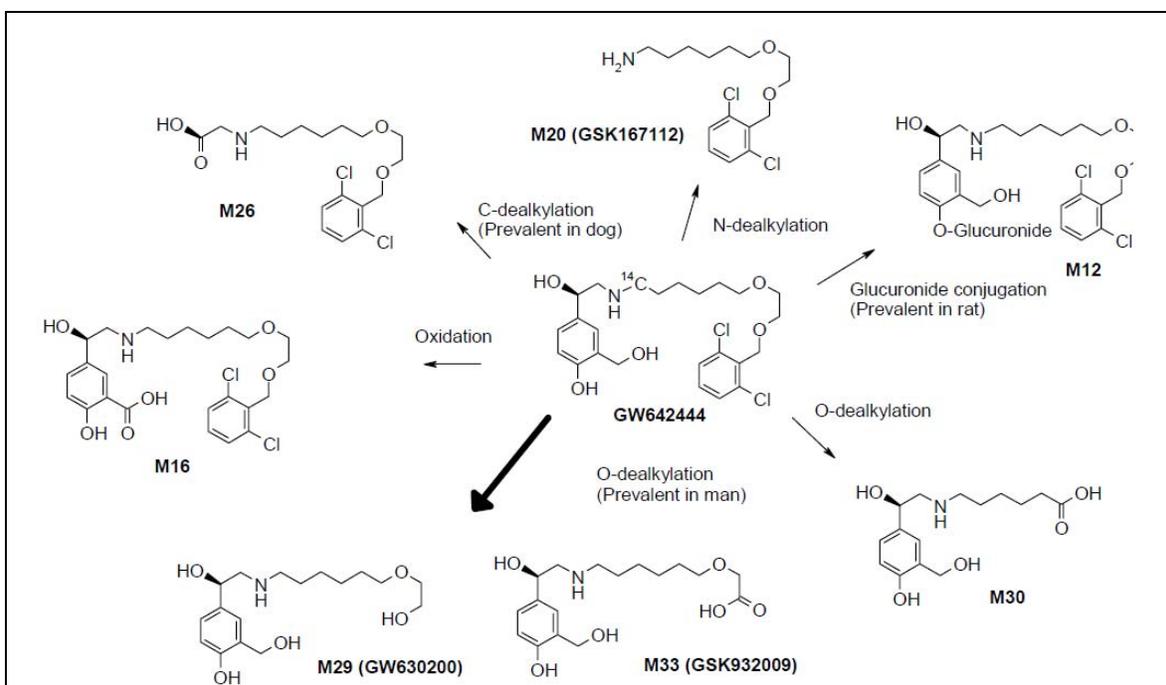


Source – adapted from Figure 3.1, Section 2.6.4, Pharmacokinetics Written Summary

VI

The proposed metabolic pathway for VI is shown in Figure 2.5.7b. Both *in vitro* and *in vivo* studies indicate that VI is extensively metabolized. The principal route of metabolism was by O-dealkylation to a range of metabolites with significantly reduced β_1 - and β_2 -agonist activity that included GW630200 and GSK932009. N-dealkylation (to M20) and C-dealkylation (to M26) were minor pathways in human representing a combined 5% of the recovered dose.

Figure 2.5.7b: Putative Metabolic Scheme for VI in Animals and Human.



Bold arrow represents major metabolic pathway

Source – adapted from Figure 2, Section 2.7.2, Summary of Clinical Pharmacology

2.5.8 Is there evidence for excretion of parent drug and/or metabolites into bile?

Both UMEC and VI excreted into bile.

UMEC

Following intravenous administration of [^{14}C]UMEC to healthy male subjects (study AC4112014), 58% of the total radioactivity was excreted in feces, indicating biliary excretion.

VI

The excretion of VI in bile was investigated in healthy male subjects (study B2C106181). Following oral administration of [^{14}C]VI, duodenal bile collected using the exploratory EnteroTest device technique contained low levels of radioactivity, suggesting low level of biliary excretion.

2.5.9 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Analysis of the available plasma concentration-time profile information does not suggest enterohepatic recirculation for UMEC or VI.

2.5.10 What are the characteristics of drug excretion in urine?

Mass balance study suggested that renal clearance constitutes only 22% of UMEC elimination, and approximately 70% of the total clearance of VI metabolites following IV dosing.

2.5.11 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Both UMEC and VI show approximate dose proportional exposure at the investigated doses.

UMEC

Over the dose range studied in healthy subjects and in subjects with COPD, UMEC systemic exposure showed dose proportionality. Study DB2114635 (TQT, healthy subjects), which administered UMEC/VI 125/25 mcg, UMEC 500 mcg, and UMEC/VI 500/100 mcg, UMEC systemic exposures at the 2 supra-therapeutic doses (UMEC 500 mcg and UMEC/VI 500/100 mcg) were approximately 4-fold higher compared with UMEC systemic exposure following UMEC/VI 125/25 mcg, which is in line with the 4-fold difference in UMEC dosing.

Table 2.5.11a: UMEC Dose Proportionality Following Single Doses of UMEC/VI Administered via NDPI in Healthy Subjects and COPD patients.

Analysis/Study Number/ N	Treatment Arm	AUC _(0-τ) (pg·h/mL) Geometric Mean (95%CI)	C _{max} (pg/mL) Geometric Mean (95%CI)
NCA PK TQT DB2114635 / 74	UMEC/VI 125/25 mcg	495 (431, 569)	334 (294, 379)
NCA PK Hepatic (Data from healthy cohort) DB2114637 / 9	UMEC 125 mcg	482 (383, 607)	283 (220, 363)
NCA PK TQT DB2114635/ 73	UMEC 500 mcg	2444 (2278, 2623)	1541 (1412, 1682)
NCA PK TQT DB2114635/ 70	UMEC/VI 500/100 mcg	2145 (1977, 2328)	1400 (1285, 1525)

Source: Table 77, Summary of Clinical Pharmacology

VI

Although dose proportionality of VI was not assessed formally in any UMEC/VI study, VI systemic exposure following a supra-therapeutic dose of UMEC/VI 500/100 mcg was approximately 4-fold higher compared with VI systemic exposure following the UMEC/VI combination dose of 125/25 mcg (Table 2.5.1d). Dose proportionality is also assessed for single dose of VI administered via DISKUS in COPD patients (Table 2.5.11b). C_{max} and AUC₍₀₋₁₎ increased in an approximately proportional manner within 25 to 100 mcg dose of VI (GW642444M).

Table 2.5.11b: ANOVA analysis of VI (GW642444M) Dose Proportionality Following Single Doses Administered via DISKUS in COPD Subjects [B2C110165].

Parameter	Treatment Comparison	Ratio (90% CI)
C _{max} (pg/mL)	GW642444M 25 mcg vs. GW642444M 50 mcg ¹	1.04 (0.84, 1.28)
	GW642444M 100 mcg vs. GW642444M 50 mcg ¹	0.91 (0.68, 1.22)
	GW642444M 100 mcg vs. GW642444H 100 mcg ¹	4.04 (3.05, 5.36)
AUC ₍₀₋₁₎ (pg.h/mL)	GW642444M 25 mcg vs. GW642444M 50 mcg	1.09 (0.90, 1.31)
	GW642444M 100 mcg vs. GW642444M 50 mcg	0.98 (0.79, 1.22)
	GW642444M 100 mcg vs. GW642444H 100 mcg	4.05 (2.98, 5.50)

GW642444M dose comparisons analysed using mixed models with dose as a fixed effect and subject fitted as a random effect. GW642444M vs GW642444H comparison analysed using fixed effect analysis of variance adjusting for period and treatment

Source: Table 11, B2C110165 report

2.5.12 How do the PK parameters change with time following chronic dosing?

There is no indication of time-dependent PK after multiple dosing for both UMEC and VI.

UMEC

The pharmacokinetics of UMEC after once daily dosing with the to-be-marketed formulation in healthy subjects was evaluated in study DB2114637. In this study, all subjects received a single dose of UMEC/VI (125 mcg/25 mcg), followed after a 7 to 14 day washout by UMEC (125 mcg) once daily for 7 days. The accumulation of C_{max} on Day 7 over Day 1 was 1.3. AUC_{inf} on Day 1 was not calculated because UMEC levels were mostly below detection limit after 2 hours of dosing on Day 1.

PK information was collected in Phase 2 and Phase 3 studies in COPD patients. While limited by assay sensitivity, the available time-concentration profiles of UMEC and VI are similar between day 14 and day 28; and day 84 and day 168.

Table 2.5.12a: UMEC Pharmacokinetic Parameters after Single Dose vs Steady State in COPD Patients (AC4115408).

Parameter	Dose (mcg)	Day Comparison	Ratio	90% CI
AUC _(0-0.25) (h*pg/mL)	62.5	Day 28 vs. Day 1	1.857	(1.389, 2.482)
	125	Day 28 vs. Day 1	1.454	(1.041, 2.031)
	62.5	Day 84 vs. Day 1	1.824	(1.347, 2.471)
	125	Day 84 vs. Day 1	1.640	(1.082, 2.485)
C _{max} (pg/mL)	62.5	Day 28 vs. Day 1	1.641	(1.407, 1.914)
	125	Day 28 vs. Day 1	1.448	(1.151, 1.821)
	62.5	Day 84 vs. Day 1	1.653	(1.372, 1.992)
	125	Day 84 vs. Day 1	1.633	(1.255, 2.126)

Source: Table 42, AC4115408 study report

VI

VI AUC_{inf} after a single dose of UMEC/VI can not be assessed due to limited sensitivity of analytical method. PK information was collected in Phase 2 and Phase 3 studies in

COPD patients. While limited by assay sensitivity, the available time-concentration profiles of VI are similar between day 14 and day 28 (Table 2.5.12a); and day 84 and day 168. There is no evidence of time dependent PK.

Table 2.5.12a: Summary of Results of Statistical Analysis of Derived Plasma VI Parameters to Assess Accumulation (DB2113120).

Parameter	Day	Adjusted Geo Mean	Ratio	90% CI of Ratio
AUC _(0-0.25) (h•pg/mL)	Day 1	17.93	---	---
	Day 14	17.61	Day 14 vs. Day 1 / 0.98	0.71, 1.36
	Day 28	15.68	Day 28 vs. Day 1 / 0.87	0.63, 1.22
AUC _(0-0.5) (h•pg/mL)	Day 1	34.05	---	---
	Day 28	39.96	Day 28 vs. Day 1 / 1.09	0.82, 1.44
C _{max} (pg/mL)	Day 1	107.61	---	---
	Day 14	141.00	Day 14 vs. Day 1 / 1.31	1.05, 1.63
	Day 28	111.41	Day 28 vs. Day 1 / 1.04	0.83, 1.30

Source: Table 9.09, DB2113120 study report

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C_{max}, C_{min}) in patients with the target disease and how much of the variability is explained by the identified covariates?

Population PK models were developed to describe the UMEC and VI systemic exposure in patients with COPD. Please see Pharmacometrics review in Appendix 4.1 for additional details.

Weight, age and creatinine clearance were statistically significant covariates on apparent inhaled clearance (CL/F) of UMEC and weight was significant covariate on UMEC volume of distribution (V₂/F). For every 10% increase in weight the CL/F increased approximately by 2%. The apparent volume of distribution of central compartment V₂/F increased approximately 6% for every 10% increase in body weight from 70 kg. With 10% increase in age from 60 years of age, the CL/F decreased by approximately 7%. Regarding creatinine clearance, the CL/F decreased by approximately 3% with every 10% decrease in creatinine clearance from 110 mL/min. The changes in CL/F and V₂/F due to differences in age, weight and creatinine clearance are marginal and do not warrant any dose adjustments for UMEC based on these covariates in population spanning the observed weight, age and creatinine clearance range.

Systemic exposure of UMEC for East Asian, Japanese and South Asian subjects were on average 23% to 49% higher compared with white Caucasian subjects. This finding is consistent with results seen previously in healthy subjects of East Asian origin. There was no effect of race on the pharmacokinetics of VI in subjects with COPD.

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

No dose adjustments are needed for any of the aforementioned covariates.

2.6.2.1 Severity of Disease State

Not assessed.

2.6.2.2 Body Weight

As stated in section 2.6.1.

2.6.2.3 Elderly

As stated in section 2.6.1.

2.6.2.4 Pediatric Patients

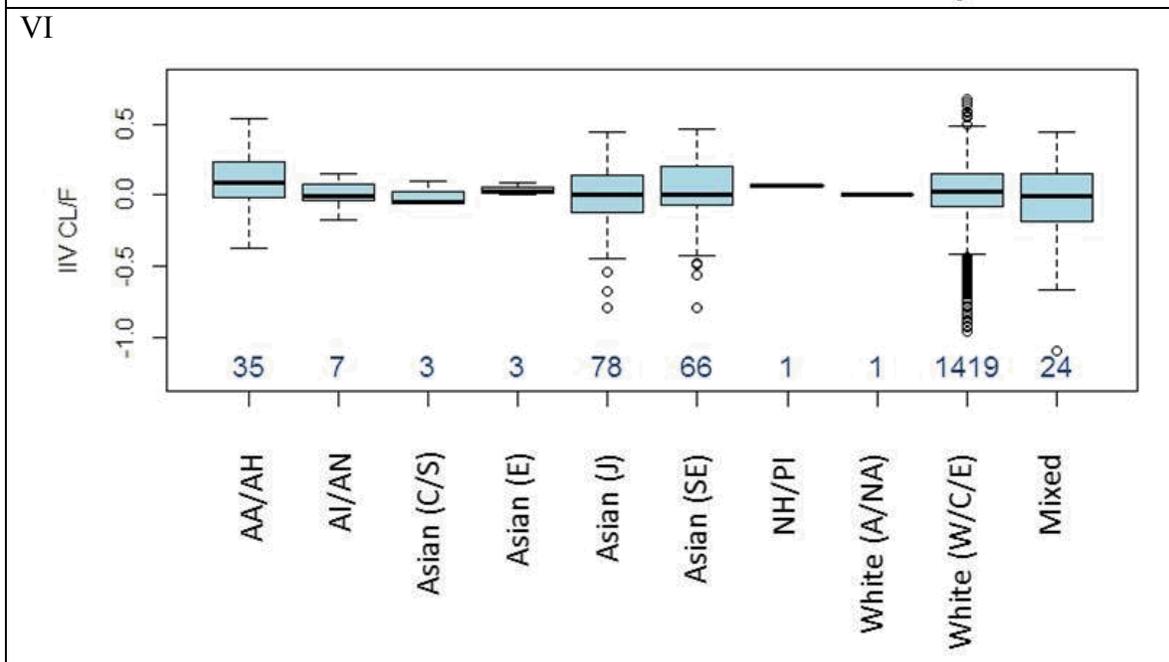
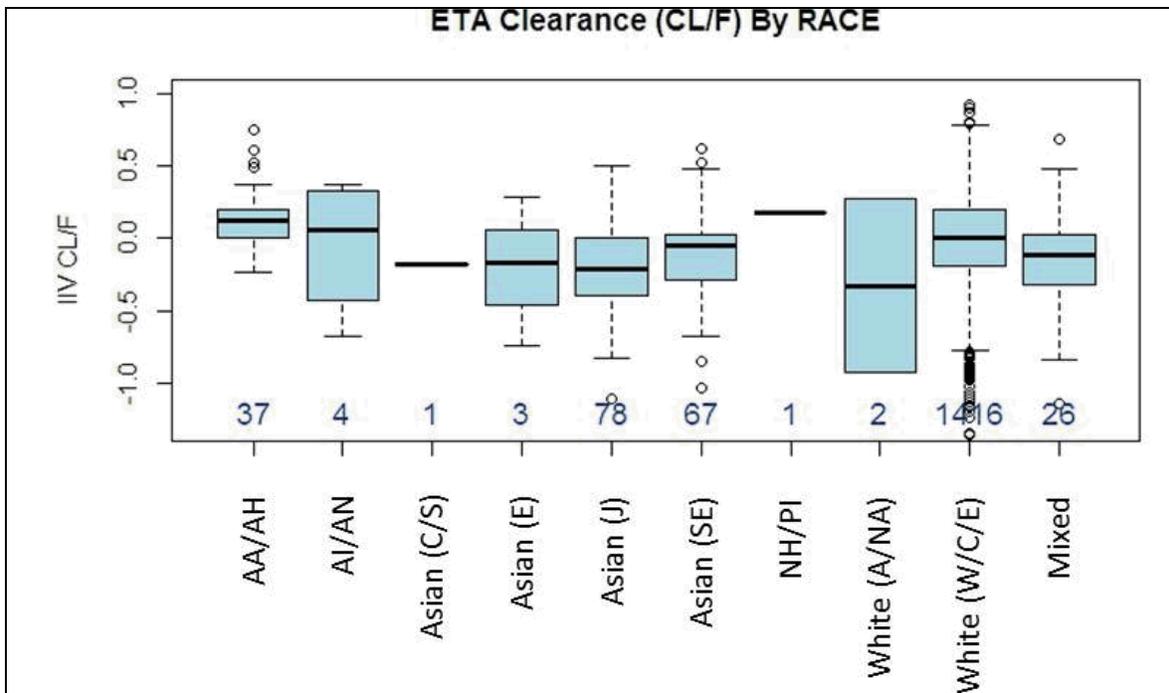
Since COPD is a disease of adults and has no pediatric correlate, sponsor has requested a full waiver from the requirement to conduct pediatric research with UMEC/VI for COPD. Two studies were conducted and one study is ongoing in pediatric asthma patients (5-11yrs old). In the sponsor proposed label, it states “*The safety and efficacy in pediatric patients have not been established.*”

2.6.2.5 Race/Ethnicity

No specific studies were conducted to evaluate the effect of race on PK or PD parameters. Population PK datasets for both UMEC (n=1635) and VI (n=1637) were evaluated for an effect of race on the PK of UMEC and VI (DB2116975). No effect of race/ethnicity on PK was seen for both UMEC and VI.

Figure 2.6.2.5: UMEC and VI Base Model Interindividual Variability (ETA) vs. Covariate Plots (DB2116975).

UMEC



2.6.2.6 Renal Impairment

Comparable exposure was observed for UMEC between healthy and severe renal impairment patients. Although higher exposure was observed for VI in severe renal impaired patients, it is not likely to cause safety concerns and dose modification is not needed.

UMEC

The effect of renal function on the PK of UMEC was evaluated in Study DB2114636 (UMEC and UMEC/VI). Study DB2114636 was a single-blind, non-randomized, single-dose study to investigate the PK and safety of UMEC alone (125 mcg) and UMEC/VI (125/25 mcg) in subjects with severe renal impairment compared with healthy subjects. Nine subjects with severe renal impairment were enrolled along with 9 matched healthy control subjects. All subjects received a single dose of UMEC 125 mcg followed by a single dose of UMEC/VI 125/25 mcg, separated by a washout of at least 7 days. Comparable exposure was observed between healthy and severe renal impairment patients.

Table 2.6.2.6a: Summary of Results from Statistical Analysis of Derived UMEC Plasma PK Parameters.

Parameter	Group Comparison	Adjusted Geometric Mean	Ratio of Adjusted Geometric Mean	90% CI of Ratio
AUC ₍₀₋₂₎ (h*pg/mL)	Severe renal impairment / healthy	59 / 66	0.90	0.64, 1.26
C _{max} (pg/mL)	Severe renal impairment / healthy	113 / 128	0.89	0.58, 1.35

Source: Table 10.3, Study DB2114636 report

VI

The effect of renal function on the PK of VI was evaluated in Study DB2114636 (UMEC/VI) and Study HZA113970 (VI).

Higher VI exposure in renal impairment patients:

In study DB2114636, subjects with severe renal impairment had 21% (-13%, 70%) increase in VI AUC(0-1h) compared to healthy subjects. Data for later time points were not available due to analytical difficulties.

Table 2.6.2.6b: Summary of VI Plasma PK Parameters in Subjects with Severe Renal Impairment and Healthy Subjects After Single Dose UMEC/VI (125/25 mcg).

Parameter	Group Comparison	Adjusted Geometric Means	Ratio of Adjusted Geometric Means	90% CI of Ratio
AUC ₍₀₋₁₎ (h*pg/mL)	Severe renal impairment / healthy	34.8 / 28.7	1.21	0.87, 1.70
C _{max} (pg/mL)	Severe renal impairment / healthy	77.1 / 74.8	1.03	0.73, 1.46

Source: Table 10.6, Study DB2114636 report

In study HZA113970, subjects with severe renal impairment had 56% (27%, 92%) increase in VI AUC compared to healthy subjects. There was no evidence for reduced plasma protein binding of VI in plasma from subjects with severe renal impairment,

compared with plasma from healthy subjects (90.1% vs. 95.4% for VI).

Table 2.6.2.6c: Summary of VI Pharmacokinetic Parameters in Subjects with Severe Renal Impairment and Healthy Subjects After Single and Repeat Dose (7 Days) FF/VI (200/25 mcg).

Drug	Parameter	Day	Group comparison	Adjusted geometric means	Ratio of adjusted geometric means	90% CI of the ratio
VI	AUC ₍₀₋₈₎ [pg.h/mL]	1	Severe renal impairment / healthy	181.12 / 103.38	1.75	(1.00, 3.07)
	AUC ₍₀₋₂₄₎ [pg.h/mL]	7	Severe renal impairment / healthy	604.26 / 386.35	1.56	(1.27, 1.92)
	C _{max} [pg/mL]	1	Severe renal impairment / healthy	126.70 / 107.80	1.18	(0.54, 2.56)
		7	Severe renal impairment / healthy	164.73 / 152.88	1.08	(0.49, 2.35)

Source –Table 9, Study HZA113970 report

Maximum heart rate increased by 0.3 bpm in severe renal impairment patients compared to healthy subjects. Minimum serum potassium (0-4h) were on average 0.4 mmol/L higher. The increased PK exposure of VI did not result in significant heart rate increase or serum potassium decrease in severe renal impairment patients, thus does not warrant dose adjustment.

2.6.2.7 Hepatic Impairment

No change in exposure for UMEC or VI in hepatic impairment patients. Therefore, no dose adjustment for UMEC/VI is needed in hepatic impairment patients.

UMEC

The effect of hepatic impairment on the PK of UMEC was evaluated in DB2114637 (UMEC/VI).

There was no evidence of increased UMEC systemic exposure in subjects with moderate hepatic impairment compared with healthy subjects, following either single or repeat dose administration of UMEC 125 mcg, or single dose administration of UMEC/VI 125/25 mcg. Results of the statistical analysis for AUC and C_{max}, as presented below, showed that the systemic exposure was not increased in moderate hepatic impairment patients.

Table 2.6.2.7a: UMEC: Summary of Statistical Analysis of Derived Plasma

Pharmacokinetic Parameters.						
UMEC Parameter	Treatment (mcg)	Group Comparison	Day	Adjusted Geometric Means	Ratio	90% CI of the Ratio
AUC ₍₀₋₂₎ (h*pg/mL)	UMEC 125	Moderate	1	74 / 87	0.85	(0.63, 1.15)
	UMEC 125	Hepatic	7	105 / 122	0.86	(0.64, 1.17)
	UMEC/VI 125/25	Impairment / Healthy	1	66 / 72	0.92	(0.68, 1.24)
AUC ₍₀₋₇₎ (h*pg/mL)	UMEC 125	Moderate Hepatic Impairment / Healthy	7	438 / 482	0.91	(0.72, 1.15)
C _{max} (pg/mL)	UMEC 125	Moderate	1	165 / 220	0.75	(0.49, 1.14)
	UMEC 125	Hepatic	7	214 / 283	0.76	(0.50, 1.15)
	UMEC/VI 125/25	Impairment / Healthy	1	160 / 190	0.85	(0.56, 1.28)

CI=confidence interval.
As the dosing interval for UMEC is once-daily, AUC₍₀₋₂₄₎ corresponds to AUC₍₀₋₇₎.

Source: Table 10, study report DB2114637

VI

The effect of hepatic impairment on the PK of VI was evaluated in study DB2114637 (UMEC/VI) and HZA111789 (VI).

No change of VI exposure in hepatic impairment patients: Subjects with various degrees of hepatic impairment had no significant change in AUC and C_{max} of VI compared to normal hepatic function. There is no VI related PD changes observed in hepatic impairment patient.

There was no evidence for reduced plasma protein binding of either UMEC or VI in plasma from subjects with varying degrees of hepatic impairment, compared with plasma from healthy subjects.

Table 2.6.2.7b: VI PK Parameters (day 7): Hepatic Impairment Groups vs. Normal Hepatic Function Group.

Parameter	Day	Group Comparison	Adjusted Geometric Means	Ratio of Adjusted Geometric Means	90% CI of The Ratio
AUC(0-8)	1	Hepatic Mild /Healthy	81.76 / 204.61	0.40	(0.26, 0.62)
		Hepatic Moderate /Healthy	189.74 / 204.61	0.93	(0.58, 1.48)
		Hepatic Severe /Healthy	118.17 / 204.61	0.58	(0.37, 0.91)
AUC(0-24)	7	Hepatic Mild /Healthy	335.74 / 511.10	0.66	(0.40, 1.08)
		Hepatic Moderate /Healthy	678.27 / 511.10	1.33	(0.78, 2.26)
		Hepatic Severe /Healthy	367.69 / 511.10	0.72	(0.43, 1.20)
C _{max}	1	Hepatic Mild /Healthy	107.08 / 225.69	0.47	(0.33, 0.69)
		Hepatic Moderate /Healthy	167.93/ 225.69	0.74	(0.50, 1.11)
		Hepatic Severe /Healthy	167.02 / 225.69	0.74	(0.50, 1.09)
	7	Hepatic Mild /Healthy	154.51 / 246.82	0.63	(0.43, 0.91)
		Hepatic Moderate /Healthy	193.31/ 246.82	0.78	(0.52, 1.17)
		Hepatic Severe /Healthy	206.04 / 246.82	0.83	(0.57, 1.23)

Source: Table 8, Study HZA111789 report

There was no evidence of increased VI systemic exposure in subjects with moderate hepatic impairment compared with healthy subjects, following single dose administration of UMEC/VI 125/25 mcg. The results of the statistical analysis of derived plasma VI pharmacokinetic parameters as presented below showed that the mean ratio of AUC and C_{max} between moderate hepatic impairment and healthy subjects was 0.77 and 0.78, respectively.

Table 2.6.2.7c: Summary of Statistical Analysis of Derived Plasma Pharmacokinetic Parameters.

VI Parameter	Treatment (mcg)	Group Comparison	Day	Adjusted Geometric Means	Ratio	90% CI of the Ratio
AUC ₍₀₋₁₎ (h*pg/mL)	UMEC/VI 125/25	Moderate Hepatic Impairment / Healthy	1	36 / 46	0.77	(0.55, 1.08)
C _{max} (pg/mL)	UMEC/VI 125/25	Moderate Hepatic Impairment / Healthy	1	96 / 124	0.78	(0.54, 1.11)

CI=confidence interval.

Source: Table 17 DB2114637 study report.

2.6.3 Does genetic variation impact exposure and/or response?

In vitro, UMEC is a substrate of cytochrome P450 (CYP) 2D6. Clinically relevant effects of CYP2D6 phenotype on UMEC PK were not observed in a prospectively designed healthy subject study.

2.7 Extrinsic Factors

The potential for drug-drug interaction because of induction or inhibition of CYP

enzymes by UMEC/VI is less likely at the low concentrations with clinical doses. Please see sections 2.7.2 and 2.7.4 for further details.

2.7.2 Is the drug a substrate of CYP enzymes?

Yes, UMEC is a substrate for CYP2D6, and VI is a substrate of CYP3A4.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes/transporters?

UMEC

The induction and inhibitory potential of UMEC on metabolizing enzymes and membrane-based transporters investigated is negligible at low inhalation doses.

VI

Vilanterol is an *in vitro* inhibitor of CYP3A4 and CYP2D6 (IC₅₀ values between 3.5 and 12 microM). At clinical doses, UMEC and VI concentrations are at least 1000-fold lower than the lowest IC₅₀ values. UMEC and VI are not inducers of CYP enzymes.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

UMEC

In vitro permeability assessments indicated that UMEC is a substrate of P-gp. GSK573719 was a substrate for the human organic cation transporters OCT1 and OCT2, but not for OCT3, OCTN1 or OCTN2. The inhibition potential of UMEC at the inhaled clinical dose is considered to be negligible.

VI

In vitro permeability assessments indicated that VI is a substrate for P-gp.

2.7.5 Are there other metabolic/transporter pathways that may be important?

No other metabolic enzyme or transporters are known to be important for disposition of UMEC/VI in addition to those already discussed in sections 2.7.2 and 2.7.4

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Among extrinsic factors, only the effect of co-administration with other drugs on UMEC/VI exposure has been evaluated, which is discussed under section 2.7.7. The differences in measured systemic exposures are not relevant for efficacy; however, it may have implications with respect to safety.

2.7.7 Is there any drug-drug and/or formulation interaction between the UMEC and VI when delivered via the NDPI device?

There were no clinically relevant differences (<20% difference between the geometric means) in the pharmacokinetics of either UMEC or VI when administered in combination compared with single component administration.

There is no theoretical or data-driven basis for a PK drug-drug interaction between UMEC and VI resulting in increased systemic exposure of either compound at low IH doses. Study DB2114635 allows the evaluation of a potential effect of VI on UMEC PK. The population analysis allows the evaluation of effect of UMEC on VI PK. These analyses showed no difference in PK parameters when UMEC or VI was administered as monotherapy compared with when administered in combination, thereby indicating a lack of a PK interaction between UMEC and VI.

Table 2.7.7a: UMEC Cmax and AUC on Day 10 after Once Daily Administration of UMEC or UMEC/VI in Healthy Subjects.

Parameter	Treatment	N	n	Geometric Mean	95% CI	CVb(%)
Cmax (pg/mL)	UMEC 500 mcg	75	73	1541	(1412, 1682)	38.8
	UMEC/VI 125/25 mcg	75	74	334	(294, 379)	59.1
	UMEC/VI 500/100 mcg	73	70	1400	(1285, 1525)	37.1
AUC(0- τ) (h*pg/mL)	UMEC 500 mcg	75	73	2444	(2278, 2623)	31.0
	UMEC/VI 125/25 mcg	75	74	495	(431, 569)	65.6
	UMEC/VI 500/100 mcg	73	70	2145	(1977, 2328)	35.2
tmax (h)*	UMEC 500 mcg	75	73	0.10	(0.08, 0.23)	NA
	UMEC/VI 125/25 mcg	75	74	0.10	(0.08, 0.15)	NA
	UMEC/VI 500/100 mcg	73	70	0.10	(0.08, 0.12)	NA

Source: Table 11.2, DB2114625 study report.

Table 1.7.7b: Summary of the Statistical Analysis of VI PK Parameters Comparing UMEC/VI to VI/placebo in COPD Patients.

Study	Treatment	VI Dose	Geometric Mean (95%CI)	
			AUC _{ss} (pg*h/ml)	C _{max-ss} (pg/ml)
DB2113361, DB2113373	All arms combined	25 mcg	614.7 (602.8 – 627.0)	127.9 (124.9 – 131.0)
DB2113361	UMEC/VI (125/25 mcg)	25 mcg	616.7 (592.1 – 642.1)	128.4 (122.3 – 135.0)
	VI 25 mcg	25 mcg	610.5 (586.7 – 635.1)	128.2 (122.0 – 134.9)
DB2113373	UMEC/VI (62.5/25 mcg)	25 mcg	612.3 (588.6 – 636.7)	128.2 (122.1 – 134.6)
	VI 25 mcg	25 mcg	612.8 (589.3 – 637.3)	128.2 (122.0 – 134.6)

Data Source: Study DB2116975, Table 12.11 and Table 12.12.
Note: Steady state AUC and Cmax calculated from individual CL/F estimates and individual concentration-time profiles obtained by simulating 100 studies (each study with 1637 subjects) with PK parameter estimates from the final VI PK model.

Source: Table 26, Summary of Clinical Pharmacology

2.7.8 What are the drug-drug interactions?

There are no clinically meaning drug-drug interactions for both UMEC and VI. No dose adjustment is needed for patients using concomitant CYP2D6 inhibitors, CYP3A4 inhibitors, or P-gp inhibitors.

UMEC

In a clinical study conducted in healthy normal metabolizer subjects and healthy CYP2D6 poor metabolizer subjects, there was no clinically significant difference in the systemic exposure to UMEC following 7 days of repeat dosing with IH doses up to 1000 mcg. No dose adjustment is needed in patients using concomitant CYP2D6 inhibitors or subjects with genetic polymorphisms of CYP2D6 metabolism.

The effects of verapamil 240 mg once daily on the steady state PK of IH UMEC and IH UMEC/VI was evaluated in Study DB2113950. Both UMEC and VI are substrates of P-gp. IH UMEC and VI were co-administered with verapamil, a potent inhibitor of P-gp and moderate inhibitor of CYP3A4. There was no effect of verapamil on C_{max}, and a moderate increase (1.4-fold) in AUC for UMEC. The dose demonstrating this moderate increase in AUC for UMEC was 8-fold greater than 62.5 mcg, the proposed to-be-marketed UMEC dose. Therefore, no dose adjustment is needed for the use of P-gp transporter inhibitors with UMEC/VI. It is of note that this study used earlier clinical formulation.

Table 2.7.8: Effect of Co-Administered Drugs on UMEC.			
Co-administered drug	UMEC/VI	GMR* (90% CI)	
		AUC	C_{max}
CYP2D6 Poor Metabolizer vs healthy volunteers	GSK573719 500 µg once daily for 7 days	1.029 (0.789, 1.343)	0.8 (0.59, 1.08)
	GSK573719 1000 µg once daily for 7 days	1.33 (0.98, 1.8)	1.07 (0.76-1.5)
Verapamil (potent P-gp inhibitor and moderate CYP3A4 inhibitor) 240 mg QD (with GSK573719/VI on days 9-13)	GSK573719/VI (500/25 mcg) inhaled once daily on days 1-13.	1.39 (1.18-1.64)	0.89 (0.73-1.07)

Source: AC4110106 study report, DB2113950 study report.

VI

Based on in vitro data, the major routes of metabolism of VI in humans are mediated primarily by CYP3A4. Results from Study HZA105548 and Study B2C112205 support the position that caution is advised when administering VI in the presence of strong CYP3A4 inhibitors. Effects of co-administered drugs on VI PK are summarized in Table 2.7.8.

Table 2.7.8: Effect of Co-administered Drugs on VI.		
Co-administered	UMEC/VI	GMR* (90% CI)

drug		VI	
		AUC	C _{max}
		Ketoconazole (potent P-gp and CYP3A4 inhibitor) 400 mg QD	FF/VI (200/25 mcg) inhaled once daily on days 5-11.
	VI (25 mcg) Inhaled on day 5	1.90 (1.37-2.64)	0.89 (0.67-1.18)
Verapamil (potent P-gp inhibitor and moderate CYP3A4 inhibitor) 240 mg QD (with GSK573719/VI on days 9-13)	GSK573719/VI (500/25 mcg) inhaled once daily on days 1-13.	1.14 (0.94-1.37)	1.05 (0.90-1.22)

*GMR: Ratio of Geometric Means

Source: Table 14, Study DB2113950 report.

The increased PK exposure of VI did not result in significant heart rate increase or serum potassium decrease when FF/VI was co-administered with ketoconazole. However, prolongation of QT interval was observed with ketoconazole coadministration. While ketoconazole alone may be associated with QTc increases, the increased VI exposure may also have contributed to the QT prolongation. This study did not have a ketoconazole only arm to determine the QT effect of ketoconazole alone. This reviewer does not concur with the sponsor's interpretation of these results as stated in the proposed product label (line 438) "The increase in vilanterol exposure was not associated with an increase in beta-agonist-related systemic effects on heart rate, blood potassium, (b) (4)

2.7.9 Does the label specify co-administration of another drug?

The UMEC/VI label does not mention specific co-administration with other drugs.

2.7.10 What other co-medications are likely to be administered to the target population?

All COPD patients are likely to take antibiotics and sometimes oral glucocorticoids.

COPD is more likely to occur in old age patients; therefore, there is a potential for other drugs such as anti-hypertensives, anti-diabetics, anti-hyperlipidemics, etc. to be administered with UMEC/VI.

2.7.11 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

VI is a long acting beta agonist. Co-administration of beta-blockers may block the bronchodilatory effect and produce severe bronchospasm. Monoamine oxidase inhibitors and tricyclic antidepressants may potentiate effect of vilanterol on vascular system. Co-administration of LABA and diuretics may worsen the hypokalemia and electrocardiographic changes.

2.8 General Biopharmaceutics

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

This is an inhalation drug and the sponsor did not provide BCS classification information in this submission.

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

UMEC/VI

Phase 3 clinical supplies (2 active blister strips) are identical to the intended marketed product. As there were no formulation changes and no relevant device changes after phase 3 studies, no relative BA or BE studies were conducted.

Early phase clinical studies were initiated using a DISKUS/ACCUHALER inhaler with umeclidinium bromide (b) (4) added to the formulation. (b) (4) magnesium stearate added to produce a (b) (4) of umeclidinium/lactose monohydrate/magnesium stearate which was used in all key clinical studies. Phase 3 clinical studies utilized UMEC/VI, and the associated monotherapies, UMEC and VI, administered via DPI.

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

The effect of food on the PK of UMEC/VI is not assessed. Since the oral bioavailability of UMEC and VI is minimal, it is not likely that inhaled UMEC/VI PK is changed by food.

2.8.4 Was the bioequivalence of the different strengths of the to-be-marketed formulation tested? If so were they bioequivalent or not?

Although multiple strengths had been tested during clinical development, only strength (62.5/25, UMEC/VI) was proposed for marketing in the labeling. Therefore, no bioequivalence study was evaluated.

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the

analytical methods used to measure them in plasma and other matrices?

The methods for analysis of UMEC and VI in plasma samples involved (b) (4) and high pressure liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS).

Different analytical methods were developed and validated throughout the development, and there are 12 analytical reports (6 for UMEC and 6 for VI) submitted in this NDA. Analytical methods used in different studies are listed in Table 2.9.1. The most sensitive lower limit of quantification (LLOQ) for both drugs was 10 pg/mL. At the proposed dose of UMEC/VI (62.5/25 mcg), most plasma concentrations of UMEC and VI were only above the LLOQ for a transient time postdose (~ 1-2 h). Many clinical pharmacology studies were conducted with supra-therapeutic doses of UMEC/VI.

Table 2.9.1: Summary of Analytical Methods for Analysis of UMEC/VI in Clinical Trials.

Validation Report No.	Clinical Study No.	Summary of Method and Validation Parameters	
Umeclidinium (GSK573719)			
WD2006/00081	AC4105209 AC4105211* AC4106889 AC4108123 AC4110106 AC4112008* AC4113073* AC4113589*	GSK573719 is extracted from 100 mL of human plasma by protein precipitation using acetonitrile containing an isotopically labeled internal standard ([¹³ C ₁₂]-GSK573719). Extracts are analyzed by HPLC-MS/MS using a TurbolonSpray™ interface and multiple reaction monitoring.	
		LLQ	0.02 ng/mL
		Validated Range	0.02 to 10 ng/mL
		Within-run Precision (%CV)	≤11.2%
		Between-run Precision (%CV)	≤5.5%
		Accuracy (%Bias)	-11.3% ≤ bias ≤1.8%
		Stability in Human Plasma	3 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature
Processed Extract Stability	at least 72 hours at ambient temperature		
WD2006/03251	AC4105209 AC4106889 AC4108123	Human urine (1 mL) is diluted with acetonitrile containing an isotopically labeled internal standard ([¹³ C ₁₂]-GSK573719). Extracts are analyzed by HPLC-MS/MS using a TurbolonSpray™ interface and multiple reaction monitoring.	
		LLQ	0.1 ng/mL
		Validated Range	0.1 to 50 ng/mL
		Within-run Precision (%CV)	≤10.1%
		Between-run Precision (%CV)	≤10.1%
		Accuracy (%Bias)	-12.2% ≤ bias ≤11.0%
		Stability in Human Urine	3 freeze-thaw cycles at approximately -20°C at least 38 days at -20°C at least 24 hours at ambient temperature
Processed Extract Stability	at least 48 hours at 4°C		
WD2008/00425	AC4105211* AC4110106 AC4112008* AC4113073* DB2113950*	Human urine (50 mL) is diluted with acetonitrile containing an isotopically labeled internal standard ([¹³ C ₁₂]-GSK573719). Extracts are analyzed by HPLC-MS/MS using a TurbolonSpray™ interface and multiple reaction monitoring.	
		LLQ	0.1 ng/mL
		Validated Range	0.1 to 50 ng/mL
		Within-run Precision (%CV)	≤14.5%
		Between-run Precision (%CV)	Not determined
		Accuracy (%Bias)	-8.2% ≤ bias ≤10.1%
		Stability in Human Urine	3 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature
Processed Extract Stability	at least 120 hours at ambient temperature		
WD2010/00910	AC4112014 DB2113374	GSK573719 is extracted from 50 mL of human plasma by protein precipitation using acetonitrile containing an isotopically labeled internal standard ([¹³ C ₁₂]-GSK573719). Extracts are analyzed by HPLC-MS/MS using a TurbolonSpray™ interface and multiple reaction monitoring.	
		LLQ	20.0 pg/mL
		Validated Range	20.0 to 10,000 pg/mL
		Within-run Precision (%CV)	≤11.5%
		Between-run Precision (%CV)	≤3.7%
		Accuracy (%Bias)	-6.3% ≤ bias ≤5.0%
		Stability in Human Plasma	3 freeze-thaw cycles at approximately -20°C
Processed Extract Stability	at least 120 hours at ambient temperature		

Validation Report No.	Clinical Study No.	Summary of Method and Validation Parameters	
2011N129207 (in studies starting AC, only GSK573719 quantified)	AC4115321* AC4115408* AC4115487* DB2113361* DB2113373* DB2114635*	GSK573719 and GW642444 are extracted from 200 mL of human plasma using isotopically labeled [¹³ C ₁₂]-GSK573719 and [³ H]-GW642444 as internal standards. Quantification of GSK573719 in human plasma over the calibration range 10 to 2000 pg/mL and GW642444 in human plasma over the calibration range 10 to 1000 pg/mL using LC-MS/MS with a TurbolonSpray™ interface and multiple reaction monitoring. (b) (4) using	
		LLQ	10.0 pg/mL for GSK573719 10.0 pg/mL for GW642444
		Validated Range	10.0 to 2000 pg/mL for GSK573719 10.0 to 1000 pg/mL for GW642444
		Within-run Precision (%CV)	≤5.6% for GSK573719 ≤8.1% (15.7% at LLQ) for GW642444
		Between-run Precision (%CV)	≤4.7% for GSK573719 ≤14.4% for GW642444
		Accuracy (%Bias)	-11.0% ≤ bias ≤5.2% for GSK573719 -9.0% ≤ bias ≤8.0% for GW642444
		Stability in Human Urine	4 freeze-thaw cycles at approximately -80°C at least 24 hours at ambient temperature at least 434 days for both analytes at -80°C
		Processed Extract Stability	at least 3 days at 4°C
2011N129205	AC4115321* AC4115408 AC4115487*	Human urine samples (1 mL) are diluted with acetonitrile containing an isotopically labeled internal standard ([¹³ C ₁₂]-GSK573719). Then an aliquot is further diluted with acetonitrile: water (1:1) prior to being analyzed by HPLC-MS/MS using a TurbolonSpray™ interface and multiple reaction monitoring.	
		LLQ	0.01 ng/mL
		Validated Range	0.01 to 5 ng/mL
		Within-run Precision (%CV)	≤12.5%
		Between-run Precision (%CV)	≤11.0%
		Accuracy (%Bias)	-14.6% ≤ bias ≤6.0%
		Stability in Human Urine	3 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature at least 203 days at -20°C
		Processed Extract Stability	at least 8 days at 4°C
WD2009/00970	DB2113120* DB2113208 DB2113950*	GSK573719 and GW642444 are extracted from 100 mL of human plasma by protein precipitation using acetonitrile containing isotopically labeled internal standards ([¹³ C ₁₂]-GSK573719 and [³ H]-GW642444). Extracts are analyzed by HPLC-MS/MS using a TurbolonSpray™ interface and multiple reaction monitoring.	
		LLQ	20.0 pg/mL for GSK573719 30.0 pg/mL for GW642444
		Validated Range	20.0 to 20,000 pg/mL for GSK573719 30.0 to 30,000 pg/mL for GW642444
		Within-run Precision (%CV)	≤9.1% for GSK573719 ≤8.9% for GW642444
		Between-run Precision (%CV)	≤2.9% for GSK573719 ≤3.0% for GW642444
		Accuracy (%Bias)	-3.2% ≤ bias ≤5.9% for GSK573719 -0.6% ≤ bias ≤11.4% for GW642444
		Stability in Human Plasma	3 freeze-thaw cycles at approximately -80°C at least 24 hours at ambient temperature for both analytes
		Processed Extract Stability	at least 24 hours at ambient temperature

2012N143617	DB2114636* DB2114637*	GSK573719 and GW642444 are extracted from 250 mL of human plasma using (b) (4) using isotopically labeled [¹³ C ₁₂]-GSK573719 and [³ H]-GW642444. Extracts are analyzed by HPLC-MS/MS using a TurbolonSpray™ interface and multiple reaction monitoring.	
		LLQ	10.0 pg/mL for GSK573719 and GW642444
		Validated Range	10.0 to 2000 pg/mL for GSK573719 10.0 to 1000 pg/mL for GW642444
		Within-run Precision (%CV)	≤6.3% for GSK573719 ≤5.9% for GW642444
		Between-run Precision (%CV)	≤9.7% for GSK573719 ≤11.4% for GW642444
		Accuracy (%Bias)	-2.1% ≤ bias ≤3.3% for GSK573719 -3.9% ≤ bias ≤5.0% for GW642444
		Stability in Human Plasma	5 freeze-thaw cycles at approximately -80°C at least 24 hours at ambient temperature for both analytes at least 34 days at -20°C at least 3 months at -80°C
		Stability in Human Whole Blood Processed Extract Stability	at least 4 hours at room temperature and on ice at least 144 hours at 4°C
2012N143619	DB2114636* DB2114637*	GSK573719 is extracted from 50 mL human urine (treated with 20% Tween solution) using (b) (4) using isotopically labeled [¹³ C ₁₂]-GSK573719. Extracts are analyzed by HPLC-MS/MS using a TurbolonSpray™ interface and multiple reaction monitoring.	
		LLQ	10.0 pg/mL
		Validated Range	10.0 to 5000 pg/mL
		Within-run Precision (%CV)	≤6.9% (15.8% at LLQ)
		Between-run Precision (%CV)	≤7.3% (16.5% at LLQ)
		Accuracy (%Bias)	-2.7% ≤ bias ≤0.9%
		Stability in Human Urine	5 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature at least 32 days at -20°C
		Vilanterol (GW642444X)	
WD2003/01624	B2C10001	GW642444X is extracted from 500 mL human plasma by (b) (4) using [³ H]-GW642444 as an internal standard. Extracts are analyzed by HPLC-MS/MS using a TurbolonSpray™ interface and multiple reaction monitoring.	
		LLQ	30.0 pg/mL
		Validated Range	30.0 to 10,000 pg/mL
		Within-run Precision (%CV)	≤13.4%
		Between-run Precision (%CV)	≤6.2%
		Accuracy (%Bias)	-5% ≤ bias ≤12.7%
		Stability in Human Plasma	3 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature at least 33 days at -20°C
		Processed Extract Stability	at least 96 hours at ambient temperature
WD2004/01473	B2C101762 B2C106093	GW642444X is extracted from 100 mL human plasma by protein precipitation with acetonitrile using [³ H]-GW642444 as an internal standard. Extracts are analyzed by HPLC-MS/MS using a TurbolonSpray™ interface and multiple reaction monitoring.	
		LLQ	30.0 pg/mL
		Validated Range	30.0 to 10,000 pg/mL
		Within-run Precision (%CV)	≤14.1%
		Between-run Precision (%CV)	≤1.0%
		Accuracy (%Bias)	-7.1% ≤ bias ≤14.8%
		Stability in Human Plasma	3 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature
		Processed Extract Stability	at least 96 hours at ambient temperature

Req.	Study Req.	Summary of methods and validation attributes	
WD2006/02197	HZA102940 HZA105871 B2C104604 B2C108562 B2C106996 B2C108784 B2C110165	GW642444X, GW630200, and GSK932009 are extracted from 150 mL human plasma by protein precipitation with 0.1% formic acid in 95/5 acetonitrile/methanol (v/v) using [³ H]-GW642444 as an internal standard. Extracts are analyzed by HPLC-MS/MS using a TurboIonSpray™ interface and multiple reaction monitoring.	
		LLQ	30.0 pg/mL for GW642444 90.0 pg/mL for GW630200 180 pg/mL for GSK932009
		Validated Range	30.0 to 15,000 pg/mL for GW642444 90.0 to 45,000 pg/mL for GW630200 180 to 90,000 pg/mL for GSK932009
		Within-run Precision (%CV)	GW642444 ≤12.4% GW630200 ≤13.9% GSK932009 ≤12.4%
		Between-run Precision (%CV)	GW642444 ≤1% GW630200 ≤5.4% GSK932009 ≤4.4%
		Accuracy (%Bias)	GW642444 -6.4% ≤ bias ≤4.6% GW630200 -9.1% ≤ bias ≤8.2% GSK932009 -8.0% ≤ bias ≤8.3%
		Stability in Human Plasma	3 freeze-thaw cycles at approximately -80°C at least 24 hours at ambient temperature at least 16 days at -20°C or -80°C for all 3 analytes
		Processed Extract Stability	at least 72 hours at ambient temperature
		Processed Extract Stability	at least 24 hours at ambient temperature
		2010N107977	HZA106827 HZA106829
LLQ	10.0 pg/mL		
Validated Range	10.0 to 1000 pg/mL		
Within-run Precision (%CV)	≤6.7%		
Between-run Precision (%CV)	Not determined		
Accuracy (%Bias)	-8.6% ≤ bias ≤3.8%		
		Stability in Human Plasma	4 freeze-thaw cycles at approximately -80°C at least 24 hours at ambient temperature
		Processed Extract Stability	at least 96 hours at 4°C
2011N118917	HZA111789 HZA113970	GW642444X are extracted from 200 mL human plasma by (b) (4) using [³ H]-GW642444 as an internal standard. Extracts are analyzed by HPLC-MS/MS using a TurboIonSpray™ interface and multiple reaction monitoring.	
		LLQ	10.0 pg/mL
		Validated Range	10.0 to 1000 pg/mL
		Within-run Precision (%CV)	≤9.4% (6.4% at LLQ)
		Between-run Precision (%CV)	≤7.2% (7.7% at LLQ)
		Accuracy (%Bias)	-2.0% ≤ bias ≤10.0%
		Stability in dimethyl formamide	33 days at 4°C 6 hours at ambient temperature
		Stability in Human Blood	At least 4 hours at ambient temperature or 4°C
		Stability in Human Plasma	4 freeze-thaw cycles at approximately -80°C at least 24 hours at ambient temperature at least 379 days at -80°C
		Processed Extract Stability	at least 7 days at 4°C

WD2008/01238 and 2011N113073	HZA102932	GW642444X is extracted from 200 mL human plasma by (b) (4) using [³ H]-GW642444 as an internal standard. Extracts are analyzed by HPLC-MS/MS using a TurboIonSpray™ interface and multiple reaction monitoring.	
	HZA102934		
	HZA102936		
	HZA105548		
	HZA106851		
	B2C106180		
	B2C106181		
	B2C111401		
	H2C111348		
	B2C112205		
HZA110946	LLQ	10.0 µg/mL	
HZA106839	Validated Range	10.0 to 10,000 µg/mL	
H2C112206	Within-run Precision (%CV)	≤14.4%	
H2C112207	Between-run Precision (%CV)	≤4.3%	
	Accuracy (%Bias)	-13.8% ≤ bias ≤0.1%	
	Stability in Human Plasma	At least 375 days at -80°C	
	Processed Extract Stability	At least 24 hours at ambient temperature	
WD2008/00604	B2C106180	An aliquot of human urine (25 mL) is diluted with 0.1% formic acid in acetonitrile containing [³ H]-GW642444 as an internal standard for the analysis of GW642444. The diluted samples are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring. To aid the solubility of GW642444 in urine, human serum albumin (HSA) is added to the urine to give a concentration of approximately 1 mg/mL prior to being stored frozen.	
		LLQ	0.5 ng/mL
		Validated Range	0.5 to 500 ng/mL
		Within-run Precision (%CV)	≤4.9%
		Accuracy (%Bias)	2.8% ≤ Bias ≤7.0%
		Stability in Human urine	At least 3 freeze-thaw cycles at approximately -20°C in urine containing HSA at least 24 hours at ambient temperature in urine with and without HSA present
		Processed Extract Stability	at least 72 hours at 4°C
WD2008/00423	DB1111509 DB1111581 DB1112146	GSK233705 and GW642444 are extracted from 100 mL of human plasma by protein precipitation using acetonitrile containing isotopically labelled [³ H]-GSK233705 and [³ H]-GW642444. Extracts are analyzed by HPLC-MS/MS using a TurboIonSpray™ interface and multiple reaction monitoring.	
		LLQ	10.0 µg/mL for GSK233705 30.0 µg/mL for GW642444
		Validated Range	10.0 to 10000 µg/mL for GSK233705 30.0 to 30000 µg/mL for GW642444
		Within-run Precision (%CV)	≤7.3% for GSK233705 ≤5.8% for GW642444
		Between-run Precision (%CV)	≤4.5% for GSK233705 Negligible for GW642444
		Accuracy (%Bias)	-9.7% ≤ bias ≤2.8% for GSK233705 -3.4% ≤ bias ≤4.4% for GW642444
		Stability in Human Plasma	At least 3 freeze-thaw cycles at approximately -80°C at least 72 hours at ambient temperature for both analytes
		Processed Extract Stability	at least 72 hours at ambient temperature

Source – Appendix Table 3, Section 2.7.1, Summary of Biopharmaceutical Studies and Associated Analytical Methods

2.9.2 Which metabolites have been selected for analysis and why?

No metabolites were measured in PK samples. As stated in section 2.5.7, the metabolites are not active metabolites.

2.9.3 For all moieties measured, is free, bound, or total measured?

Total (bound + unbound) concentrations were measured in plasma PK samples.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Table presents a summary of analytical methods used for quantification of UMEC/VI and lists out the respective validation report numbers. Details of the main bioanalytical methods are discussed in section 2.9.1.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

The standard curve for UMEC's analysis in plasma ranged from 0.2 to 10 ng/mL. A linear regression model, with weighting factor of $1/\text{concentration}^2$ was used for the curve fitting for UMEC.

The standard curve for VI's analysis in plasma ranged from 10 to 1000 pg/mL and 30 to 15000 pg/mL. A linear regression model, with weighting factor of $1/\text{concentration}^2$ was used for the curve fitting for VI.

2.9.5.1 What are the lower and upper limits of quantitation?

LLOQ and ULOQ for UMEC were 10 pg/mL and 10 ng/mL, respectively. Ten fold dilution factor was also validated for concentrations above ULOQ.

LLOQ and ULOQ for VI were 10 pg/mL and 15000 pg/mL, respectively. Ten fold dilution factor was also validated for 30000 pg/mL concentration.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

The accuracy and precision of analytical methods for UMEC and VI are listed in Table 2.9.1. For both analytical methods bias and imprecision for 10 fold dilution factor was less than 8%.

The selectivity of both the methods was evaluated by extracting and analyzing blank human plasma from six individual sources both with and without addition of internal standard. All lots were free from significant interfering peaks in the drug and internal standard regions.

2.9.5.3 What is the sample stability under conditions used in the study?

For the bioanalytical methods for both analytes, stability was demonstrated under different conditions as discussed below:

UMEC

Stability of UMEC was established under various conditions: stability of UMEC in human whole blood at 37°C for at least 4 hours. stability of UMEC in human plasma for at least 24 hours at room temperature and for at least 412 days at -20°C; stability for 3 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature; stability of processed samples (auto sampler reinjection and reproducibility) under ambient conditions (bench-top) for at least 72 hours. For each of these stability assessments %CV was less than 15%. Stock solution stability was also assessed for 44 days at 4°C.

VI

Stability of VI was established under various conditions: stability of VI in human whole blood at 37°C for at least 4 hours. stability of VI in human plasma for at least 24 hours at ambient temperature and for at least 375 days at -80°C; stability for five freeze thaw cycles at -80°C; stability of processed samples (auto sampler reinjection and reproducibility) at 4°C for 7 days. For each of these stability assessments %CV was less than 15%. Stock solution stability was also assessed for 27 days at 4°C.

3. Detailed Labeling Recommendations

The labeling language proposed by the sponsor needs substantial revisions because of redundant information in the clinical pharmacology section. The revised labeling language based on the preliminary review is as below

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Vilanterol, a component of ANORO ELLIPTA, is a substrate of cytochrome P450 3A4 (CYP3A4). Concomitant administration of the potent CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known potent CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) [see Warnings and Precautions (5.6), Clinical Pharmacology (12.3)].

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Vilanterol, like other beta₂-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, but may produce severe bronchospasm in patients with (b) (4). Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non-Potassium-Sparing Diuretics

The electrocardiographic changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium-sparing diuretics.

7.5 Anticholinergics

There is potential for an interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects [see Warnings and Precautions (5.6, 5.8, 5.9), Adverse Reactions (6)].

12.3 Pharmacokinetics

(b) (4)

(b) (4)

Absorption: Umeclidinium: Following inhaled administration of umeclidinium in healthy subjects, C_{max} occurred at 5 to 15 minutes. (b) (4)

Umeclidinium is mostly absorbed from lung after inhaled doses with minimum contribution from oral absorption. Following repeat dosing of inhaled umeclidinium, steady state was achieved within (b) (4) accumulation.

Vilanterol: Following inhaled administration of vilanterol in healthy subjects, C_{max} occurred at 5 to 15 minutes. (b) (4)

Vilanterol is mostly absorbed from lung after inhaled doses with negligible contribution from oral absorption. Following repeat dosing of inhaled vilanterol, steady state was achieved within (b) (4) accumulation.

Distribution: Umeclidinium: Following intravenous administration to healthy subjects, the mean volume of distribution was 86 L. In vitro plasma protein binding in human plasma was on average 89%.

Vilanterol: Following intravenous administration to healthy subjects, the mean volume of distribution at steady state was 165 L. In vitro plasma protein binding in human plasma was on average 94%.

Metabolism: Umeclidinium: In vitro data showed that umeclidinium is primarily metabolized by the enzyme cytochrome P450 2D6 (CYP2D6) and is a substrate for the P-glycoprotein (P-gp) transporter. The primary metabolic routes for umeclidinium are oxidative (hydroxylation, O dealkylation) followed by conjugation (e.g., glucuronidation), resulting in a range of metabolites with either reduced pharmacological activity or for which the pharmacological activity has not been established. Systemic exposure to the metabolites is low.

Vilanterol: In vitro data showed that vilanterol is metabolized principally by CYP3A4 and is a substrate for the P-gp transporter. Vilanterol is metabolized to a range of metabolites with significantly reduced β_1 - and β_2 -agonist activity.

Elimination: Umeclidinium: (b) (4)

~~(b) (4) -Following intravenous dosing with radio-labeled umeclidinium, mass balance showed 58% of the radio-label in the feces and 22% in the urine. The excretion of the drug related material in the feces following intravenous dosing indicated elimination in the bile. Following oral dosing to healthy male subjects, radio label recovered in feces was 92% of the total dose and that in urine was less than 1% of the total dose, suggesting negligible oral absorption. (b) (4)~~

~~(b) (4) -The effective half life after once daily dosing is about 11 hours.~~

Vilanterol: (b) (4)

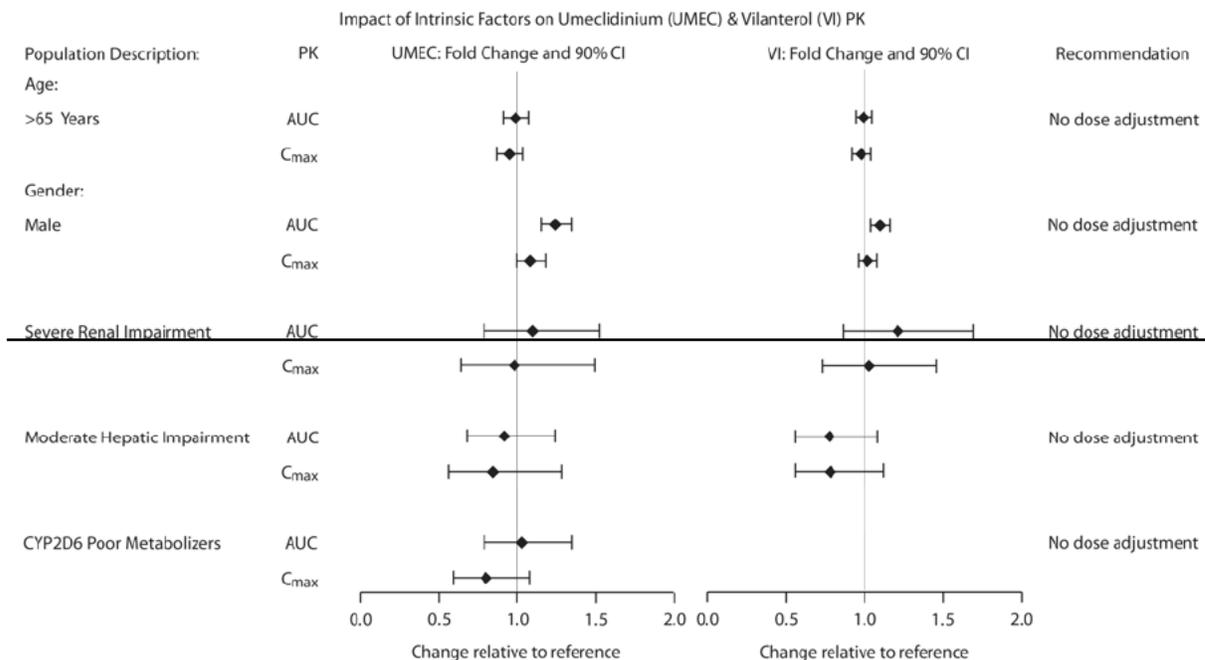
~~(b) (4) Following oral administration of radio-labeled vilanterol, mass balance showed 70% of the radio-label in the urine and 30% in the feces. (b) (4)~~

~~(b) (4) -The effective elimination half-life for vilanterol, as determined from inhalation administration of multiple doses, is 11 hours (b) (4)~~

Special Populations: ~~The effects of renal and hepatic impairment and other~~

~~intrinsic factors on the pharmacokinetics of umeclidinium and vilanterol are shown in Figure 1. Population pharmacokinetic analysis showed no evidence of a clinically significant effect of age, (40 to 93 years) (see Figure 1), gender, (69% male) (see Figure 1), inhaled corticosteroid use, (48%), or weight (34 to 161 kg) on systemic exposure of either umeclidinium or vilanterol. In addition, there was no evidence of a clinically significant effect of race.~~

Figure 1. Impact of Intrinsic Factors on the Pharmacokinetics (PK) of Umeclidinium and Vilanterol



Hepatic Impairment: The impact of hepatic impairment on the pharmacokinetics of ANORO ELLIPTA has been evaluated in subjects with moderate hepatic impairment (Child-Pugh score of 7-9). There was no evidence of an increase in systemic exposure to either umeclidinium or vilanterol (C_{max} and AUC) (see Figure 1). There was no evidence of altered protein binding in subjects with moderate hepatic impairment compared with healthy subjects. ANORO ELLIPTA has not been evaluated in subjects with severe hepatic impairment.

Renal Impairment: The pharmacokinetics of ANORO ELLIPTA has been evaluated in subjects with severe renal impairment (creatinine clearance <30 mL/min).

(b) (4)
Vilanterol systemic exposure (AUC(0-24)) was 56% higher in subjects with severe renal impairment compared with healthy subjects.
 There was no evidence of altered protein binding in subjects with severe renal impairment compared with healthy subjects (see Figure 1) [see Clinical Pharmacology (12.3)].

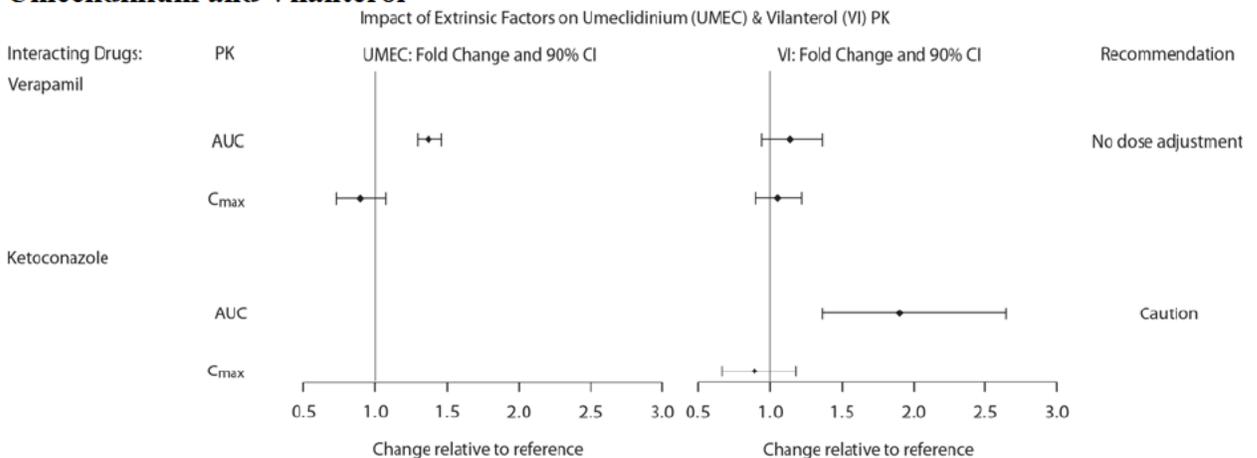
Drug Interactions: (b) (4)

Inhibitors of Cytochrome 450 3A4: Vilanterol is a substrate of CYP3A4. A double-blind, repeat-dose, 2-way crossover drug interaction trial was conducted in healthy subjects to investigate the pharmacokinetic and pharmacodynamic effects of vilanterol 25 mcg as an inhalation powder with ketoconazole 400 mg. The plasma concentrations of vilanterol were higher after single and repeated doses when coadministered with ketoconazole than with placebo (see Figure (b) (4) 2). The increase in vilanterol exposure was not associated with an increase in beta-agonist-related systemic effects on heart rate, or blood potassium, (b) (4)

(b) (4) *P-glycoprotein Transporter:* Umeclidinium and vilanterol are both substrates of P-gp. The effect of the moderate P-gp transporter inhibitor verapamil (240 mg once daily) on the steady-state pharmacokinetics of umeclidinium and vilanterol was assessed in healthy subjects. No effect on umeclidinium or vilanterol C_{max} was observed; however, an approximately 1.4-fold increase in umeclidinium AUC was observed with no effect on vilanterol AUC (see Figure (b) (4) 2)

(b) (4) *Cytochrome P450 2D6:* In vitro metabolism of umeclidinium is mediated primarily by CYP2D6. However, no clinically meaningful difference in systemic exposure to umeclidinium (500 mcg) was observed following repeat daily inhaled dosing to in CYP2D6 normal (ultrarapid, extensive, and intermediate metabolizers) and (b) (4) poor metabolizer subjects (see Figure 1).

Figure 1. Impact of Extrinsic Factors on the Pharmacokinetics (PK) of Umeclidinium and Vilanterol



4. Appendix

4.1 PM Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

NDA Number	203975
Brand Name	ANORO ELLIPTA
Drug Components	Umeclidinium (UMEC) and vilanterol (VI)
Proposed dosing	UMEC / VI (62.5 or 125 mcg / 25 mcg) once daily
Pharmacometrics Reviewer	Hongshan Li, Ph.D.
Pharmacometrics Team Leader	Atul Bhattaram, Ph.D.
Sponsor	GlaxoSmithKline

1 Summary of Findings

1.1 Key Review Questions

The purpose of this review is to address the following six key questions.

1.1.1 Are the two dose regimens selected for the Phase 3 clinical trials appropriate regarding dosing amounts and dosing frequency?

Yes, UMEC/VI 62.5 mcg/25 mcg QD and 125 mcg/25 mcg QD were selected for Phase 3 trials based on efficacy and safety data from Phase 2 clinical trials. The dosing range of each individual component has been explored in Phase 2 trials although no dose-ranging studies of any UMEC/VI combinations had been executed before Phase 3 clinical trials.

- For UMEC, the drug development program includes dose-ranging information of four Phase 2 studies in COPD patients.
- For VI, the drug development program includes dose-ranging information of one Phase 2 study in asthma patients and one Phase II study in COPD patients.
- As a result, two dosing regimens, UMEC/VI 62.5 mcg/25 mcg and 125 mcg/25 mcg, were agreed upon by the FDA for Phase 3 trials in COPD patients.

For the UMEC component, four dose-ranging trials were conducted in COPD patients exploring daily doses from 15.6 mcg to 1000 mcg (Figure 1 and Table 1). An overall dose response was observed for UMEC QD doses ranging from UMEC 15.6 mcg to 125 mcg, with no consistent additive benefit for UMEC doses above 125 mcg. The results of these four trials in COPD were the basis for the selection of UMEC 62.5 and 125 mcg for further evaluation in confirmatory trials. Of all 1204 patients, 118 patients reported AEs. Total 107 moderate or severe AEs were reported. The most frequently reported moderate or severe AEs are 24 headaches, 8 cases of common cold, 8 coughs, 5 cases of COPD exacerbation, 4 cases of hoarseness, 4 sore throats, and 4 cases of sinusitis.

Figure 1. Change from baseline in trough FEV1 in COPD patients for umeclidinium daily doses ranging from 15.6 to 1000 mcg QD or BID and the comparison to tiotropium and placebo.

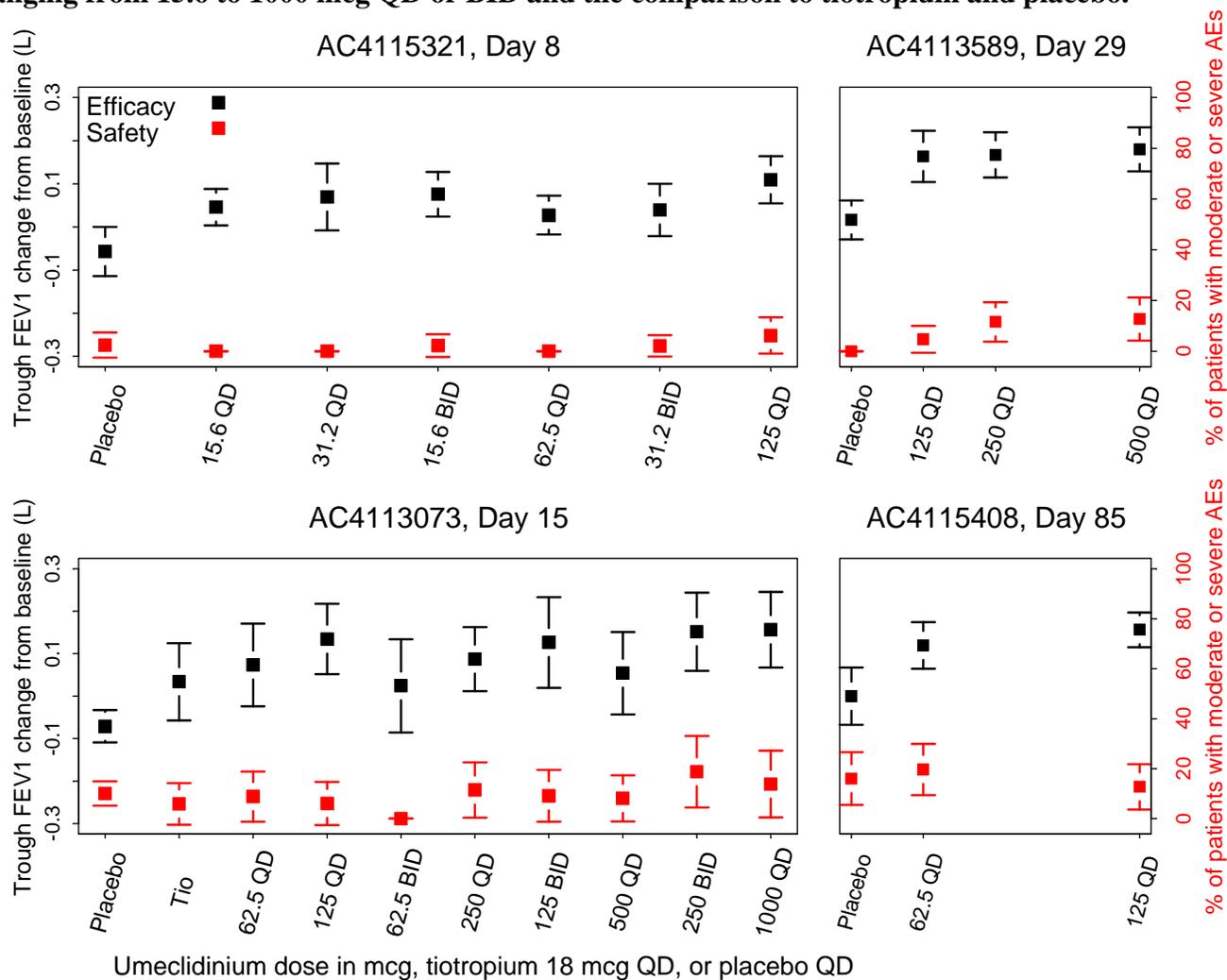


Table 1: Mean change from baseline in trough FEV1 (L) for umeclidinium once or twice daily doses.								
	AC4115321 on Day 8		AC4113073 on Day 15		AC4113589 on Day 29		AC4115408 on Day 85	
Treatment	FEV1TRC (CI _{95_lo} , CI _{95_hi})	N	FEV1TRC (CI _{95_lo} , CI _{95_hi})	N	FEV1TRC (CI _{95_lo} , CI _{95_hi})	N	FEV1TRC (CI _{95_lo} , CI _{95_hi})	N
Placebo	-0.057 (-0.114, 0.000)	41	-0.071 (-0.109, -0.033)	150	0.016 (-0.029, 0.061)	67	0.000 (-0.068, 0.068)	50
Tio			0.034 (-0.057, 0.125)	34				
15.6 QD	0.046 (0.004, 0.088)	51						
31.2 QD	0.069 (0.009, 0.147)	46						
15.6 BID	0.076 (0.024, 0.127)	45						
62.5 QD	0.027 (-0.018, 0.072)	48	0.073 (-0.024, 0.171)	34			0.119 (0.064, 0.174)	61
31.2 BID	0.039 (-0.021, 0.100)	48						
125 QD	0.109 (0.054, 0.164)	48	0.135 (0.052, 0.217)	33	0.163 (0.104, 0.223)	64	0.156 (0.115, 0.197)	55
62.5 BID			0.024 (-0.085, 0.134)	31				
250 QD			0.087 (0.012, 0.163)	35	0.167 (0.115, 0.219)	69		
125 BID			0.126 (0.020, 0.233)	33				
500 QD			0.054 (-0.043, 0.151)	37	0.180 (0.128, 0.231)	63		
250 BID			0.152 (0.059, 0.244)	32				
1000 QD			0.157 (0.068, 0.246)	29				

FEV1TRC: change from baseline in trough FEV1 at the end of Day 28; CI_{95_lo}: the lower boundary of 95% confidence interval; CI_{95_up}: the upper boundary of 95% confidence interval; N: number of patients in the group; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; Tio: tiotropium 18 mcg once daily dose; 15.6 QD: umeclidinium 15.6 mcg once daily dosing, other numbers followed by QD have the similar explanation; 15.6 BID: umeclidinium 15.6 mcg twice daily dosing, other numbers followed by BID have the similar explanation

Dosing frequency with UMEC, QD versus BID (twice daily), was explored in patients with COPD (left two panels of **Figure 1**). In the randomized, double-blind, placebo-controlled, cross-over trial (AC4115321) in patients with COPD, the efficacy and safety was compared between UMEC 31.2 mcg BID, UMEC 62.5 mcg QD, and UMEC 125 mcg QD. Based on trough FEV₁, 62.5 mcg QD and 31.2 mcg BID appeared similar, whereas 125 mcg QD resulted in numerically the highest trough FEV₁ effect. These results supported the selection of the QD regimen of 62.5 and 125 mcg of UMEC for further evaluation. Another study in COPD patients (AC4113073) demonstrated the efficacy profile of 125 mcg QD was numerically better than 62.5 mcg BID, and the safety profile of 125 mcg QD was comparable to 62.5 mcg BD (Table 1 and lower left panel of Figure 1)

For VI, a range of doses were explored in both COPD patients (Study B2C111045) and persistent asthma patients (B2C109575). In each patient population, a randomized, double-blind, placebo-controlled, parallel group, 28-day trials evaluated five doses of VI (3, 6.25, 12.5, 25, and 50 mcg) administered once daily. Trough FEV₁ results demonstrated an approximate dose-response between the lowest and highest doses (Figure 2) for both studies. The 25 mcg dose was identified as optimal dose in asthma study. In the COPD study, 25 mcg also demonstrated comparable efficacy/safety profile to 50 mcg QD, the best regimen based on efficacy and safety data (Table 2 and Figure 2).

Out of all 537 COPD patients of Study B2C111045, 67 patients reported AEs. Moderate or severe AEs totaled 71 cases, including the following most frequently reported cases: 6 headaches, 5 intensified back pains, 3 common colds, and 3 cases of sinusitis.

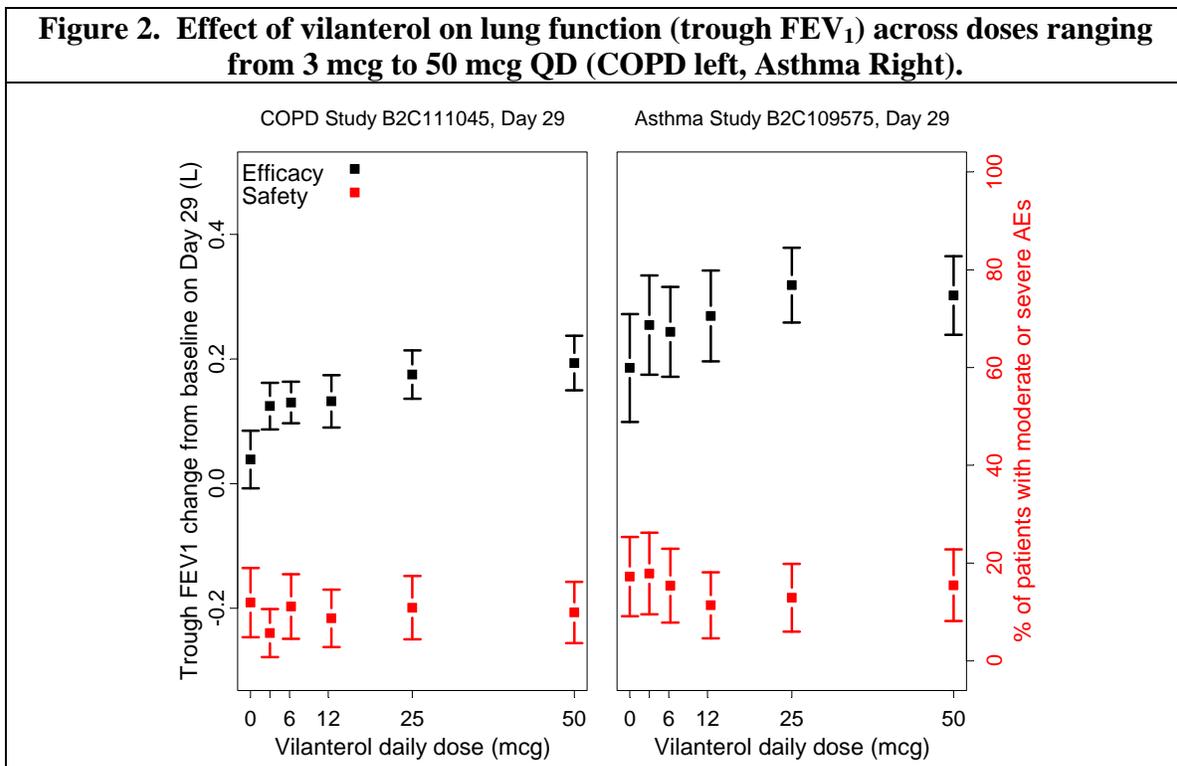


Table 2. Mean change from baseline in trough FEV1 in L for vilanterol once daily doses.				
Dose (mcg)	Study B2C111045 in COPD Patients		Study B2C109575 in Asthma Patients	
	FEV1TRC (CI _{95_lo} , CI _{95_up})	N	FEV1TRC (CI _{95_lo} , CI _{95_up})	N
0	0.039 (-0.008, 0.085)	84	0.186 (0.099, 0.272)	87
3	0.124 (0.087, 0.162)	88	0.254 (0.175, 0.334)	84
6.25	0.130 (0.097, 0.164)	90	0.243 (0.171, 0.316)	91
12.5	0.132 (0.090, 0.174)	92	0.269 (0.196, 0.342)	88
25	0.175 (0.136, 0.214)	92	0.318 (0.258, 0.378)	93
50	0.193 (0.150, 0.237)	91	0.302 (0.239, 0.365)	97

FEV1TRC: change from baseline in trough FEV1 at the end of Day 28; CI_{95_lo}: the lower boundary of 95% confidence interval; CI_{95_up}: the upper boundary of 95% confidence interval; N: number of patients in the group; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second

Regarding dosing frequency of VI, a Phase 2 study (HZA113310) conducted in subjects with persistent asthma supported the comparability of once and twice daily dosing, where the improvement of mean FEV1 (0-24h) was similar between VI 6.25 mcg twice daily and VI 12.5 mcg once daily dosing.

In summary, that UMEC 62.5 mcg QD and UMEC 125 mcg QD being carried forward for combination studies in the Phase 3 COPD program was supported by dose frequency and dose-ranging data of the UMEC component in COPD patients. In terms the selection of VI 25mcg QD for the Phase 3 COPD program, it was supported by the results of dose-ranging studies in both COPD and asthma patients and the dosing frequency study in asthma patients.

1.1.2 Do Phase III confirmatory study results support the approval of the two dose regimens, UMEC/VI 62.5 mcg/25 mcg QD and UMEC/VI 125 mcg/25 mcg QD, for COPD patients?

The efficacy and safety data collected from 6 Phase 3 clinical trials demonstrated that UMEC/VI 62.5 mcg/25 mcg QD is appropriate for COPD patients. However, UMEC/VI 125 mcg/25 mcg QD didn't demonstrate additional benefit to UMEC/VI 62.5 mcg/25 mcg QD.

Trough FEV1 change from baseline data on Day 169 of the four Phase 3 clinical trials (DB2113360, DB2113361, DB2113373 and DB2113374) demonstrated that UMEC/VI 62.5/25 and 125/25 improved lung function, as presented in Table 3 and Figure 3.

- The combination of UMEC/VI 62.5 mcg/25 mcg QD demonstrated added benefit to individual treatment of VI 25 mcg or UMEC 62.5 mcg, and both VI 25 mcg and UMEC 62.5 demonstrated higher efficacy than the placebo while safety profiles were comparable amongst the 4 treatments (Table 3 and middle right panel of Figure 3).
- The combination of UMEC/VI 125 mcg/25 mcg QD demonstrated added benefit to individual treatment of VI 25 mcg or UMEC 125 mcg, and both VI 25 mcg and

UMEC 125 demonstrated higher efficacy than the placebo while safety profiles were comparable amongst the 4 treatments (Table 3 and middle left panel of Figure 3).

- The efficacy and safety profiles were comparable between the two combinations UMEC/VI 62.5 mcg/25 mcg and 125 mcg/25 mcg while they are numerically better than tiotropium 18 mcg QD (Table 3 and side panels of Figure 3). Similar FEV1 results were obtained in another two Phase 3 studies (DB2114417 and DB2114418) as shown in left columns of Table 4 and in the two lower panels of Figure 4.

The safety profiles were comparable between different treatments of the 6 Phase 3 studies. Out of all 4647 patients of the 6 studies, 1502 patients reported AEs. Moderate or severe AEs totaled 1155 cases, including the following most frequent ones: 155 cases of headache, 81 cases of common cold, 78 exacerbations of COPD, 50 cases of upper respiratory infection, 49 cases of cough, 46 cases of toothache, 43 cases of back pains and 32 cases of pneumonia.

In summary, the efficacy and safety data collected from 6 Phase 3 clinical trials demonstrated that UMEC/VI 62.5 mcg/25 mcg QD is appropriate for COPD patients. However, UMEC/VI 125 mcg/25 mcg QD didn't demonstrate additional benefit to UMEC/VI 62.5 mcg/25 mcg QD.

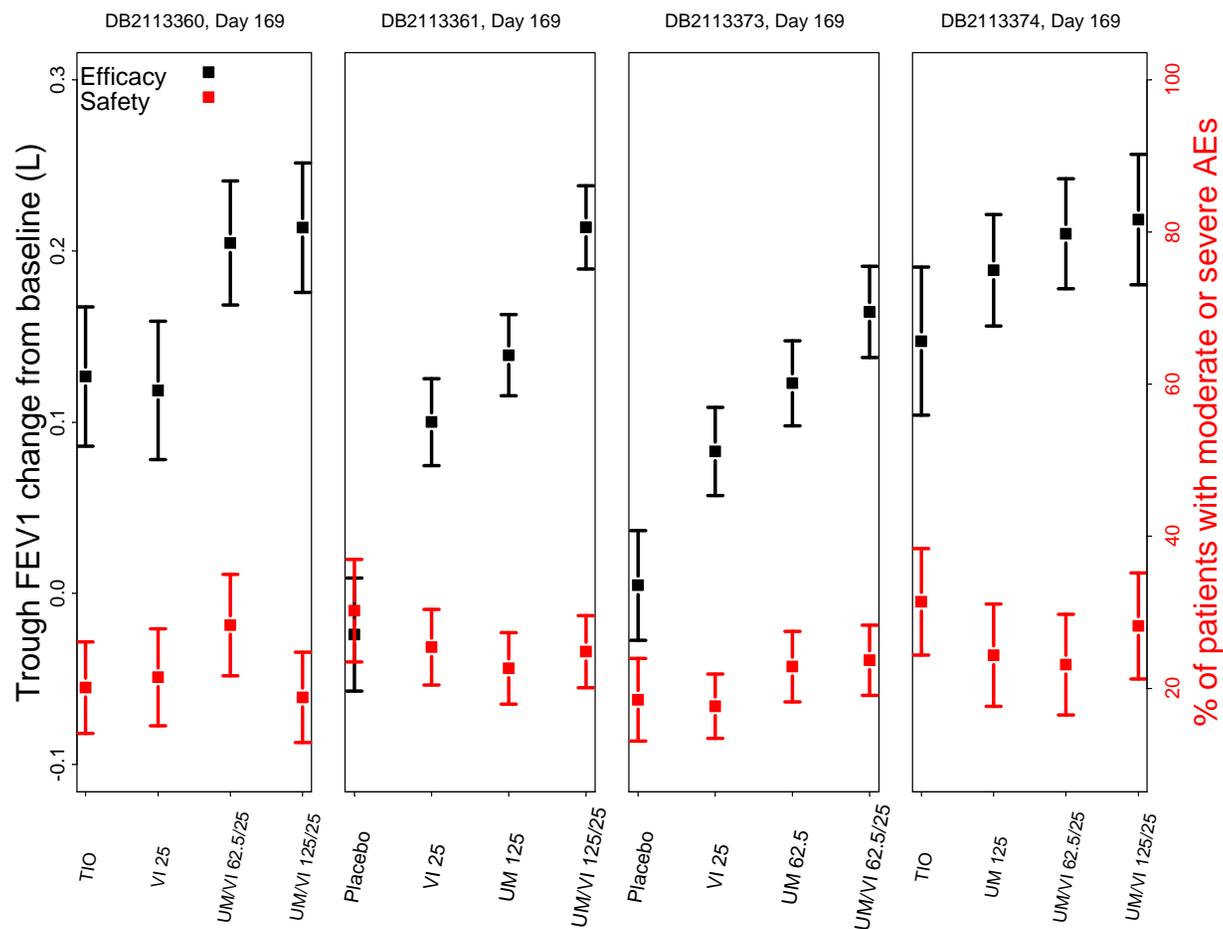
1.1.3 Are there any covariates that influence the systemic exposure of UMEC and VI that need dose adjustment?

No, there were no covariates found in the population PK of UMEC and VI that warrant any dose adjustment of either component.

For pooled population PK data of Study DB2113361 and DB2113373, Both UMEC and VI PK can be best described by a two-compartment model with first order absorption. The population PK parameters and associated inter-individual variability were adequately characterized. There was no apparent PK interaction with co-administration of UMEC with VI.

Weight, age and creatinine clearance were statistically significant covariates on apparent inhaled clearance (CL/F) of UMEC and weight was significant covariate on UMEC volume of distribution (V_2/F). For every 10% increase in weight the CL/F increased approximately by 2%. The apparent volume of distribution of central compartment V_2/F increased approximately 6% for every 10% increase in body weight from 70 kg. With 10% increase in age from 60 years of age, the CL/F decreased by approximately 7%. Regarding creatinine clearance, the CL/F decreased by approximately 3% with every 10% decrease in creatinine clearance from 110 mL/min. The changes in CL/F and V_2/F due to differences in age, weight and creatinine clearance are marginal and do not warrant any dose adjustments for UMEC based on these covariates in population spanning the observed weight, age and creatinine clearance range.

Figure 3. Change from baseline in trough FEV1 in COPD patients for umeclidinium, vilanterol, and combination of them in once daily doses and the comparison to tiotropium and placebo.

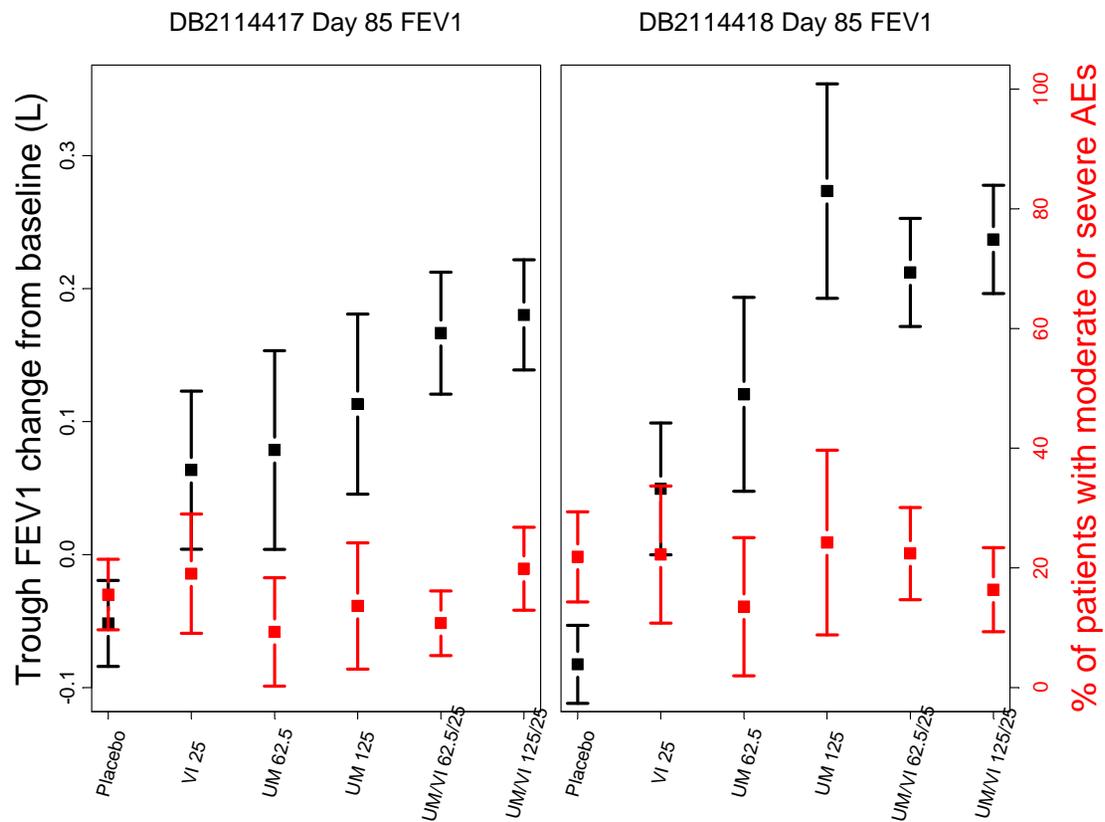


Tio: tiotropium 18 mcg QD; VI 25: vilanterol 25 mcg QD, UM 62.5: umeclidinium 62.5 mcg QD; UM 125: umeclidinium 125 mcg QD; UM/VI 62.5/25: umeclidinium 62.5 mcg and vilanterol 25 mcg QD; UM/VI 125/25: umeclidinium 125 mcg and vilanterol 25 mcg QD

Table 3. Mean change from baseline in trough FEV1 (L) for once daily treatments of Phase 3 studies on Day 169.								
	DB2113360		DB2113361		DB2113373		DB2113374	
Treatment	FEV1TRC (CI95_lo,CI95_hi)	N	FEV1TRC (CI95_lo,CI95_hi)	N	FEV1TRC (CI95_lo,CI95_hi)	N	FEV1TRC (CI95_lo,CI95_hi)	N
Placebo			-0.024 (-0.057, 0.009)	182	0.005 (-0.027, 0.037)	200		
Tio	0.127 (0.086, 0.167)	174					0.147 (0.104, 0.191)	172
VI 25	0.119 (0.078, 0.159)	163	0.1 (0.075, 0.125)	299	0.083 (0.057, 0.109)	317		
UM 62.5					0.123 (0.098, 0.148)	319		
UM 125			0.139 (0.115, 0.163)	309			0.189 (0.156, 0.221)	160
UMEC/VI 62.5/25	0.205 (0.168, 0.241)	180			0.164 (0.138, 0.191)	329	0.21 (0.178, 0.242)	160
UMEC/VI 125/25	0.214 (0.176, 0.251)	170	0.214 (0.19, 0.238)	322			0.218 (0.18, 0.256)	163

FEV1TRC: change from baseline in trough FEV1 at the end of Day 84; CI95_lo: the lower boundary of 95% confidence interval; CI95_up: the upper boundary of 95% confidence interval; N: number of patients in the group; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; VI 25: vilanterol 25 mcg; UMEC 62.5 : umeclidinium 62.5 mcg; UMEC 125 : umeclidinium 125 mcg; UMEC/VI 62.5/25: the combination of umeclidinium 62.5 mcg and vilanterol 25 mcg; UMEC/VI 125/25: the combination of umeclidinium 125 mcg and vilanterol 25 mcg; Tio: tiotropium 18 mcg once daily

Figure 4. Change from baseline in trough FEV1 in COPD patients for umeclidinium, vilanterol, and combination of them in once daily doses and the comparison to tiotropium and placebo.



VI 25: vilanterol 25 mcg QD, Tio: tiotropium 18 mcg QD; UM 62.5: umeclidinium 62.5 mcg QD;

Table 4. Mean change from baseline in trough FEV1 (L) for once daily treatments of Phase 3 studies on Day 84.				
	Study DB2114417		Study DB2114418	
Treatment	FEV1TRC (CI95_lo,CI95_hi)	N	FEV1TRC (CI95_lo,CI95_hi)	N
Placebo	-0.052 (-0.084, -0.019)	148	-0.083 (-0.112, -0.053)	119
VI 25	0.063 (0.004, 0.123)	63	0.049 (0.000, 0.099)	54
UMEC 62.5	0.079 (0.004, 0.153)	43	0.121 (0.048, 0.193)	37
UMEC 125	0.113 (0.045, 0.181)	44	0.273 (0.193, 0.354)	33
UMEC/VI 62.5/25	0.167 (0.121, 0.212)	130	0.212 (0.171, 0.253)	116
UMEC/VI 125/25	0.18 (0.139, 0.222)	131	0.237 (0.196, 0.278)	110

FEV1TRC: change from baseline in trough FEV1 at the end of Day 84; CI95_lo: the lower boundary of 95% confidence interval; CI95_up: the upper boundary of 95% confidence interval; N: number of patients in the group; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; VI 25: vilanterol 25 mcg; UMEC 62.5 : umeclidinium 62.5 mcg; UMEC 125 : umeclidinium 125 mcg; UMEC/VI 62.5/25: the combination of umeclidinium 62.5 mcg and vilanterol 25 mcg; UMEC/VI 125/25: the combination of umeclidinium 125 mcg and vilanterol 25 mcg

Weight and age were statistically significant covariates on VI apparent inhaled clearance (CL/F). For every 10% increase in weight the CL/F increased by about 2%. With a 10% increase in age from 60 years, the CL/F decreased by approximately 4%. The changes in CL/F due to age and weight are marginal and do not warrant any dose adjustments for VI based on these covariates in population spanning the observed weight and age range.

1.2 Recommendations

The Pharmacometrics reviewer finds the application acceptable.

1.3 Label Statements

Labeling statements to be removed are shown in ~~blue strikethrough font~~ and suggested labeling to be included is shown in underline red font.

12.3 Pharmacokinetics

Special Populations: Population pharmacokinetic analysis showed that no dose adjustment is warranted for umeclidinium or vilanterol based on the effect of age, gender, inhaled corticosteroid use, or weight. There was also no evidence of a clinically significant effect of race on systemic exposure to either umeclidinium or vilanterol.

2 Pertinent regulatory background

Co-administration of long-acting muscarinic antagonist (LAMAs) and long-acting beta-2 agonists (LABAs) is more effective than either drug class alone in managing stable COPD to improve lung function, symptoms and health status. By targeting 2 different pharmacologic mechanisms, a LAMA/LABA combination product could potentially optimize bronchodilator therapy of COPD while avoiding the risk of side effects associated with increasing the dose of a single bronchodilator. However, no LAMA/LABA combination products are currently licensed for COPD treatment. GSK has developed the inhaled UMEC/VI combination as a first line treatment for COPD patients, with benefit demonstrated over bronchodilator monotherapy. UMEC/VI offers a once daily dosing interval which could improve treatment adherence and convenience for patients. Neither UMEC nor VI is approved for treatment of COPD, so the clinical development program aimed to demonstrate the effectiveness of the UMEC/VI combination and the effectiveness of UMEC and VI individually, as well as their contribution to the combination. In addition, safety was assessed for UMEC/VI, UMEC, and VI compared with placebo as well as for UMEC/VI compared with UMEC and VI individually.

The global clinical program for UMEC/VI comprised a total of 50 clinical and clinical pharmacology studies, including 7 Phase 3 efficacy/safety studies in subjects with COPD. Table depicts the treatments of the primary and supportive efficacy and safety studies. The 7 Phase 3 studies to evaluate the efficacy and safety of UMEC/VI combination treated a total of 5950 subjects with COPD in 32 countries as follows:

- Two 24-week placebo-controlled safety and efficacy studies (DB2113361 and DB2113373) and two 24-week TIO comparator studies (DB2113360 and DB2113374) which provide the majority of the efficacy and safety data (hereafter referred to as Primary Efficacy studies),
- Two 12-week exercise endurance studies (DB2114417 and DB2114418) (hereafter referred to as Exercise studies), and

- A 52-week safety study (DB2113359) (hereafter referred to as the Long-term Safety study). The application also includes 3 Phase 2b studies to support dose selection of UMEC, 3 Phase 2b studies to support dose selection of VI and 37 Phase 1 and Phase 2a studies for the UMEC/VI combination and/or the monotherapy components including several studies of fluticasone furoate/VI (FF/VI) combination. One additional Phase 3 study to support the efficacy and safety of UMEC monotherapy (AC4115408) was included.
- VI data from 4 studies conducted as part of the Phase 3 program for FF/VI in COPD are included to support the safety of the VI component of UMEC/VI. An analysis of data from studies conducted as part of the development program for FF/VI in asthma are included to further support the safety of VI.

The Phase 2 studies that were conducted to support dose selection and dosing frequency for UMEC and VI components (conducted in both COPD and asthma) are outlined in Table . The Phase 3 clinical development program for UMEC/VI was designed based on feedback from regulatory authorities in the US, EU, Japan and Canada for UMEC/VI combination, and UMEC and VI monotherapies for the maintenance treatment of COPD.

Study	PLA	UMEC 62.5 mcg	UMEC 125 mcg	VI 25 mcg	UMEC/VI 62.5 mcg/25 mcg	UMEC/VI 125 mcg/25 mcg	Tio
DB2113361	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	
DB2113373	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>		
DB2113360				<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
DB2113374			<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>
DB2114417	<input type="checkbox"/>	<input type="checkbox"/>					
DB2114418	<input type="checkbox"/>	<input type="checkbox"/>					
DB2113359	<input type="checkbox"/>		<input type="checkbox"/>			<input type="checkbox"/>	

Abbreviations: PLA=placebo; Tio=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Source: Clinical Overview, Table 5, page 24

GSK met with the FDA on the following occasions to discuss the UMEC/VI clinical development program:

- End of Phase 2 Meeting held on October 29, 2010.
- Pre-New Drug Application (NDA) Meeting held on January 18, 2012.

At the End of Phase 2 meeting, the FDA recommended that GSK consider exploring lower doses of UMEC to determine the nominal dose and the dosing interval in the target patient population. GSK conducted a low dose study investigating UMEC treatment at the following doses and dose intervals:

- UMEC 15.6 micrograms (mcg), 31.25 mcg, 62.5 mcg, 125 mcg once-daily
- UMEC 15.6 mcg, 31.25 mcg twice-daily.

Consistent with the findings of the dose-ranging dose-ranging studies, 2 once-daily UMEC doses were carried forward into the Phase 3 clinical development program (62.5 mcg and 125 mcg), as monotherapy and in combination with VI.

Table 6. Phase 2 Studies to Select Dose Regimens of UMEC/VI Phase 3 Trials in COPD patients

Study Number	Study Objective(s)	Study Design	Duration	Treatment in mcg (once-daily or otherwise specified)	Population
UMEC dose and frequency selection					
AC4113589	Dose-ranging	R, DB, PG, PC	28 days	UMEC 125 UMEC 250 UMEC 500 PLA	COPD
AC4113073	Dose-ranging, dosing interval, And PK	R, DB, XO, PC Incomplete block	3 periods per subject, 14 days per period	Once-daily: UMEC 62.5, 125, 250, 500 or 1000, or Tio 18 OL, or PLA Twice-daily: UMEC 62.5, 125 or 250, or PLA	COPD
AC4115321	Dose-ranging and dosing interval	R, DB, XO, PC Incomplete block	3 periods per subject, 7 days per period	Once-daily: UMEC 15.6, 31.25, 62.5 or 125, or TIO 18 OL, or PLA Twice-daily: UMEC 15.6 or 31.25, or PLA	COPD
AC4115408	Efficacy and safety	R, DB, PG, PC	12 weeks	UMEC 125 or 62.5, or PLA	COPD
VI dose and frequency Selection					
B2C111045	Dose-ranging	R, DB, PG, PC Stratified a	28 days	VI 3, 6.25, 12.5, 25 or 50, or PLA	COPD
B2C109575	Dose-ranging	R, DB, PG, PC Stratified b	28 days	VI 3, 6.25, 12.5, 25 or 50, or PLA	Asthma
HZA113310	Dose-ranging and dosing interval	R, DB, XO, PC	5 periods per subject, 7 days per period	Once-daily: VI 6.25, 12.5 or 25 Twice-daily: VI 6.25 or PLA	Asthma
<p>Abbreviations: COPD=chronic obstructive pulmonary disease; DB=double-blind; OL=open-label; PC=placebo controlled; PG=parallel-group, PLA=placebo; R=randomized, TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol; XO=cross-over</p> <p>a. Subjects' reversibility to salbutamol was used to stratify the randomization.</p> <p>b. Subjects' baseline FEV1 ($\geq 40\%$ to $\leq 65\%$ and $> 65\%$ to $\leq 90\%$ of predicted normal) was used to stratify the randomization.</p>					

Source: Clinical Overview, Table 1, page 16-17

At the pre-NDA meeting, the FDA commented that a relevant patient population for the proposed combination product must be identified and that the TIO comparator studies and the endpoint of reduction in salbutamol use would provide useful data in identifying this. The content and format of the integrated summaries were agreed as well as the size of the safety database. Known adverse effects of special interest associated with anticholinergic or muscarinic antagonists and beta-agonists for evaluation in the Phase 3 UMEC/VI clinical studies were proposed and agreed. These included cardiovascular effects, other anticholinergic effects (e.g., urinary retention and ocular disorders) and beta-adrenergic effects (e.g., electrolyte imbalances

and tremor). An evaluation of pneumonia was also requested. In addition to the adjudication of serious adverse events (SAEs) from the Phase 3 clinical development program, the FDA requested an analysis of Major Adverse Cardiac Events (MACE) and respiratory-related events such as those conducted by other COPD programs. A high-level summary of the safety findings from the asthma program with VI, including deaths, non-fatal SAEs, AEs leading to discontinuation, and common AEs was also requested. Other points raised are addressed under the appropriate heading within the Clinical Overview.

3 Results of Sponsor’s Analysis

3.1 Population PK Analysis for UMEC/VI in Subjects with COPD

3.1.1 Purpose, Data and Methods

Purpose: The aim of the population PK analyses was to characterize the population pharmacokinetics (PK) of UMEC and VI, in combination or alone when administered to COPD patients.

Software: Population PK modeling was performed via NONMEM v7.1.2 (ICON Development Solutions) running in a UNIX server based environment for NONMEM analysis. Supporting application interfaces for data handling, exploratory diagnostics and simulation included Xpose V4 [Jonsson, 1999], and R (The R Foundation for Statistical Computing Version 2.10.1 or above) 5.2 (Pharsight Corporation).

Data Source: Data from two Phase III studies (DB2113361 and DB2113373) was utilized for the analyses. These studies were multi-center, randomized, double-blind, placebo-controlled parallel-group studies in adult subjects with COPD. Eligible subjects were randomized to receive UMEC/VI 125/25 mcg, UMEC 125 mcg, VI 25 mcg or placebo in a 3:3:3:2 ratio in study DB2113361 and receive UMEC/VI 62.5/25 mcg, UMEC 62.5 mcg, VI 25 mcg or placebo in a 3:3:3:2 ratio in study DB2113373. All treatments were administered once daily in the morning by using a Novel Dry Powder Inhaler (Novel DPI) for 24 weeks. Sparse PK samples were collected from subjects on visit 2 (Day 1), Visit 5 (Week 8) and Visit 8 (Week 24) in each of the studies. A subset of subjects that were evaluated over 24 hours (13- 14% across treatment arms) in each study were to provide serial sampling on visits 2, 6 and 8.

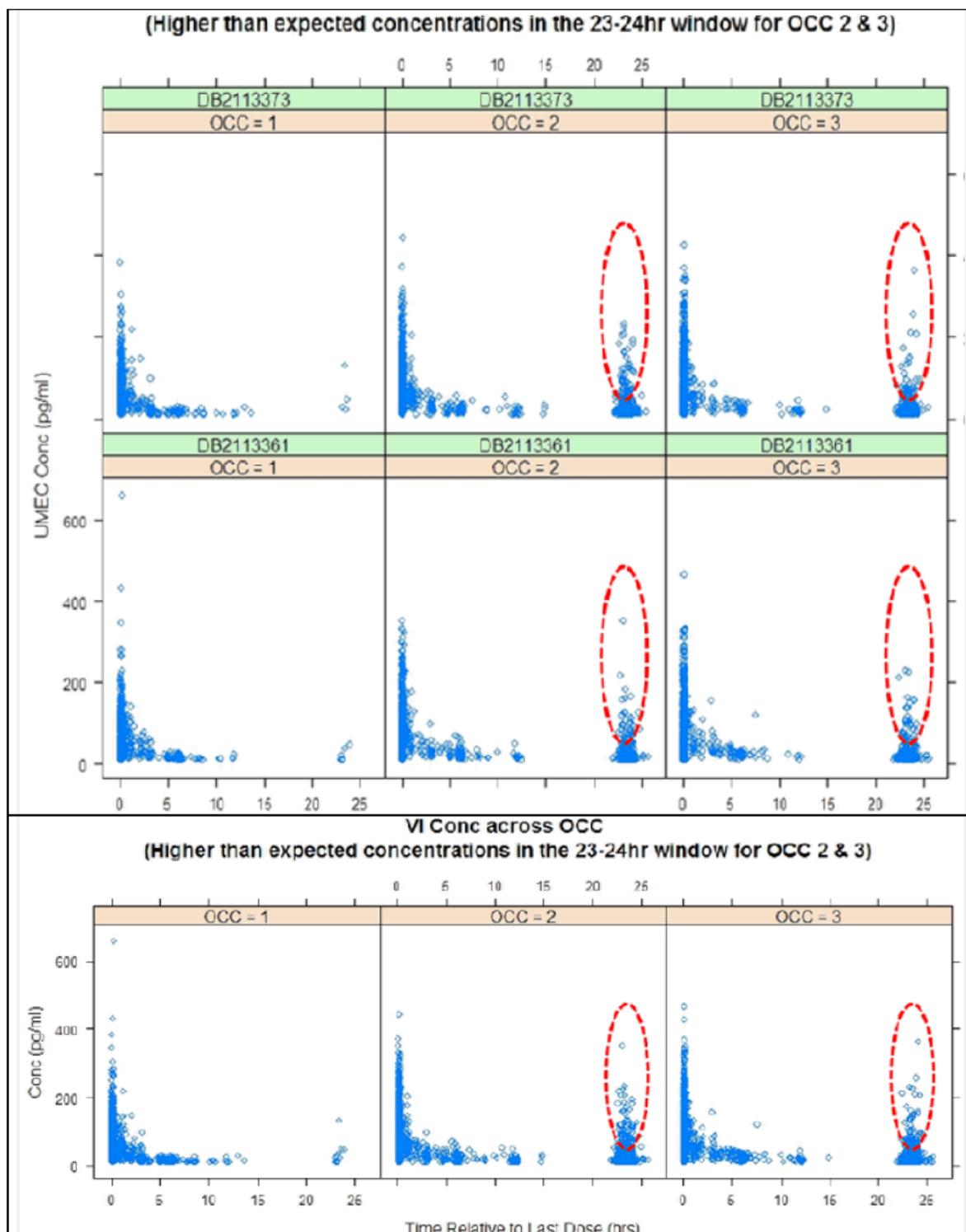
The PK sampling scheme is outlined in Table . Total 1635 subjects (406+402+417+410) contributed UMEC PK samples for 8498 UMEC observations and total 1637 subjects (404+402+421+410) contributed VI PK samples for 8405 VI observations. Plasma samples were analyzed for UMEC and VI using validated analytical methods based on solid phase extraction, followed by high-pressure liquid chromatography with tandem mass spectrometric analysis for detection analysis. The lower limit of quantification (LLQ) for UMEC and VI in plasma was 10.0 pg/mL and the higher limit of quantification (HLQ) was 1000 pg/mL for VI and 2000 pg/mL for UMEC.

<i>Study</i>	<i>Doses (mcg)</i>	<i>Sampling Window (nominal)</i>
DB2113361	<input type="checkbox"/> UMEC/VI 125/25 (N=402) <input type="checkbox"/> UMEC 125 (N=406) <input type="checkbox"/> VI 25 (N=404)	Pre-dose and 1-15 minutes post-dose on days 1, 56 and 168. For a subset of subjects, pre-dose and one sample post-dose in each of the following sampling time windows; 1–15 minutes, 20 mins–4 hours, 4.5–15 hours and 23–24 hours

	<input type="checkbox"/> Placebo	(after previous day's morning dose) on treatment days 1, 84 and 168.
DB2113373	<input type="checkbox"/> UMEC/VI 62.5/25 (N=410) <input type="checkbox"/> UMEC 62.5 (N=417) <input type="checkbox"/> VI 25 (N=421) <input type="checkbox"/> Placebo	Pre-dose and 1-15 minutes post-dose on days 1, 56 and 168. For a subset of subjects, pre-dose and one sample post-dose in each of the following sampling time windows; 1-15 minutes, 20 mins-4 hours, 4.5-15 hours and 23-24 hours (after previous day's morning dose) on treatment days 1, 84 and 168.
N: number of subjects who contributed PK samples in the arm. The N numbers for the 2 placebo groups are both 266 and 399 for all other groups as described in the protocol.		

Handling Outlier Data: About 4-5% of PK samples (for 23-24 h post-dose window) had unexpectedly high concentration values. In some cases these were higher than the 0-15 min post-dose sample in the same subject. Such observations occurred only with data obtained on second and third PK occasions (PK sampling Days 56, 84 and 168; OCC=2 and OCC=3) as displayed in Figure 5. This phenomenon was observed for UMEC and VI across all treatment arms. As another case of outlier data, anomalous plasma concentration-time profiles were noted for 14-15 % of subjects in dataset for each analyte. These subjects were those who provided 2 PK samples (pre-dose and 0-15 minute post dose). Instead of observing high plasma concentration for 0-15min post-dose sample (corresponding to rapid absorption- which is a characteristic for UMEV and VI) and almost non-quantifiable concentration at pre-dose sample (corresponding to rapid elimination of drug thereby resulting in disappearance from systemic circulation), the plasma concentrations of these subjects were similar at both of these time points. It was observed that such PK profiles were concentrated at few centers. The model parameters were estimated with and without data from these centers as a part of sensitivity analysis to gauge impact of data from these centers on population PK parameters. Sensitivity analyses were performed by estimating the population PK parameters with the structural model by including and excluding those outlier data for above two cases of outlier data. It was observed that the population PK parameter estimates obtained from the model that excluded these subjects/centers from the dataset were close to estimates obtained by including all such data. As expected, the variability estimates were higher when the data were excluded from the analyses. Since the overall fit of the model to the data and population PK parameters remain unchanged, the entire dataset was used for modeling purpose. None of the available PK concentrations were excluded from final analyses for being outliers.

Figure 5. Plasma concentration data for the population PK analysis of UMEC and VI



Handling Concentration Data for Unintended Analyte: About 1-2% of samples (in the analysis dataset) were for the analyte that was not administered to the individual subject. (For example, samples from UMEC mono treatment exhibiting VI concentration and vice versa).

Every attempt was made to resolve this issue starting with querying clinical site, confirming shipping and handling procedures, reanalyzing the samples if possible and/or to identify the source of any contamination during sample handling/analysis or other reasons. The data of the unintended analyte was not included in the datasets. The data of the analyte from the randomized treatment were incorporated into the analyses datasets. (For example, some samples exhibited UMEC and VI concentrations when the subject was on UMEC monotherapy. In such scenario only UMEC data was included in the dataset).

Handling Placebo Samples: In the early stages of ongoing bioanalysis for study DB2113361, 220 samples from subjects on placebo regimen were analyzed (approximately 13% of placebo samples and 2.5% of total study samples) and for study DB2113373, 33 samples from subjects on placebo regimen were analyzed (approximately 2% of placebo samples and 0.3% of total study samples) None of these samples showed active drug concentrations for either UMEC or VI. Analysis of any further placebo samples was immediately discontinued following this finding.

Handling Pre-dose Samples: Pre-dose samples were collected (from each subject on Day 1) before the beginning of the study treatment. There were 1609 samples collected and analyzed for UMEC, of which 1449 samples (90%) were below quantification limit and about 10% of samples had quantifiable UMEC concentrations ($>$ BQL). There were 1619 samples collected and analyzed for VI, of which 1440 samples (89%) were below quantification limit and about 11% of samples had quantifiable VI concentrations ($>$ BQL). Every attempt was made to resolve this issue starting with querying clinical sites for any anomalies, querying recording of dosing and sampling times, confirming shipping and handling procedures, reanalysing samples if possible and/or to identify the source of any contamination during sample handling/analysis or other reasons. There is no physiological explanation for presence of drug levels in these samples. Since the post-dose sample was to be taken within 0-15 minute window post inhalation, such occurrence of pre-dose concentrations may be attributed to inaccurate sampling time and/or sampling very close to or immediately after inhalation of test drug. These data were present in the dataset but were excluded from the analyses. These quantifiable pre-dose UMEC samples are listed in the population PK report.

Covariates Analysis: Total 11 covariates were included in the UMEC and VI population PK datasets and were tested during the population PK modeling process. They are: Age, Body Weight, Gender, Race, Percent Predicted Baseline FEV1, Influence of UMEC on VI PK and vice versa, Inhaled Corticosteroids, Post Albuterol/Salbutamol Reversibility, Post Albuterol/Salbutamol and Ipratropium Reversibility, Baseline Creatinine Clearance and Smoking Status. The concomitant medications are described in detail in the Section 11.4.1 of the population PK Reporting and Analysis Plan. It was noted that less than 2% of the subjects took any of the concomitant medications described as strong inhibitors of CYP3A4 (n=17 subjects), CYP2D6 (n=13 subjects) or Pgp (n=0). Hence, the effect of these concomitant medications on UMEC and VI population PK was not tested. For categorical covariates such as RACE, only the subgroups with reasonably sufficient number ($>$ 5% of total population) were tested.

Potential covariate relationships were primarily explored graphically using the individual inter-individual variability (ETAs) versus covariate plots. After addition of any covariate on the population PK parameters, changes in GOF plots, plausibility of population PK parameters,

precision of estimates, physiologic relationship of the covariate to the parameter and change in the minimum objective function value were used collectively to arrive at the decision of including or excluding the covariate from the final model. If a trend/correlation was observed in the ETA versus covariate plot for any particular covariate, that covariate was subsequently tested by adding it to the structural model. If the resulting model had a lower objective function value (greater than 3.84 points for chisquare distribution and $df=1$ at p value 0.05) and/or the trend in the ETA versus covariate plot disappeared, the covariate was include and tested with other significant covariates in the final model. Change in objective function was also used to evaluate the final model by eliminating each covariate, one at a time from the final model (backward elimination). If after eliminating the covariate, the objective function value increased by more than 6.62 points (for chi-square distribution and $df=1$ at p value 0.01) the covariate was retained in the model. The inclusion of covariates was collectively determined by the goodness-of-fit criteria discussed above.

Handling BQL Data: Approximately 20-25% of the data (in the UMEC and VI PK dataset) were below quantification limit (BQL). The maximum likelihood methods implemented in NONMEM were used to analyze such BQL data [Ahn, 2008]. Actual sampling times were used in the dataset for all concentration data. The Stochastic Approximation Expectation Maximization (SAEM) with interaction was the method used in NM 7.1 for UMEC and VI population PK analyses. Under this method, the BQL data was considered to be censored. The F_FLAG method in NM 7.1 was used to estimate the likelihood for BQL data while simultaneously fitting and estimating the model parameters using the data above BQL.

Population PK Analysis Scheme: The schematic for population PK analyses for each analyte is Exploratory Graphs → Structural Model → ETA versus Covariate Plots → Covariate Addition → Full Model → Covariate Elimination → Final Model.

Structure Model: Observed analyte concentration–time profiles from the subset of subjects with serial sampling were utilized to decide the initial population PK model. No covariates were included in the structural model. The goodness-of-fit (GOF) plots, residual plots, standard error of parameters and distribution of individual population PK parameters were primarily used to evaluate the fit of the structural model to the data. The structural base model was also used to estimate the population PK parameters and perform sensitivity analyses by excluding data from certain centers and /or subjects.

Model Validation: The final model performance was evaluated by visual predictive check (VPC) [Holford, 2005]. This involved simulating new trial replicates (at least $n=100$) with the final model. The 5th, 50th and 95th percent model predictions obtained by simulating the model were plotted to generate the 90% prediction interval which was overlaid with the observed data to evaluate the model performance. Similar approach was taken to evaluate the model performance in terms of predicting the proportion of BQL data. The predicted proportion of data to be BQL was compared to the actual observed BQL proportion over time by using VPC plots.

Simulating Exposure: For each analyte, the final population PK model was used to simulate exposure parameters such as area under the concentration-time curve (AUC) using the individual PK parameters generated by the post hoc step. This involved estimating individual subject AUCs by dividing the analyte dose by the post-hoc inhaled clearance ($AUC = \text{Dose} \cdot F / CL$). The C_{max} for each analyte was obtained by simulating individual concentration – time profiles using the parameter and variability estimates from the final population PK model.

3.1.2 Results

The final 2-compartment model parameters for UMEC and VI are presented in Table 5. The individual apparent inhaled clearance and apparent volume of distribution for UMEC in the final model are listed below.

$$(CL/F)_{ind} = (CL/F)_{pop} * (WT_{ind}/70)^{0.16} * (Age_{ind}/60)^{-0.731} * (CrCl_{ind}/110)^{0.271}$$

$$(V2/F)_{ind} = (V2/F)_{pop} * (WT_{ind}/70)^{0.616}$$

Weight on UMEC Exposure: For every 10% increase in weight the CL/F increased approximately by 2%. A 60-year individual with twice the average weight (140 kg) will have about 10-12% higher CL/F as compared to a 60-year individual weighing 70 kg. The apparent volume of distribution of central compartment V2/F increased approximately 6% for every 10% increase in body weight from 70 kg. The effect of weight on UMEC exposure is marginal and does not warrant any dose adjustment.

Age Effect on UMEC Exposure: For every 10% increase in age from 60 years of age, the CL/F decreased by approximately 7%. The effect of age on UMEC exposure is marginal and does not warrant any dose adjustment.

Creatinine Clearance Effect on UMEC Exposure: the CL/F decreased by approximately 3% with every 10% decrease in creatinine clearance from 110 mL/min. The effect of creatinine clearance on UMEC exposure is marginal and does not warrant any dose adjustment.

The individual apparent inhaled clearance for VI in the final model is listed below.

$$(CL/F)_{ind} = (CL/F)_{pop} * (WT_{ind}/70)^{0.192} * (Age_{ind}/60)^{-0.398} * (CrCl_{ind}/110)^{0.271}$$

Weight on VI Exposure: For every 10% increase in weight the CL/F increased approximately by 2%. A 60-year individual with twice the average weight (140 kg) will have about 14% higher CL/F as compared to a 60-year individual weighing 70 kg. The effect of weight on VI exposure is marginal and does not warrant any dose adjustment.

Age Effect on VI Exposure: For every 10% increase in age from 60 years of age, the CL/F decreased by approximately 4%. The effect of age on VI exposure is marginal and does not warrant any dose adjustment.

VPC: Visual predictive checks were performed by simulating the final model. The VPC displays 90% prediction intervals for UMEC or VI concentrations at steady state over a dosing interval. The observed UMEC or VI data was overlaid on the 90% prediction intervals from model simulations. The model was able to predict most of the data well except for the unexpectedly high concentrations observed from the 23-24 hour window. This may be explained by the fact that the dosing time for these samples was reported by the subjects as detailed in Section 3.1.1. The simulations were also used to compare the predicted and observed proportion of BQL data. The model performed reasonably except for over-predicting BQL observations around 23-24 hour post-dose window which is explained in Section 3.1.1.

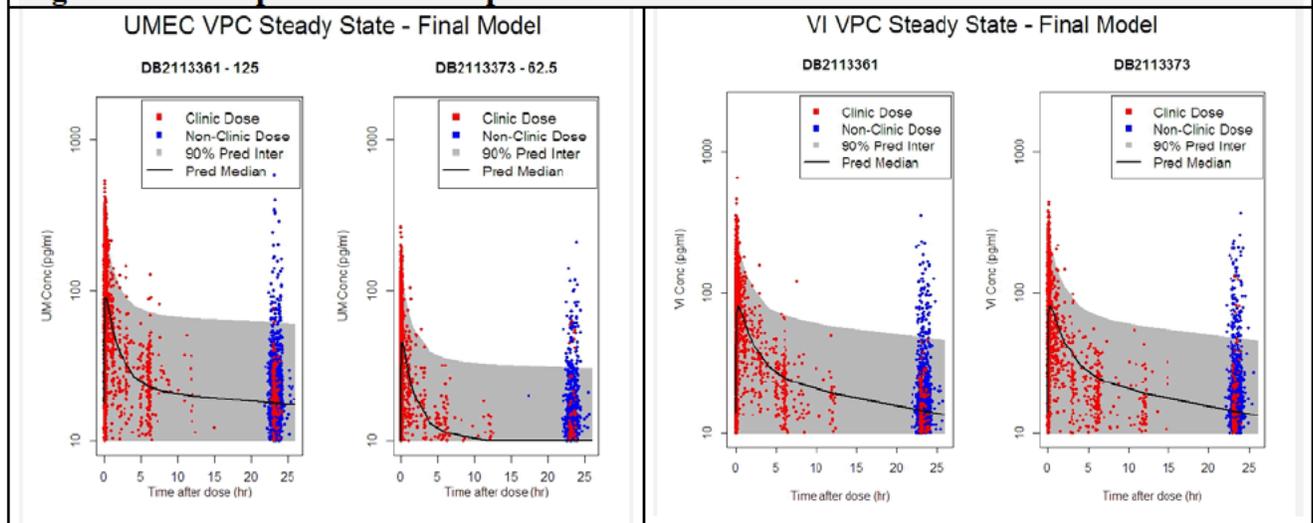
3.1.3 Conclusion

- Both UMEC and VI PK can be best described by a two-compartment model with first order absorption. The population PK parameters and associated inter individual variability were adequately characterized. There was no apparent PK interaction with co-administration of UMEC with VI
- Weight, age and creatinine clearance were statistically significant covariates on apparent inhaled clearance (CL/F) of UMEC and weight was significant covariate on UMEC

volume of distribution (V2/F). Weight and age were statistically significant covariates on VI apparent inhaled clearance (CL/F). However, the magnitude of effect of these covariates on UMEC and VI PK is marginal and therefore do not warrant any dose adjustment based on these covariates.

- No other covariates such as gender, post albuterol/salbutamol reversibility, post albuterol/salbutamol and ipratropium reversibility, use of inhaled corticosteroids at screening, smoking status, race, and percent predicted baseline FEV1 had significant effect on UMEC and VI PK parameters.
- There was no apparent trend between observed maximum heart rate and model predicted Cmax (or highest observed concentrations) for both, UMEC or VI.

Figure 6. Visual predictive check plots for UMEC and VI



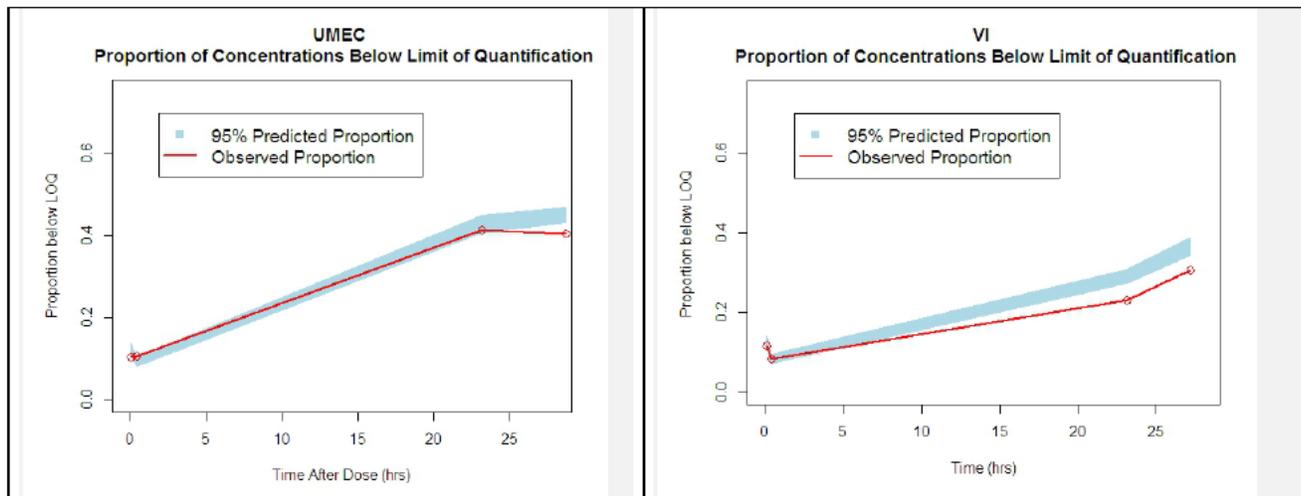
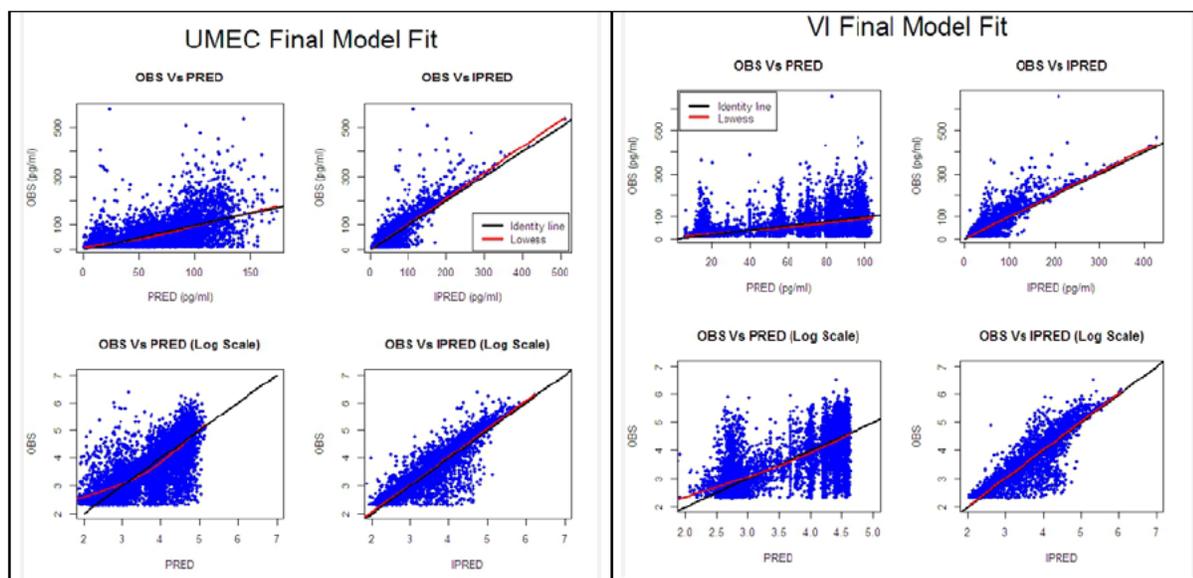


Figure 7. Goodness of Fit plots for the Final UMEC and VI Population PK Model



Reviewer's comments: A population PK analysis assessing the covariate effects on VI and UMEC exposure was performed using population PK methodology. Residual diagnostics based on the sponsor's analyses showed that the model fitted the data well. With regard to the covariates chosen, the reviewer's independent analysis of UMEC and VI resulted in similar results with similar parameter estimates. The reviewer's conclusions and interpretations were based on population PK analysis results.

In the population PK report for UMEC/VI submission (NDA 203975), a two-compartment linear model, with first-order absorption and first order elimination was found adequately described the VI concentration-time data. However, in the population PK report for Fluticasone furoate (FF)/VI submission (NDA 204275), a three-compartment linear model, with zero-order absorption and first order elimination was found adequately described the VI concentration-time data. In both submissions, the final population PK models incorporated the effect of age, weight on CL/F for subjects with COPD. Although the models are different, the final conclusion about covariate effect on VI exposure remains similar.

4 Reviewer's Analysis

4.1 Objectives

Analysis objectives are:

1. To verify the dose and frequency selection of UMEC/VI for Phase III studies.
2. To find out if the selected dose regimens of UMEC/VI for COPD patients appropriate.

4.2 Methods and Software

For Objectives 1 and 2, TIBCO Spotfire S-PLUS 8.0 was used for data organization, as well as graphical and statistical analysis based on sponsor's datasets.

For Objective 3, TIBCO Spotfire S-PLUS 8.0 was used for data organization, as well as graphical analysis based on sponsor's population PK results.

4.2.1 Data Sets

Data sets used are summarized in Table .

Table 8. Analysis Data Sets		
Study Phase	Dataset Names	Link to EDR
Data from Phase 2 monotherapy studies	umec3073AE.xpt umec3089AE.xpt umec5321AE.xpt umec5408AE.xpt umec3073eff.xpt umec3089eff.xpt umec5321eff.xpt umec5408eff.xpt vi1045AE.xpt vi9575AE.xpt vi1045eff.xpt vi9575eff.xpt	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\UMEC-VI_NDA203975_HL\Sponsor's data and reports\Phase2
Data from Phase 3 UMEC/VI combination studies	umecvi3360AE.xpt umecvi3361AE.xpt umecvi3373AE.xpt umecvi3374AE.xpt umecvi4417AE.xpt umecvi4418AE.xpt umecvi3360eff.xpt umecvi3361eff.xpt umecvi3373eff.xpt umecvi3374eff.xpt umecvi4417eff.xpt umecvi4418eff.xpt	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\UMEC-VI_NDA203975_HL\Sponsor's data and reports\Phase3

4.2.2 Software

TIBCO Spotfire S-PLUS 8.0 was used for data organization, as well as graphical and statistical analysis.

4.2. Pharmacogenomics Review

NDA/BLA Number	203975
Submission Date	12/18/2012
Applicant Name	Glaxo Group LTD England dba Glaxosmithkline
Generic Name	Umeclidinium and vilanterol
Proposed Indication	Chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema
Primary Reviewer	Sarah Dorff, Ph.D.
Secondary Reviewer	Michael Pacanowski, Pharm.D., M.P.H.

1 Background

Umeclidinium bromide, a long-acting muscarinic antagonist (LAMA), and vilanterol, a long-acting beta₂ agonist (LABA), are proposed in combination for the treatment of chronic obstructive pulmonary disease (COPD). *In vitro* studies indicated that umeclidinium is metabolized by the polymorphic CYP2D6 and vilanterol is metabolized by CYP3A4. The applicant assessed differences in umeclidinium pharmacokinetics (PK) based on CYP2D6 phenotype in healthy subjects. No difference in exposure based on CYP2D6 phenotype was observed, and the applicant has proposed labeling to this effect. The purpose of this review is to evaluate the role of CYP2D6 phenotype on umeclidinium exposure and whether these results are appropriate to include in labeling.

2 Submission Contents Related to Genomics

The applicant submitted the following report related to CYP2D6 phenotype effects on umeclidinium PK:

Table 1. Studies with subject-level CYP2D6 phenotype data

Report ID	Title
GM2008/00374/00 (Study AC4110106)	A single centre, randomised, double-blind, dose ascending, placebo-controlled study, in two parts, to evaluate the safety, tolerability and pharmacokinetics of escalating single and repeat inhaled doses of GSK573719 and placebo formulated with the excipient magnesium stearate, in healthy subjects and in a healthy population of Cytochrome P450 Isoenzyme 2D6 poor metabolisers.

The applicant conducted a phase 1 study to evaluate escalating single and repeat doses of umeclidinium (100 µg, 500 µg, and 1000 µg) in healthy subjects according to CYP2D6 phenotype. The study was comprised of two parts, with subjects assigned based on their genotype-derived phenotype. Genotyping was performed using the Roche AmpliChip CYP450 test. Part 1 enrolled 20 healthy subjects (HVT) to include ultra-rapid metabolizers (UM, N = 1), extensive metabolizers (EM, N = 16), or intermediate metabolizers (IM, N = 3). All HVT

subjects received placebo or escalating single umeclidinium doses of 100 µg, 500 µg, and 1000 µg followed by a repeat dose (7 days) of placebo, 500 µg or 1000 µg (Table 2). Part 2 consisted of 16 subjects determined to be poor metabolizers (PM) split into two cohorts. Cohort I received a single dose followed by a repeat dose (7 days) of umeclidinium at first 100 µg and then 500 µg, or matched duration placebo. Cohort II followed the same design and dosing schedule as Cohort I using umeclidinium doses of 500 µg and 1000 µg (Table 3).

Table 2. Randomization Sequence for Part 1 (HVT)

Sequence	Period 1 SD	Period 2 SD	Period 3 SD	Period 4 RD
1 (8 subjects)	100 µg	500 µg	1000 µg	500µg
2 (8 subjects)	100 µg	500 µg	1000 µg	1000 µg
3 (4 subjects)	Placebo	Placebo	Placebo	Placebo

SD, Single Dose. RD, Repeat Dose for 7 days.

Table 3. Randomization Sequence for Part 2 (PM)

Cohort	Sequence	Period 1 SD	Period 2 RD	Period 3 SD	Period 4 RD	Period 5 SD	Period 6 RD
I	1 (6 subjects)	100mcg	100mcg	500mcg	500mcg	X	X
	2 (2 subjects)	Placebo	Placebo	Placebo	Placebo	X	X
II	3 (6 subjects)	X	X	500mcg	500mcg	1000mcg	1000mcg
	4 (2 subjects)	X	X	Placebo	Placebo	Placebo	Placebo

SD, Single Dose. RD, Repeat Dose for 7 days.

3 Key Questions and Summary of Findings

3.1 Does CYP2D6 phenotype affect umeclidinium PK?

Clinically relevant effects of CYP2D6 phenotype on umeclidinium PK were not observed in a prospectively designed healthy subject study.

3.1.1 Applicant's analysis

The PK parameters of umeclidinium in CYP2D6 HVT and PM subjects are summarized in Table 4 and Figure 1. There was no difference between CYP2D6 phenotypes at any dose during the single dosing periods. After multiple dose treatments, C_{max} and AUC did not differ between CYP2D6 HVTs and PMs at the 500 µg and 1000 µg doses. Repeat dosing at 100 µg was not performed in HVTs, precluding comparison at this dose. The applicant concluded that there is no clinically relevant difference in exposure based on CYP2D6 phenotype (Table 5). However, the applicant did note that PMs receiving the 1000 µg repeat dose had a 47% increase in umeclidinium exposure [Ae(0-24)].

Table 4. Umeclidinium PK parameters by predicted CYP2D6 phenotype after single- and multiple-dose administration

Dose	PK parameter	Phenotype			
		Single Dose		Multiple Doses (7 days)	
		HVT	PM	HVT	PM
100 µg	N	16	6	-	6
	Cmax (ng/mL)	0.075 (0.051, 0.110)	0.111 (0.069, 0.179)	-	0.168 (0.106, 0.266)
	AUC(0-t) (h*ng/mL)	0.016 (0.011, 0.230)	0.022 (0.009, 0.053)	-	0.085 (0.053, 0.136)
	Ae(0-24) (ng)	600.104 (496.609, 725.167)	573.980 (430.362, 765.525)	-	3194.947 (2526.311, 4040.549)
500 µg	N	16	12	8	11
	Cmax (ng/mL)	0.655 (0.534, 0.803)	0.793 (0.687, 0.915)	1.458 (1.095, 1.942)	1.145 (0.935, 1.402)
	AUC(0-t) (h*ng/mL)	0.420 (0.330, 0.535)	0.491 (0.378, 0.639)	2.415 (1.930, 3.022)	2.441 (2.103, 2.833)
	Ae(0-24) (ng)	5055.417 (4293.014, 5953.217)	5846.184 (5112.129, 6685.642)	16130.340 (13232.766, 19662.395)	16614.831 (14107.423, 19567.898)
1000 µg	N	16	6	8	6
	Cmax (ng/mL)	1.565 (1.310, 1.870)	1.588 (1.036, 2.435)	1.756 (1.073, 2.873)	1.865 (1.215, 2.862)
	AUC(0-t) (h*ng/mL)	2.045 (1.628, 2.570)	2.426 (1.607, 3.663)	3.575 (2.795, 4.574)	4.763 (3.623, 6.261)
	Ae(0-24) (ng)	12578.789 (11111.074, 14240.383)	13307.637 (9615.202, 18418.042)	30316.365 (20936.129, 43899.327)	40845.998 (31502.707, 52960.387)

Data are presented as geometric mean (95% confidence interval).

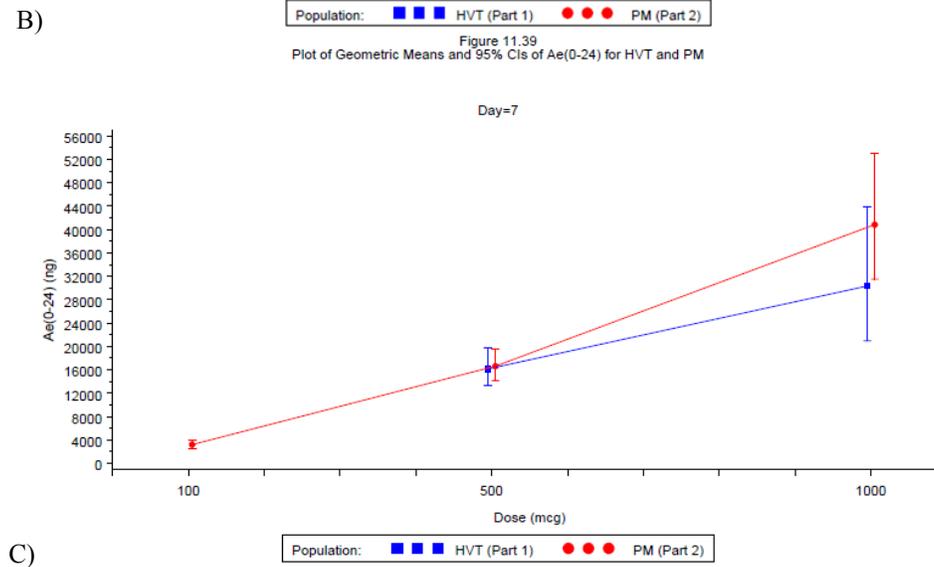
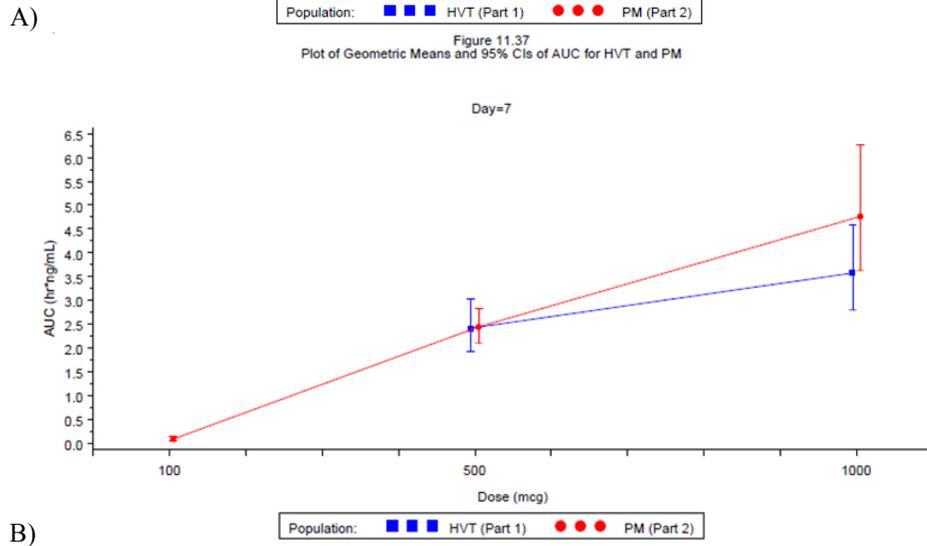
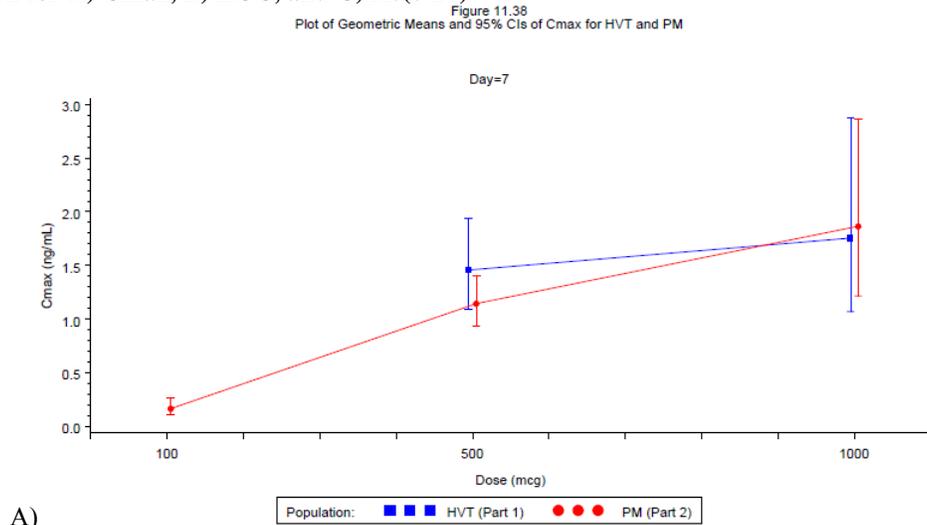
Data Source Tables 11.12 & 11.2.

Table 5. Analysis of Derived Parameters after Multiple Doses (7 days) to Assess Differences in Exposure between PM and HVT

Treatment Comparison Dose PM vs HVT	PK parameter	Ratio of Adjusted Geometric Means (90% CI)
500 µg	Cmax (ng/mL)	0.800 (0.594, 1.078)
	AUC(0-t) (h*ng/mL)	1.029 (0.789, 1.343)
	Ae(0-24) (ng)	1.012 (0.816, 1.255)
1000 µg	Cmax (ng/mL)	1.072 (0.761, .511)
	AUC(0-t) (h*ng/mL)	1.331 (0.978, 1.811)
	Ae(0-24) (ng)	1.466 (1.147, 1.875)

Source: Table 11.21 & 11.22.

Figure 1. Plots of umeclidinium PK parameters by predicted CYP2D6 phenotype after multiple-dose administration for A) Cmax, B) AUC, and C) Ae(0-24)



C)

4 Summary and Conclusions

The applicant prospectively evaluated umeclidinium PK according to CYP2D6 phenotype. CYP2D6 phenotype does not significantly affect umeclidinium exposure at the 500 µg dose. While the 1000 µg dose suggested higher concentrations of umeclidinium in subjects who were CYP2D6 poor metabolizers, this is not expected to be clinically relevant based on the applicant's proposed dose of 62.5 µg. The reviewer concurs with the applicant's assessment and no dose adjustment is needed based on CYP2D6 phenotype.

5 Recommendations

The submission is acceptable from a Genomics and Targeted Therapy Group perspective.

5.1 Post-marketing studies

None

5.2 Label Recommendations

Recommended changes to sections of the umeclidinium and vilanterol label that include references to CYP2D6 are summarized below:

12.3 Pharmacokinetics

(b) (4)

Metabolism: Umeclidinium: In vitro data showed that umeclidinium is primarily metabolized by the enzyme cytochrome P450 2D6 (CYP2D6) and is a substrate for the P-glycoprotein (P-gp) transporter. The primary metabolic routes for umeclidinium are oxidative (hydroxylation, O dealkylation) followed by conjugation (e.g., glucuronidation), resulting in a range of metabolites with either reduced pharmacological activity or for which the pharmacological activity has not been established. Systemic exposure to the metabolites is low.

(b) (4) *Cytochrome P450 2D6*: In vitro metabolism of umeclidinium is mediated primarily by CYP2D6. However, no clinically meaningful difference in systemic exposure to umeclidinium (~~500-mcg~~) was observed following repeat daily inhaled dosing (b) (4) in CYP2D6 normal (ultrarapid, extensive, and intermediate metabolizers) and (b) (4) poor metabolizer subjects (see-Figure 1 (b) (4))

4.3. Individual Study Review

Note –

In this review, early development names GW642444 is used to refer to vilanterol (VI), and GSK573719 is used to refer to Umeclidinium bromide (UMEC).

ADME In-Vitro STUDIES

Absorption and Transporters

UMEC

Report # WD2006/02657

Title: in vitro investigation of the potential for human P-glycoprotein (P-gp) to transport 14C-GSK573719 (as the bromide salt) using stable transfected MDCKII-MDR1 cells

Objective: To determine whether GSK573719 is a substrate for human P-glycoprotein (P-gp)

Method: Directional transport was determined by measurement of apical to basolateral ([A→B]) and basolateral to apical ([B→A]) rates of transport using 3 mcM 14C-GSK573719 in the absence and presence of 2 mcM GF120918, a potent P-gp inhibitor. The passive membrane permeability of 14C-GSK573719 was determined in the presence of GF120918 over pH range of 5.5 to 7.4 with samples being analysed for radioactivity. A positive control, 3H-amprenavir, was incorporated into all assays and monolayer integrity of the MDCKII-MDR1 cells was assessed using the fluorescent para-cellular marker lucifer yellow CH (100 mcM).

Results and Conclusions: GSK573719 was a substrate of human P-gp, with an apical efflux ratio ranging from 7 to 17 and 0.8 in the absence and presence of inhibitor, respectively. GSK573719 was determined to have low passive membrane permeability (average pH7.4) of 2.4 ± 0.8 nm/s. The passive membrane permeability of GSK573719 was not affected over the pH range investigated. The mass balance for 14C-GSK573719 was 76% for one plate (B→A direction only), however, this did not affect the conclusion that GSK573719 is a substrate for P-gp.

Report #WD2006/02596

Title: *In vitro* inhibition of P-gp by GSK573719 using stable transfected MDCKII-MDR1 cells.

Objective: To assess the ability of GSK573719 to inhibit human P-gp using stable transfected MDCKII-MDR1 cells.

Method: The effect of GSK573719 on the P-gp-mediated transport of [3H]-digoxin was assessed by determining the basolateral to apical ([B→A]) transport of [3H]-digoxin at 90 minutes in the absence or presence of GSK573719 at target concentrations of 0.1, 0.3, 1, 3, 10, 30 and 100 mcM (applied in both apical and basolateral wells). GF120918 (potent P-gp inhibitor) was included at 2 mcM as a positive control for P-gp inhibition. Samples from the transport studies were analysed for radioactivity using LSC. A

Results and Conclusions: GSK573719 did not inhibit transport of digoxin via human P-gp in vitro at concentrations up to 100 mcM and is not a P-gp inhibitor.

Report WD2010/00669

Title: An in vitro Investigation of the Transport of C4C]GSK573719 Bromide via Human OCT1, OCT2, OCT3, OCTN1 and OCTN2 Expressing Cell Systems

Objective: To assess whether GSK573719 is a substrate of human organic cation transporters using a human embryonic kidney (HEK293) cell line stably transfected with OCT1, OCT2, OCT3, OCTN1 or OCTN2 genes

Methods: All experiments were performed at pH 7.4 and 37°C. Initially, the uptake time course of 14C-GSK573719 was assessed at 1.8 mcM up to 60 minutes for each human organic cation transporters and the appropriate time point was selected for subsequent assessments. The uptake of 14C-GSK573719 by OCT1 and OCT2 and mock cells was further assessed over a concentration range of 1 to 100 mcM for up to 15 minutes in the presence of inhibitors 1-methyl-4-phenylpyridinium (MPP+) and cimetidine (histamine H2 receptor antagonist) for OCT1 and OCT2, respectively. The effect of sodium ions on the uptake of 14C-GSK573719 by OCTN1 or OCTN2 was also assessed.

Results and Conclusions: GSK573719 was a substrate for the human organic cation transporters OCT1 and OCT2, but not for OCT3, OCTN1 or OCTN2. Kinetic parameters were derived for OCT1 and OCT2, for OCT1 Km and Vmax were 4.42 mcM and 476 pmol/mg/protein/3 minutes, respectively, whilst for OCT2 the values were 0.157 mcM and 61 pmol/mg/protein/15 minutes, respectively. Uptake of GSK573719 by OCT1 and OCT2 was shown to be inhibited by both MPP+ and cimetidine with IC50 values of 105 mcM and 1.4 mcM, respectively, for OCT1, and 535 mcM and 103 mcM, respectively, for OCT2. Although a decrease in the uptake of GSK573719 by OCTN2 in the absence of sodium ions was observed, this was considered irrelevant as no difference was observed between cells expressing OCTN2 and mock cells.

VI

Report # WD2004/00106/00

Title: An In Vitro Investigation of Both the Transport Via Heterologously Expressed Human P-glycoprotein and the Passive Membrane Permeability of GW642444 in MDCKIIMDR1 Cells (Study No. 03DMW122)

Objective: To determine whether GW642444 is a substrate of human P-glycoprotein.

Method: The permeation of GW642444 through MDCKII-MDR1 monolayers in the absence and presence the Pgp-inhibitor GF120918 (2 μ M) was assessed by determining the apical to basolateral ([A→B]) and basolateral to apical ([B→A]) transport of GW642444 by polarized Madin-Darby canine kidney MDCKII-MDR1 cells transfected with the human MDR1 gene, which produces Pgp. Concentrations of GW642444 in each well were determined using HPLC-MS/MS.

Results: The apical efflux ratio of GW642444 at 0.5 μ M was determined as ≥ 25.7 and 0.5 in the absence and presence of P-gp inhibitor GF120918A, respectively. Under the assay conditions used, GW642444 is a substrate of human P-glycoprotein and was determined to have low passive membrane permeability (average $P_{7.4}$ of 34 ± 13 nm/s).

Results of Human P-glycoprotein-mediated Transport Studies for GW642444 in MDCKII-MDR1 Cell Monolayers

Compound	Rate A→B (nmoles/h/cm ²)	Rate B→A (nmoles/h/cm ²)	Apical Efflux Ratio	P-gp Substrate	A→B Mass Balance (%)	B→A Mass Balance (%)	$P_{7.4}$ (nm/s)	Passive Permeability Class
0.5 μ M GW642444	0.0011 \pm 0.0000 ^a	0.0295 \pm 0.0038	≥ 25.7	Y	- ^a	57 \pm 4.9	-	-
0.5 μ M GW642444 + 2 μ M GF120918A	0.0080 \pm 0.0010	0.0031 \pm 0.0011	0.5	-	74 \pm 3.0	70 \pm 2.0	34 \pm 13	Low
3 μ M [³ H]-amprenavir	0.019 \pm 0.006	0.496 \pm 0.187	25	Y	95 \pm 1.7	89 \pm 2.1	-	-
3 μ M [³ H]-amprenavir + 2 μ M GF120918A	0.277 \pm 0.024	0.348 \pm 0.010	1.3	-	95 \pm 4.7	96 \pm 3.6	330 \pm 45	High

a. The A→B transport rates were calculated using the LLQ (0.2 ng/mL) for all three receiver well concentrations. Hence the mass balance for these wells cannot be calculated. Data are the mean \pm standard deviation from three monolayers, except for $P_{7.4}$ (where n=6).

All donor compartments contained lucifer yellow CH to determine monolayer integrity (pass criterion $P_{7.4} \leq 50$ nm/s) and wells designated for P-gp inhibition contained 2 μ M GF120918A in both donor and receiver compartments.

[³H]-amprenavir was used as positive control (pass criterion apical efflux ratio ≥ 15).

A compound is classified as a P-gp substrate if the apical efflux ratio in the absence of the P-gp inhibitor GF120918A is ≥ 2 and this efflux collapses to ~ 1 in the presence of the inhibitor.

Passive membrane permeability was classed as low (< 50 nm/s), moderate (50 - 250 nm/s) or high (> 250 nm/s)

(Source – Table 1, Report WD2004/00106/00)

Conclusions: GW642444 is a substrate of human P-glycoprotein.

Distribution

UMEC

Report #WD2008/00503

Title: Investigation of the plasma protein binding of GW642444 and blood cell association of [¹⁴C]-GW642444 in mouse, rat, guinea pig, rabbit, dog and human in vitro

Objective: To determine in vitro plasma protein binding of GSK573719

Methods: Plasma protein binding was determined using equilibrium dialysis following incubation at 37°C and the dialysis was stopped after 8 hours when equilibrium was achieved. The concentration of GSK573719 in the spiked plasma and dialysate was determined by HPLC-MS/MS.

Results and Conclusion: The plasma protein binding (87.6%, 85.6%, 76.4%, 80.2% and 87.9% in the mouse, rat, rabbit, dog and human, respectively) was moderate in all species and independent of concentration.

Report #2012N144582

Title: Investigation of the plasma protein binding of GW642444 and blood cell association of [¹⁴C]-GW642444 in mouse, rat, guinea pig, rabbit, dog and human in vitro

Objective: To determine in vitro plasma protein binding of GSK573719 in patients with renal and hepatic impairment.

Methods: In addition, the protein binding of GSK573719 (1 ng/mL) was also investigated in incubations with individual human plasma proteins: human serum albumin (40 mg/mL), α -acid glycoprotein (0.8 mg/mL) and γ -globulin (7 mg/mL) dissolved in phosphate buffered saline. Plasma protein binding was determined by equilibrium dialysis following incubation for 6 hours at 37°C. The concentration of GSK573719 in respective dialysates and original incubations were determined using (b) (4) by HPLC-MS/MS.

Results and Conclusions: Protein binding of GSK573719 was similar in incubations of plasma obtained from healthy male and female subjects as well as the renally and hepatically impaired human subjects ranging from 87.5 to 95.9% bound. GSK573719 was moderately bound to human serum albumin (67.2%), γ -globulin (64.6%) α -acid glycoprotein (84.9%), although the binding was slightly higher to α -acid glycoprotein.

VI:

Report #WD2006/02044/01

Title: Investigation of the plasma protein binding of GW642444 and blood cell association of [¹⁴C]-GW642444 in mouse, rat, guinea pig, rabbit, dog and human in vitro

Objective: To determine the plasma protein binding in vitro of GW642444 in mouse, rat, guinea pig, female rabbit, dog and human, and the blood cell association in vitro of [¹⁴C]-GW642444 in mouse, rat, guinea pig, female rabbit, dog and human.

Methods: Plasma protein binding: Incubation of GW642444 with plasma at 37°C for 10 minutes followed by equilibrium dialysis for 8 hours with concentrations determined by HPLC-MS/MS.

Blood cell association: Incubation of [¹⁴C]-GW642444 with whole blood at 37°C for 2 hours. Levels determined by radio-HPLC.

Results and Conclusion:

Protein binding: The extent of plasma protein binding was high and appeared to be consistent across the concentration range within all species investigated. The mean plasma protein binding of GW642444 was 94.3, 92.3, 98.9, 93.4, 98.7% and 97.2% in the mouse, rat, guinea pig, female rabbit, dog and human, respectively.

The Extent of Binding In Vitro of GW642444, at Various Concentrations, to Plasma Proteins in Mouse, Guinea Pig, Rat, Female Rabbit, Dog and Human

Concentration tested (ng/mL)	% Bound to plasma protein					
	Mouse	Guinea pig	Rat	Female rabbit	Dog	Human
5	92.8	NR	91.4	92.0	NR	96.4
25	94.6	98.8	92.2	93.2	98.7	97.3
125	95.1	98.8	92.9	93.6	98.8	97.4
625	94.6	99.0	92.8	94.9	98.6	97.5

NR = Protein binding value could not be determined due to concentrations being below LLOQ (<0.1 ng/mL)

(Source – summarized by this reviewer based on Table 1, Report WD2006/02044/01)

Red cell distribution: The extent of blood cell association was low to moderate and there was no evidence of any concentration dependence on association. The mean blood to plasma ratios of [¹⁴C]-GW642444 were 1.0, 1.1, 0.73, 1.0, 0.50 and 0.76 in mouse, rat, guinea pig, female rabbit, dog and human, respectively. The corresponding mean blood cell association values were 41.3, 55.9, 15.6, 41.4, 10.7 and 36.1%, respectively.

The Extent of Association In Vitro of [¹⁴C]-GW642444, at Various Concentrations, with Blood Cells in Mouse, Guinea pig, Rat, Female Rabbit, Dog and Human

Concentration tested (ng/mL)	Blood to plasma ratio of ¹⁴ C-GW642444					
	Mouse	Guinea pig	Rat	Female rabbit	Dog	Human
50	1.06	0.737	1.23	1.03	0.497	0.808 ± 0.02
200	0.972	0.739	1.08	1.01	0.496	0.739 ± 0.01
500	0.963	0.712	1.04	1.05	0.502	0.726 ± 0.03

1. Mean (± S.D.) data from 3 individuals

(Source – summarized by this reviewer based on Table 2, Report WD2006/02044/01)

Conclusion: Plasma protein binding of VI is around 97% and is not concentration dependent. Blood cell association of VI is low and is not concentration dependent.

Study # 2011N118910_00

Title: Determination of the protein binding of GW642444 in human plasma from healthy, hepatically impaired and renally impaired volunteers

Objective:

- To determine the *in vitro* plasma protein binding of GW642444 in human plasma from healthy, hepatically impaired and renally impaired volunteers
- To determine the degree of protein binding of GW642444 in phosphate buffered saline (PBS) solutions containing either albumin (40 mg/mL), alpha-acid glycoprotein (0.8 mg/mL) or gamma-globulin (7 mg/mL).

Methods: Plasma protein binding was determined using ultrafiltration following incubation for 15 minutes at 37°C. The concentration of GW642444 in respective ultrafiltrates and original incubations were determined by HPLC-MS/MS.

Results: Protein binding of GW642444 was higher (corresponding to lower free drug concentrations) in plasma obtained from renal and hepatic impaired subjects (93.3 –

95.8%) compared to healthy subjects ($P < 0.001$), as presented in the following table. Protein binding of GW642444 was moderately bound to human serum albumin (mean value = 60.3%) and α -acid glycoprotein (mean value = 60.8%), whereas the extent of binding to γ -globulins was low (mean value = 7.9%).

Protein binding for UMEC and VI in healthy and disease state plasma

	VI
Healthy male	89.1-91.7
Healthy female	88.7-90.9
Mild hepatic	93.9-94.1
Moderate hepatic	93.3-95.3
Severe hepatic	93.3-95.2
Severe renal	94.9-95.8

(Source – – summarized by this reviewer based on Table 1 and 2, Report 2011N118910_00)

Conclusion: Plasma protein binding of VI is not reduced in hepatic and renal impairment subjects.

In vitro Metabolism

UMEC

Study # 05DMW039

Title: An in vitro investigation of the metabolism of GSK573719 in human, rat and dog

Objective: to provide information on the likely routes of metabolism of GSK573719 in human, rat and dog using in vitro systems. In addition, an assessment of in vitro metabolic activation was also undertaken using human liver microsomes.

Method: [^{14}C]-GSK573719 was incubated at concentrations of 10 and 50 μM in the presence of hepatocytes up to 24 hours. Samples incubated at 10 μM for 24 hours were selected for analysis by radio-HPLC and HPLC-MS $_n$ to compare the metabolism of GSK573719 across species. [^{14}C]-GSK573719 was also incubated at concentrations of 0.01, 0.1 and 1 μM in the presence of human liver microsomes for 1 hour. Additionally, [^{14}C]-GSK573719 was incubated with human liver microsomes to estimate the potential for metabolic activation. Non-extractable radioactivity was quantified by exhaustive solvent washing.

Results: HPLC-MS of selected human hepatocyte samples revealed major peaks corresponding to O-dealkyl (M14), hydroxy (M33) and hydroxy methoxy (M34) GSK573719. Other metabolites detected were a hydroxy glucuronide (M21), a hydroxy methoxy glucuronide (M22), a hydroxy dimethoxy metabolite (M54), hydrated glutathione conjugates (M13/M45), two cysteine conjugates (M52/M53) and two hydrated cysteine conjugates (M59/M60), a methoxy O-sulfate conjugate (M49) and a

dihydrodiol (M51). Minor amounts of M14 were also detected in the drug only control. Radiometabolite profiles in each of the human hepatocyte samples studied varied considerably, although they were qualitatively similar for many of the components. The major metabolites were M14, representing 20% of the total metabolism, and M33 plus M34, which co-eluted, representing 23% of the total metabolism. Radiolabelled peaks M13/M60, M22/M51 and M59 represented 9, 8 and 5% of the total metabolism respectively. All other metabolites were present at <5% of total metabolism. Metabolites M21, M22, M45, M49 and M54 were only detected in one ((b) (4) 2”) of the five human hepatocyte preparations. This preparation showed markedly greater turnover than the other four preparations and also contained several unidentified components.

Conclusions: The main routes of metabolism in man are likely to be O-dealkylation of the molecule and hydroxylation. Other likely routes are conjugation with glutathione and methylation and/or glucuronidation of the hydroxylated metabolite.

Study #06DMW086

Title: A preliminary in vitro investigation into the human oxidative enzymology of GSK573719

Objective: to provide preliminary information on the human cytochrome P450 enzymes involved in the oxidative metabolism of GSK573719 metabolism in vitro.

Methods: [¹⁴C]GSK573719 was incubated at 0.075 µM with human liver microsomes and with microsomes expressing the individual cytochrome P450 enzymes: CYP1A1, 1A2, 2A13, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 and 3A5. Further incubations with human liver microsomes were performed in the presence and absence of the selective cytochrome P450 inhibitors furafylline (CYP1A2), montelukast (CYP2C8), sulphaphenazole (CYP2C9), benzylnirvanol (CYP2C19), quinidine (CYP2D6) and azamulin (CYP3A4). Metabolites were quantified by HPLC with radiometric detection and identified by mass spectrometry.

Results: In incubations with human liver microsomes in the presence of quinidine (a selective inhibitor of CYP2D6) the production of M33 was reduced to non-quantifiable levels. Inhibition of the production of M33 was not observed with any of the other specific inhibitors investigated. M33 was the major metabolite quantified in incubations with expressed CYP2D6. It was not detected in incubations with any of the other CYPs investigated. These data indicate that CYP2D6 is the major cytochrome P450 enzyme responsible for production of M33.

The production of M14 in incubations with [¹⁴C]GSK573719 and human liver microsomes in the presence of quinidine or azamulin (a selective inhibitor of CYP3A4) was reduced by 90% and 52%, respectively. Inhibition of the production of M14 was not observed with any of the other specific inhibitors investigated. M14 was quantified in incubations with expressed CYP2D6 and expressed CYP1A1 and, to a lesser extent, with expressed CYP3A4 (identification based on retention time only). The presence of M14 was detected by LC/MS_n in incubations with expressed CYP2E1, but was not quantified

by radio-HPLC. These data indicate that CYP2D6 and CYP1A1 are the major cytochrome P450 enzymes responsible for the production of M14, with CYP3A4 playing a minor role in its production.

Conclusions: The quantifiable *in vitro* metabolism of GSK573719 in human liver microsomes is mediated primarily by CYP2D6, with some contribution from CYP3A4. GSK573719 is also metabolised by the cytochrome P450 enzyme CYP1A1, which is known to be expressed extrahepatically.

VI

Report # 2011N121880_00

Title: An *in vitro* investigation into the intrinsic clearance of GW642444 by human liver, intestinal and lung microsomes.

Objective: To investigate the intrinsic clearance of GW642444 by human liver, intestinal, and lung microsomes *in vitro*.

Methods: Incubation of GW642444 with human liver, gastrointestinal and lung microsomes, with LC-MS/MS detection.

Results: The intrinsic clearance rates (CL_i) for GW642444 when incubated with human liver, intestinal or lung microsomes are shown in the following table. Clearance of GW642444 was rapid with human liver microsomes incubation, and slower with human intestinal microsomes. GW642444 was metabolically stable in human lung microsomes.

Metabolic Stability of GW642444 in Human Liver, Intestinal, and Lung Microsomes

Substrate	Microsomal System	Mean Intrinsic Clearance (n=3)	
		mL/min/mg protein	mL/min/g liver
GW642444	Pooled Liver Microsomes	2.1	111
	Pooled Intestinal Microsomes	0.45	-
	Pooled Lung Microsomes	<0.01	-

(Source – Table 1, Report WD2011N121880_00)

Conclusion: VI is not metabolized *in vitro* by the human lung microsomes.

Report # WD2006/02720/00

Title: A preliminary *in vitro* investigation into the human oxidative enzymology of GW642444. Study Number: 03DMW085

Objective: to provide preliminary information on the human cytochrome P450 enzymology of GW642444 metabolism *in vitro*.

Methods: Incubation of GW642444 (5 mcM) with human liver microsomal preparations (0.1 mg/mL) or bacosomes expressing individual CYPs (300 pM/mL) (37°C, pH 7.4, 10 minutes), with radioHPLC and HPLC/MSn detection.

Results: Metabolite M29 was the major metabolite accounting for a mean of 22% of total radioactivity. All other metabolites were present at levels of <4% total radioactivity. Production of all metabolites was NADPH dependant, indicating the involvement of cytochrome P450 enzymes. CYP inhibition experiment suggested that CYP3A4, with minor contributions from CYP2D6, is the major enzyme responsible for the production of M29, M31, M20 and M40.

Metabolites of GW642444

Metabolites Detected ^a	% of Radiochromatogram [Microsomes]	CYP Inhibited ^{b,c} (% Inhibition of Metabolite Production)	CYP (% of Radiochromatogram) [Bacosomes]
GW642444	52	-	1A1 (84); 1A2 (92); 2C8 (95); 2C9 (100); 2C19 (96); 2D6 (75); 2E1 (97); 3A4 (41); 2A13 (NQ); 3A5 (65) 2D6 (9.8); 3A4 (1.5)
M16	NQ	-	
M20	3.3	2C8 (12%); 2C19 (0%); 2C9 (1%); 2D6 (35%); 3A4 (100%); 1A2 (0%)	1A1 (5.2); 1A2 (NQ); 2C8 (1); 2C9 (NQ); 2C19 (NQ); 2D6 (2.9); 2E1 (1.4); 3A4 (20); 2A13 (NQ); 3A5 (21) 3A4 (NQ); 3A5 (NQ)
M26	NQ	-	
M29	22	2C8 (34%); 2C19 (29%); 2C9 (54%); 2D6 (50%); 3A4 (100%); 1A2 (16%)	1A1 (NQ); 3A4 (27); 3A5 (4.4)
M31	2.7	2C8 (49%); 2C19 (35%); 2C9 (35%); 2D6 (45%); 3A4 (100%); 1A2 (20%)	1A1 (1.2); 3A4 (7.3); 3A5 (3.8)
M32	NQ	-	1A1 (NQ); 2C8 (NQ); 2C9 (NQ); 2C19 (NQ); 2D6 (8.3); 3A4 (3.5); 3A5 (NQ)
M40	2.9	2C8 (100%); 2C19 (0%); 2C9 (7%); 2D6 (3%); 3A4 (100%); 1A2 (0%)	-
M47	NQ	-	-

Key:

a = Structures of metabolites are depicted in Table C8b.

b = Individual CYPs were inhibited using: 2C8 - Montelukast (1 mcM); 2C19 - Benzylnirvanol (5 mcM); 2C9 - Sulphaphenazole (10 mcM); 2D6 - Quinidine (1 mcM); 3A4 - Azamulin (5 mcM); 1A2 - Furafylline (10 mcM).

c = Test system: GW642444 (as the α-phenylcinnamate salt, GW642444H).

CYP = Cytochrome P450 isoenzymes.

HPLC/MSⁿ = High performance liquid chromatography with multiple mass spectrometry.

NQ = Not quantifiable by radio-HPLC.

(Source – Table 1, Report WD2006/027200/00)

Conclusion: The major routes of metabolism of GW642444 in human are mediated primarily by CYP3A4.

In vitro Enzyme Inhibition

UMEC

Study # RI04088 (Report No. CH2005/00950/00)

Title: A preliminary screen of the in vitro concentration-dependent inhibition of human cytochrome P450 enzymes by GSK573719A.

Objectives and Methods: To determine the in vitro concentration dependent inhibition of human cytochrome P450 enzyme by GSK573719A. The rate of fluorescent metabolite production was determined for each well of the 96-well plate. Results from each unknown (GSK573719A and miconazole) well were expressed as a percent of the mean rate from the control (methanol) wells. Any control wells exhibiting a percent of the mean control rate of <85% or >115% were excluded from the mean. Percent control

activity versus GSK573719A or miconazole concentration plots were generated and fitted with the GraFit (Version 5.0) software program. The inhibitor concentration that resulted in 50% inhibition (IC₅₀) of enzyme activity was calculated.

Results and Conclusion: GSK573719A demonstrated a marked direct inhibitor of CYP2D6 activity (IC₅₀ = 0.1 μM) and CYP3A4 (IC₅₀ = 1.0 μM for DEF and 8.0 for 7BQ) activities. GSK573719A did not demonstrate inhibition of CYP1A2, CYP2C19, and CYP2C9. The IC₅₀ values for miconazole (positive control) obtained in these studies were consistent with the IC₅₀ values typically observed for miconazole in these assays.

VI

Study # SH2003/00040/00

Title: GW642444: The Preliminary Pharmacokinetics of GW642444

Objectives and Methods: GW642444 was submitted to the screen for assessment of the potential for inhibition of various cytochrome P450 isoforms. The details of methodology were not reported.

Results: GW642444 is an in vitro inhibitor of CYP3A4 (lowest mean IC₅₀ of 4 μM following duplicate determinations using two different probes) and a weak in vitro inhibitor of CYP2D6 (IC₅₀ of 12 μM).

The In Vitro Inhibition of CYP 450 Isoforms by GW642444 (n=2 Occasions)

CYP 450 Isoform	IC ₅₀ Value (μM)
CYP1A2	>100 ¹ >100 ¹
CYP2C9	23 ² >100
CYP2C19	70 ³ >100
CYP2D6	11 12
CYP3A4 (substrate = DEF)	4.9 ² 3.5
CYP3A4 (substrate = 7BQ)	14 8

1. Interference with assay
2. Concerns about quality of IC₅₀ curve
3. Significant concerns about quality of IC₅₀ curve

(Source – Table 13, Report SH2003/00040/00)

Conclusion: VI is unlikely to inhibit CYP 450 enzymes at clinically relevant dose.

Study # WD2007/01087/00

Title: An in vitro investigation of the inhibition by GW642444 of xenobiotic transport via human P-glycoprotein, heterologously expressed in MDCKII cells.

Objective: To determine the in vitro inhibition of human P-glycoprotein (Pgp) mediated transport by GW642444, in MDCKII cells heterologously expressing human Pgp.

Methods: The effect of GW642444 on the Pgp-mediated transport of digoxin (30 nM) was assessed by determining the basolateral to apical ([B→A]) transport of 3H-digoxin by polarized MDCKII-MDR1, which produces Pgp. Levels of 3H-digoxin in receiver wells were determined using liquid scintillation counting.

Results: GW642444 inhibited digoxin transport at the highest tested concentration of 100 μM, as presented in the following table.

The Effect of GW642444 on Human Pgp Mediated Transport of 30 nM [3H]-Digoxin, using MDCKII-MDR1 Cells

Compound	Conc. (μM)	Digoxin transport rate (pmole/cm ² /h) ± SD	Digoxin transport rate (% control) ± SD
GW642444	0.10	2.6 ± 0.17	100 ± 6.5
	0.30	2.6 ± 0.045	100 ± 1.7
	1.0	2.6 ± 0.27	98 ± 10
	3.0	2.5 ± 0.24	96 ± 9.3
	10	2.6 ± 0.045	100 ± 1.7
	30	2.5 ± 0.40	98 ± 15
	100	1.9 ± 0.15	74 ± 5.8
Digoxin Only	-	2.6 ± 0.081	100 ± 3.1
GF120918	2	0.50 ± 0.045	19 ± 1.7

SD is standard deviation.

Data are the mean and standard deviation from sets of three wells.

Quality control parameters were within acceptable limits (acceptable values: Lucifer yellow $P_{7.4} \leq 50$ nm/sec; digoxin mass balance 80 – 120 %; digoxin transport rate ≥ 1.5 pmoles transported/cm²/h; digoxin transport rate in the presence of 2 μM GF120918 $\leq 30\%$ of uninhibited rate).

(Source – Table 1, Report WD2007/01087/00)

Conclusion: VI is unlikely to inhibit P-gp metabolism at clinically relevant dose.

PHARMACOKINETICS

Mass Balance Study

UMEC

Study # AC4112014

Title: An open-label, two period study to determine the excretion balance and pharmacokinetics of [¹⁴C]-GSK573719, administered as a single dose of an oral solution and an intravenous infusion, to healthy male adults.

Objectives:

Primary:

- To compare total radioactivity (drug-related material) in plasma relative to parent plasma GSK573719 concentration following administration of a

single intravenous (IV; 65 µg) and a single oral dose (1000 µg) of [14C]-GSK573719 in healthy male subjects

- To determine the recovery and relative excretion of radioactivity in urine and faeces after a single IV and a single oral dose of [14C]-GSK573719 in healthy male subjects

Secondary:

- To determine (as data permit) the oral bioavailability of GSK573719 following a single IV and single oral dose of [14C]-GSK573719
- To determine (as data permit) other pharmacokinetic parameters of interest for GSK573719 and radioactivity following a single IV and single oral dose of [14C]-GSK573719
- To collect samples of plasma, urine, duodenal bile and feces following administration of [14C]-GSK573719 to healthy adult males to characterize and quantify the metabolic profile of GSK573719. These analytical investigations were conducted under a separate study
- To compare (as data permit) total drug-related material (radioactivity) in blood and plasma
- To further assess the safety and tolerability of single IV and/or oral doses of GSK573719 in healthy adult male subjects

Study design: non-randomized, open-label study in healthy male subjects.

Test drug and sample size: a single IV infusion (65 µg) of [14C]-GSK573719 and a single oral bolus dose (1000 µg) of [14C]-GSK573719 (batch number: R18361/114/3). There was a 28-day washout between doses. N=6.

Results:

Plasma GSK573719 pharmacokinetics: Plasma GSK573719 pharmacokinetic parameters following oral administration could not be estimated due to all non-quantifiable data for GSK573719 in plasma. Based on a lower limit of quantification of 20 pg/mL for GSK573719, maximal possible oral bioavailability was calculated as <1%. Plasma GSK573719 pharmacokinetic parameter estimates following IV administration are summarized in the table below.

Parameter (IV dosing)	N	n	Geometric mean (CVb%)	95% Confidence interval
AUC(0–1) (pg.h/mL)	6	6	262.8 (107)	105.2, 656.8
AUC(0–∞) (pg.h/mL)	6	6	268.3 (105)	108.3, 664.9
AUC(0–t) (pg.h/mL)	6	6	323.3 (70)	166.2, 628.8
CL (L/h)	6	4	151.17 (65)	58.46, 390.93
C _{max} (pg/mL)	6	6	905.80 (70)	468.73, 1750.43
t _{last} (h) ¹	6	6	1.00 (0.8, 1.0)	NA
t _{max} (h) ¹	6	6	0.53 (0.5, 0.5)	NA
V _{ss} (L)	6	4	86.22 (68)	32.42, 229.26

1. Median (range).

NA = not applicable.

Plasma total radioactivity pharmacokinetic parameter estimates following both IV and oral administrations of [14C]-GSK573719 are summarized in the table below.

Parameter	Route	N	n	Geometric mean (CVb%)	95% Confidence interval
AUC(0-1) (ng.equiv.h/mL)	IV	6	6	0.529 (51.1)	0.319, 0.876
	PO	6	6	0.014 (45.0)	0.009, 0.022
AUC(0-∞) (ng equiv.h/mL)	IV	6	6	1.041 (90.9)	0.461, 2.350
	PO	6	6	0.796 (118.3)	0.298, 2.124
AUC(0-t) (ng equiv.h/mL)	IV	6	6	1.345 (29.0)	0.998, 1.812
	PO	6	6	0.970 (89.9)	0.433, 2.176
CL (L/h)	IV	6	5	46.5 (32.7)	31.3, 69.1
CL/F (L/h)	PO	6	5	988 (96.5)	360, 2705
Cmax (ng equiv/mL)	IV	6	6	1.39 (54.7)	0.81, 2.38
	PO	6	6	0.07 (126.1)	0.03, 0.20
t _{last} (h) ¹	IV	6	6	168.0 (96.0, 168.0)	NA
	PO	6	6	168.0 (96.0, 168.1)	NA
t _{max} (h) ¹	IV	6	6	0.5 (0.5, 0.5)	NA
	PO	6	6	4.0 (3.0, 4.0)	NA
V _{ss} (L)	IV	6	5	1801 (50.1)	1000, 3243
	PO	6	5	66958 (81.2)	27670, 162030
F1 (%)	PO	6	4	5.4	1.81, 15.88
F2 (%)	PO	6	6	4.7	2.13, 10.31

1. Median (range).

NA = not applicable; F1 = oral bioavailability calculated based on AUC(0-∞); F2 = oral bioavailability calculated based on AUC(0-t).

Conclusions:

- GSK573719 represented approximately 20% of the total radioactivity in plasma based on AUC(0-∞) following IV administration, indicating the presence of metabolites in the plasma
- Urine and feces were predominant routes of excretion following IV administration. Approximately 81% of the administered dose was recovered, with fecal excretion and urinary excretion accounting for approximately 58% and 22%, respectively
- Total radioactivity was eliminated primarily in feces following oral administration of [14C]-GSK573719, accounting for approximately 92% of the orally administered dose. Less than 1% of the oral administered dose was excreted in urine suggesting negligible absorption following oral dose.
- Overall results from this study suggest very low absorption of GSK573719 following oral administration and all of the absorbed drug undergoing metabolism with negligible (non-quantifiable) parent drug in systemic circulation. The IV arm data from this study suggest that systemically delivered GSK573719 is removed from plasma via multiple pathways including metabolism and biliary secretion, with a small percentage eliminating in urine
- GSK573719 was well tolerated. There were no SAEs and no AEs leading to withdrawal from the study. There were no clinically significant safety laboratory, vital signs or ECG findings

VI

Study # B2C106181

Title: An open-label, single-arm study to determine the excretion balance and metabolic disposition of [¹⁴C]GW642444 administered as a single dose of an oral solution to healthy male volunteers.

Objective: The objective of this study was to compare total radioactivity (drug related material) in plasma relative to parent plasma vilanterol concentrations and to determine the rate and extent of excretion of total radioactivity in urine and faeces and the total recovery of radioactivity.

Study design: non-randomized, open-label, single-arm study.

Test drug and sample size: 200 mcg (2 µCi) oral solution dose of [¹⁴C] vilanterol. N=6.

Samples: Vilanterol and its metabolites pharmacokinetics was evaluated from all/selected blood, urine and feces samples. Blood was collected at 0 (just before dosing), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 12, 24, 48, 72, 96, 120, 144, and 168 hours postdose. Urine and faeces were collected at pre-dose, then over 24 h collection periods as follows: 0–24 h, 24–48 h, 48–72 h, 72–96 h, 96–120 h, 120–144 h, 144–168 h.

Results:

The overall recovery of the administered dose was approximately 71.6%. The majority of the urinary-excreted radioactivity was eliminated within 24h. The majority of feces-excreted radioactivity was eliminated within 72h. Cumulative total, urine, and fecal recovery of vilanterol following oral administration is shown in the following figure. Vilanterol plasma concentration was too low to be assessed in cold assay, so only PK for the total radioactivity was reported in this study.

Absorption:

On average, the maximum plasma concentrations of ¹⁴C-radioactivity were achieved 3 h post-dose. Mean C_{max} value for total radioactivity was 2058 pg-equiv/mL. Mean AUC_{0-t} values for total radioactivity was 66015 pg-equiv*h/mL.

Metabolism:

Comparison of the radiolabel C_{max} and potential maximum plasma vilanterol concentrations indicated that vilanterol only represented <0.5% of the circulating drug-related material. These results are indicative of extensive first-pass metabolism of the orally absorbed vilanterol.

Percentage of total dose recovered as parent drug on metabolites in urine and feces are shown in the table below.

Summary of [¹⁴C]GW642444 metabolites in human urine and feces obtained following oral administration of [¹⁴C]GW642444 (M salt) to healthy male subjects.

Peak ID	% Radioactivity in Urine and Faecal extracts (% recovered dose)	
	Pooled Urine	Pooled Faeces
A	ND	2.8 (0.8)
B (M1)	9.4 (6.8)	ND
D (M3)	13.5 (9.5)	ND
E (M30, M4)	9.0 (6.3)	13.8 (4.1)
F (M6, M7, M19, M29, M39)	31.0 (21.7)	21.5 (6.4)
G (M33)	19.3 (13.5)	33.9 (10.2)
H	2.0 (1.4)	ND
I (M20)	ND	1.3 (0.4)
J1 GW642444 (P)	ND	15.4 (4.6)
J2 (M26)	6.5 (4.6)	ND

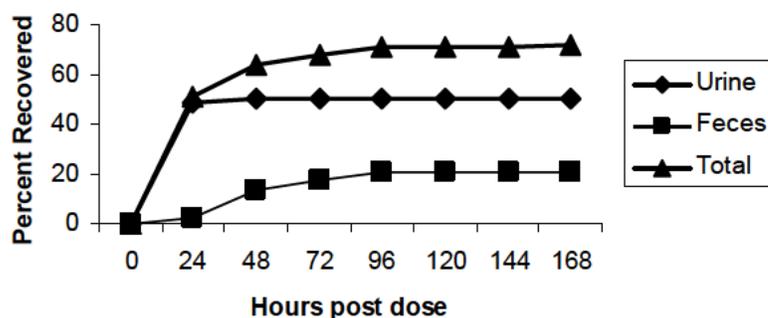
ND Not Detected.

Peak J was assigned as unchanged GW642444 in faeces (J1) and M26 in urine (J2).
Radioactive extraction efficiency from pooled human faeces was estimated as 73%.

(Source – Table 7, Study B2C106181 report)

Elimination:

Urinary excretion of ¹⁴C-radioactivity accounted for on average 50.4% of the radioactive dose, and fecal excretion accounted for 21.2%.



Cumulative Mean Recovery of Administered Radioactivity in Urine and Feces from Male Subjects over 168 Hours Following Oral Administration of a Single 200 mcg Dose of [14C]Vilanterol

Reviewer's comment:

The total recovery of vilanterol radioactivity in feces and urine was relatively low (71.6%). The sponsor suggested several possible explanations including excretion of radioactivity by exhalation and the non-conventional application of accelerator mass spectrometry (AMS) in a mass balance study. Since VI is an inhalation drug, we find this is acceptable.

Single dose rising

UMEC

Trial # AC4105209

Title: A randomised double-blind, placebo-controlled, crossover, dose escalation study to

examine the safety, tolerability, pharmacodynamics and pharmacokinetics of single inhaled doses of GSK573719 (10-350 µg).

Objectives:

Primary

- To investigate the safety and tolerability of single inhaled doses of GSK573719 in healthy male subjects.

Secondary

- To investigate the bronchodilatory effect and duration of action of single inhaled doses of GSK573719 as measured by plethysmography (specific airways conductance [sG_{aw}], airways resistance [R_{aw}]) and spirometry forced expiratory volume in 1 second (FEV₁) endpoints in healthy male subjects.
- To investigate the pharmacokinetics of single inhaled doses of GSK573719 in healthy male subjects.
- To investigate the effect of single doses of tiotropium on plethysmography, and spirometry lung function endpoints in healthy male subjects.
- To evaluate the safety and tolerability of single doses of tiotropium in healthy male subjects.

Study design and treatment schedule: This was a randomised, double-blind, placebo-controlled cross-over, first time in human (FTIH) study to investigate the safety, tolerability, pharmacodynamic effects and pharmacokinetics of single doses of GSK573719 in normal healthy male volunteers. The treatment schedule is as follows:

Number of Subjects	Placebo	Tio-tropium	GSK573719					
			10 µg	20 µg	60 µg	100 µg	250 µg	350 µg
Planned	20	20	10	10	10	10	10	10
Randomised	20	20	10	10	10	10	10	10
Treated	19	19	10	10	10	9	10	9
Completed	19	19	10	10	10	9	10	9
Total Withdrawn (any reason), n	1	1	0	0	0	0	0	0
Withdrawn due to AE*, n	1	0	0	0	0	0	0	0
Subject withdrew consent, n	0	1	0	0	0	0	0	0

Note: Withdrawals are assigned to the treatment group with which the subject was last dosed, prior to withdrawal.

* In the case of the AE withdrawal, the last dose received prior to the actual AE was placebo – however the subject was then dosed with GSK573719 350 µg, as the diagnosis was not made until availability of the bio-chemistry results.

GSK573719 was provided as 10 µg, 50 µg and 250 µg/blister to be administered via the DISKUS™ inhaler and formulated with lactose and (b) (4) 1 % as a vehicle to make 12.5mg. Matching placebo via the DISKUS inhaler formulated with lactose only as a vehicle to 12.5mg. The dose of (b) (4) used in this study was 0.125mg per inhalation (1% of 12.5mg blister). Tiotropium bromide 18 µg (as bromide monohydrate) was administered via the HandiHaler device.

Drug	Dose / Route	Batch Number	Expiry Date
GSK573719	10 µg / Inhaled DISKUS	R220067	31 DEC 2006
GSK573719	50 µg / Inhaled DISKUS	R220071	31 DEC 2006
GSK573719	250 µg / Inhaled DISKUS	R220073	31 DEC 2006
Placebo DPI	NA / Inhaled DISKUS	B138493	31 DEC 2006
Tiotropium	18 µg / Inhaled HandiHaler	198973	31 DEC 2006
Placebo (tiotropium)	NA / Inhaled HandiHaler	T04/014A	28 FEB 2007

NA: not applicable

PK Results:

The PK results are shown in the tables below:

Parameter	Dose	N	n	Geometric Mean	95% Confidence Interval	CV _b (%)
AUC _(0-t) (h*ng/mL)	60 µg	10	7	0.00165	(0.00116,0.00235)	39.6
	100 µg	9	8	0.00403	(0.00194,0.00835)	106.9
	250 µg	10	10	0.08053	(0.05245,0.12365)	65.8
	350 µg	9	9	0.13233	(0.10524,0.16640)	30.5
C _{max} high (ng/mL)	10 µg*	10	10	0.0200	(0.0200,0.0200)	0.0
	20 µg*	10	10	0.0200	(0.0200,0.0200)	0.0
	60 µg**	10	10	0.0316	(0.0227,0.0441)	48.9
	100 µg***	9	9	0.0449	(0.0298,0.0676)	57.1
	250 µg	10	10	0.2658	(0.1996,0.3539)	41.7
	350 µg	9	9	0.2694	(0.2024,0.3586)	38.5
t _{max} (h)****	60 µg	10	7	0.08	(0.08, 0.10)	NA
	100 µg	9	8	0.08	(0.07, 0.25)	NA
	250 µg	10	10	0.08	(0.08, 0.12)	NA
	350 µg	9	9	0.08	(0.08, 0.10)	NA
t _{last} (h)****	60 µg	10	7	0.08	(0.08, 0.10)	NA
	100 µg	9	8	0.165	(0.08, 0.25)	NA
	250 µg	10	10	1.00	(0.50, 6.00)	NA
	350 µg	9	9	2.00	(1.00, 2.00)	NA

* Given that all subjects have C_{max} values of NQ, variability observed is zero.

** 3 values substituted by 0.02 ng/mL

*** 1 value substituted by 0.02 ng/mL

**** Median and range.

n: Number of subjects with non-missing values.

N: Number of subjects in treatment groups.

NA : not applicable

CV_b: between subject coefficient of variation

Parameter	Dose	N	n	Geometric Mean	95% Confidence Interval	CV _b (%)
Ae ₍₀₋₂₎ (ng)	10 µg	10	5	21.44	(11.41, 40.31)	54.3
	20 µg	10	5	39.03	(23.12, 65.89)	44.1
	60 µg	10	10	122.16	(91.68, 162.78)	41.8
	100 µg	9	9	195.15	(120.03, 317.26)	70.1
	250 µg	10	10	760.21	(590.93, 977.99)	36.3
	350 µg	9	9	1071.2	(783.29, 1464.9)	42.5
Ae ₍₀₋₁₂₎ (ng)	60 µg	10	10	308.3	(208.5, 455.8)	59.0
	100 µg	9	9	576.0	(439.5, 754.8)	36.3
	250 µg	10	10	1881.9	(1450.8, 2441.1)	37.6
	350 µg	9	9	2584.7	(1925.3, 3469.9)	39.8
Ae ₍₀₋₂₄₎ (ng)	60 µg	10	10	449.6	(349.3, 578.7)	36.4
	100 µg	9	9	763.7	(580.5, 1004.6)	36.8
	250 µg	10	10	2555.7	(1966.1, 3322.1)	37.9
	350 µg	9	9	3368.6	(2586.3, 4387.5)	35.4
Fe (%)*	10 µg	10	5	0.238	(0.083, 0.394)	NA
	20 µg	10	6	0.356	(0.180, 0.532)	NA
	60 µg	10	10	0.791	(0.601, 0.981)	NA
	100 µg	9	9	0.812	(0.559, 1.064)	NA
	250 µg	10	10	1.284	(1.010, 1.558)	NA
	350 µg	9	9	1.206	(0.805, 1.607)	NA

n: Number of subjects with non-missing values.

N: Number of subjects in treatment groups.

* arithmetic mean value

NA : not applicable

The PK concentrations are only measurable up to 2 hours. All measurable C_{max} values occurred early (at the first observation except in one subject where it occurred at 15 minutes) at a median t_{max} of 5 minutes. The maximum observed C_{max} in any individual subject in this study was 0.593 ng/mL. After C_{max}, concentrations declined rapidly to become below the lower limit of quantification (LLQ) by 6 hour (latest measurable concentration at GSK573719 250 µg).

PK Conclusions:

- Over the dose range studied, plasma (C_{max} and AUC (0-t)) and urine Ae ((0-2), Ae (0- 8), Ae (0-12), Ae (0-24) and Ae (0-48), AUER (0-18)) measures increased with increase in dose. The highest amount excreted was in the 0-2 hour sample time collection.
- At the highest doses of GSK573719 250 µg and 350 µg on average approximately 1.2 % of the total dose was excreted unchanged in urine within the 24/48 hour urine collection.
- Over the dose range studied, C_{max} and AUC (0-t) increased with increase in dose although the increase in C_{max} between the 250 µg and 350 µg dose is nearly nil.

VI

Trial # B2C10001

Title: A randomised, double blind, placebo controlled study to examine the safety, tolerability, pharmacodynamics and systemic pharmacokinetic profile of single inhaled doses of GW642444 in healthy male subjects.

Objective:

Primary

- To investigate the safety and tolerability of single inhaled doses of GSK642444 in healthy subjects.

Secondary

- To assess the systemic pharmacodynamics of GW642444 as measured by heart rate, potassium, glucose, 12-lead Electrocardiogram (ECG) including QTc(b) and (f) plus blood pressure in healthy subjects.
- To assess the systemic pharmacokinetics of GW642444 and its counterion, α -phenylcinnamic acid, following single inhaled doses (12.5, 50, 100, 200, 400, 600 and 800 μ g) in healthy subjects.
- To assess the extent and duration of bronchodilation as measured by sGaw in healthy subjects.

Study design and treatment schedule: This was a single-centre, double-blind, randomised, dose-ascending, placebocontrolled study in 20 healthy male subjects. GSK 642444 was provided as a-phenylcinnamate salt, with 12.5 μ g and 100 μ g/blister to be administered via the DISKUS/ACCUHALER inhaler.

PK Results:

Plasma concentrations of GW642444 were below limits of quantification (LLQ of 30pg/mL) in the majority of subjects (9/10) following a single inhaled dose of 12.5 μ g GW642444. Individual plasma GW642444 PK parameters are presented in table below.

Summary plasma GW642444 PK parameters

Treatment (μ g)	N (n)	Geometric mean (CV%) C _{max} (pg/mL)	Geometric mean (CV%) AUC(0-t) (pg.h/mL)	Median (range) T _{max} (h)
12.5	10 (1)	37.6	----	0.08
50	10 (10)	60.3 (35.7)	15.3 (26.8) ¹	0.08 (0.08-0.33)
100	9 (9)	118.4 (41.4)	59.0 (50.5)	0.08 (0.08-0.50)
200	18 (18)	259.8 (46.9)	185.2 (46.7)	0.08 (0.08-0.33)
400	10 (10)	498.8 (58.7)	520.6 (48.2)	0.08 (0.08-0.33)
600	6 (6)	800.3 (55.0)	821.7 (36.2)	0.10 (0.08-0.33)

¹: n=5

Data Source: Table 17.5 CV (%) = SD of Logs * 100

- Data too limited to define parameter (<3 quantifiable values)

The PK concentrations are only measurable up to 2 hours. All measurable C_{max} values occurred early at a median t_{max} of 5 minutes. After C_{max}, concentrations declined rapidly to become below the lower limit of quantification (LLQ).

PK Conclusions:

- GW642444 was rapidly absorbed following a single inhaled administration via DISKUS/ACCUHALER. Maximum plasma concentrations were generally achieved 5 minutes post-dose.
- Systemic exposure of GW642444 increased with dose.

Reviewer's comment:

This study was done with an earlier formulation in a different device, therefore, the PK result is not applicable to the to-be marketed product.

Multiple Rising Dose

UMEC

Trial # AC4106889

Title: A single-centre, randomised, double-blind, placebo-controlled, dose-ascending, 3-cohort parallel-group study to evaluate the safety, tolerability, pharmacodynamics and pharmacokinetics of GSK573719 administered as single doses (750 µg and 1000 µg) and repeat doses over 14 days (250 µg–1000 µg once-daily) of GSK573719 in healthy male and female subjects.

Objective:

Primary

- To evaluate the safety and tolerability of GSK573719 administered as single inhaled doses of 750 and 1000 µg in healthy subjects.
- To evaluate the safety and tolerability of GSK573719 administered once-daily by inhalation for 14 days in healthy subjects.

Secondary

- To evaluate the pharmacodynamic effects of GSK573719 administered as single inhaled doses of 750 and 1000 µg in healthy subjects.
- To evaluate the pharmacodynamic effects of GSK573719 administered once-daily by inhalation for 14 days in healthy subjects.
- To evaluate the pharmacokinetics of GSK573719 administered as single inhaled doses of 750 and 1000 µg in healthy subjects.
- To evaluate the pharmacokinetics of repeat inhaled doses of GSK573719 administered once-daily by inhalation for 14 days in healthy subjects.

Study design and treatment schedule: This was a single-centre, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the safety, tolerability, pharmacodynamics and pharmacokinetics of single and 14 day repeat inhaled doses of GSK573719 across a range of doses.

36 subjects were enrolled and randomised in equal numbers to one of three cohorts (12 subjects per cohort). The ratio of subjects receiving active:placebo drug in each group was 3:1, thus nine subjects in total received each treatment. Each cohort completed the whole dosing period before the next cohort began dosing.

Each GSK573719 dose was inhaled daily from a DISKUS™ dry powder inhaler. Subjects in Cohort I were randomised to GSK573719 250 µg for 14 day repeat dosing. As 750 and 1000 µg had not previously been administered to man, subjects in cohorts II

and III received a single dose of 750 and 1000 µg, respectively, and after safety and pharmacokinetic data had been reviewed from the single dose, they received GSK573719 750 and 1000 µg doses (or placebo), respectively, once-daily for 14 days. There was a minimum of 7 days between each cohort.

PK Results:

Following both single and repeat inhaled doses, GSK573719 was rapidly absorbed after morning dosing with a median t_{max} of 5–15 minutes.

The mean t_{1/2} of GSK573719 following 14 day repeat dosing ranged from 26 to 28 h. Visual assessment of C_τ data suggested that steady state was achieved following 6 to 8 days of dosing; however, the statistical analysis of the 750 µg and 1000 µg treatment groups inferred that steady state had been achieved following 4 days of GSK573719 dosing. Summary statistics of GSK573719 pharmacokinetic parameters on Day 14 are presented below.

Parameter	Dose (µg)	N	n	Geometric Mean	95% Confidence Interval	CV(%)
AUC(0–2) (h*ng/mL)	250	9	9	0.192	(0.153, 0.243)	30.8
AUC(0–4) (h*ng/mL)	750	9	9	1.12	(1.03, 1.23)	11.8
AUC(0–8) (h*ng/mL)	1000	9	9	1.79	(1.56, 2.05)	17.8
AUC(0–t) (h*ng/mL)	250	9	9	0.874	(0.668, 1.15)	36.2
	750	9	9	3.21	(2.87, 3.59)	14.7
	1000	9	9	3.23	(2.84, 3.67)	16.6
C _{max} (ng/mL)	250	9	9	0.203	(0.163, 0.255)	29.8
	750	9	9	0.935	(0.740, 1.18)	31.3
	1000	9	9	1.08	(0.770, 1.51)	45.8
C _τ	250	9	9	0.0259	(0.0205, 0.0328)	19.2
	750	9	9	0.0860	(0.0661, 0.112)	35.2
	1000	9	9	0.0828	(0.0706, 0.0972)	21.0
t _{max} (h) ¹	250	9	9	0.08	(0.08, 0.25)	NA
	750	9	9	0.08	(0.07, 0.25)	NA
	1000	9	9	0.12	(0.08, 0.25)	NA
t _{1/2} (h)	250	9	9	NC	NC	NC
	750	9	9	26.3	(23.4, 29.4)	15.0
	1000	9	9	27.7	(19.8, 38.6)	45.7

1. Presented as median and range.

NA=not applicable; NC=not calculable; AUC(0–t)=area under concentration-time curve from time 0 to time of last quantifiable concentration; C_{max}=maximum observed plasma concentration; t_{max}=time of maximum observed plasma concentration; C_τ=trough concentration; t_{1/2}=terminal phase half life.

Urine pharmacokinetic data for GSK573719 showed that on Day 1 about 1 to 1.5% of the total dose administered was excreted unchanged in urine over the dosing interval and at steady-state, about 3.9 to 4.5% of the total GSK573719 administered was excreted unchanged in urine over the dosing interval.

Both plasma and urine pharmacokinetic data suggested a greater than dose proportional

increase in systemic exposure following inhaled GSK573719. The accumulation following repeat dosing with GSK573719 (ratio of Day 14:Day 1) ranged from 1.5 to 3 fold based on plasma data and 3 to 4.5 fold based on urine data.

Mean renal clearance ranged from 10.1 to 12.2 L/h on Day 1 and 9.6 to 12.3 L/h on Day 14. The $t_{1/2}$ based on the urine data were similar to plasma $t_{1/2}$ and the means ranged from 28 to 33 h following single dosing and 25 to 35 h following repeat dosing.

PK Conclusions:

- The mean $t_{1/2}$ of GSK573719 following 14 day repeat dosing ranged from 26 to 28 h. Visual assessment of C_{τ} data suggested that steady state was achieved following 6 to 8 days of dosing; however, the statistical analysis inferred that steady state had been achieved for the 750 μg and 1000 μg treatment groups following 4 days of GSK573719 dosing.
- Urine pharmacokinetic data for GSK573719 showed that on Day 1 about 1 to 1.5% of the total dose administered was excreted unchanged in urine over the dosing interval and at steady-state, about 3.9 to 4.5% of the total GSK573719 administered was excreted unchanged in urine over the dosing interval.
- Both plasma and urine pharmacokinetic data suggested a greater than dose proportional increase in systemic exposure following inhaled GSK573719. The mean accumulation following repeat dosing with GSK573719 (ratio of Day 14:Day 1) ranged from 1.5 to 3 fold based on plasma data and 3 to 4.5 fold based on urine data.
- Mean renal clearance ranged from 10.1 to 12.2 L/h on Day 1 and 9.6 to 12.3 L/h on Day 14. The $t_{1/2}$ based on the urine data were similar to plasma $t_{1/2}$ and the means ranged from 28 to 33 h following single dosing and 25 to 35 h following repeat dosing.

Reviewer's comments: The lowest dose investigated is 4-fold higher than the proposed dose of 62.5 μg .

Trial # AC4113377

Title: Phase I study of GSK573719 -A randomized, double blind, placebo controlled, dose ascending, single and repeat dose study to investigate the safety, tolerability, and pharmacokinetics of inhaled dose of GSK573719 from a novel dry powder device in healthy Japanese male subjects

Objective:

Primary:

- To evaluate the safety and tolerability of GSK573719 following single and once daily 7-day repeat inhaled doses at 250, 500 and 1000 μg in healthy Japanese male subjects.

Secondary:

- To investigate the pharmacokinetics of GSK573719 following single and once daily 7-day repeat inhaled doses at 250, 500 and 1000 μg in healthy Japanese male subjects.
- To investigate the dose proportionality and accumulation of GSK573719 following single and once daily 7-day repeat inhaled doses at 250, 500 and 1000 μg in healthy Japanese male subjects.

Study design and treatment schedule: This was a single centre, randomized, double blind, placebo controlled, dose-ascending study of single and once daily 7-day repeat inhaled doses of

GSK573719 via a novel dry powder inhaler. Forty-eight healthy subjects split into 3 cohorts of 16 participated in this study.

Cohort	Group	N	Part 1	Part 2	Part 3
1	A	12	GSK573719 250 µg	-	-
	B	4	Placebo	-	-
2	C	12	-	GSK573719 500 µg	-
	D	4	-	Placebo	-
3	E	12	-	-	GSK573719 1000 µg
	F	4	-	-	Placebo

Criteria for evaluation:

Primary endpoint:

- Safety and tolerability endpoints: adverse events, vital signs, 12-lead ECG, Holter monitoring, gallbladder ultrasound, ophthalmoscopy and clinical laboratory safety tests

Secondary endpoint:

- Plasma and urine concentrations of GSK573719 and derived pharmacokinetic parameters

PK Results:

Following both single and repeat dose administration, GSK573719 was rapidly absorbed with median t_{max} values of 5 minutes post dose at all dose levels, following which plasma concentrations declined rapidly. The plasma concentration was often below LLQ at later time points following 250 and 500 µg GSK573719, which indicated rapid distribution and elimination and precluded $t_{1/2}$ and $AUC_{0-\infty}$ calculation.

Plasma Pharmacokinetic Parameters after Single Inhaled Dosing of GSK573719 (Day 1)

Parameter	Dose	n	Geometric Mean	95% CI	CVb(%)
$AUC_{0-1.5}$ (h·ng/mL)	250 µg	12	0.135	(0.116, 0.158)	25.2
	500 µg	12	0.284	(0.242, 0.334)	25.7
	1000 µg	12	0.897	(0.809, 0.995)	16.4
AUC_{0-2} (h·ng/mL)	500 µg	12	0.316	(0.268, 0.372)	26.4
AUC_{0-8} (h·ng/mL)	1000 µg	12	1.494	(1.354, 1.648)	15.5
AUC_{0-last} (h·ng/mL)	250 µg	12	0.170	(0.131, 0.220)	42.9
	500 µg	12	0.410	(0.324, 0.520)	38.7
	1000 µg	12	1.987	(1.651, 2.393)	29.8
C_{max} (ng/mL)	250 µg	12	0.370	(0.275, 0.497)	49.1
	500 µg	12	0.927	(0.772, 1.112)	29.3
	1000 µg	12	2.477	(2.051, 2.991)	30.4
Parameter	Dose	n	Median	Range	
t_{max} (h)	250 µg	12	0.08	(0.08, 0.25)	
	500 µg	12	0.08	(0.08, 0.08)	
	1000 µg	12	0.08	(0.08, 0.08)	
t_{last} (h)	250 µg	12	2.00	(1.50, 4.00)	
	500 µg	12	4.00	(2.00, 8.00)	
	1000 µg	12	24.0	(8.00, 48.00)	

CI: confidence interval

**Plasma Pharmacokinetic Parameters after 7-day Repeat Inhaled Dosing of GSK573719
(Day 10)**

Parameter	Dose	n	Geometric Mean	95% CI	CVb(%)
AUC _{0-τ} (h·ng/mL)	250 µg	10	1.081	(0.937, 1.247)	20.2
	500 µg	12	2.196	(1.860, 2.594)	26.6
	1000 µg	12	4.894	(4.139, 5.788)	26.9
AUC _{0-last} (h·ng/mL)	250 µg	11	1.259	(0.881, 1.780)	57.1
	500 µg	12	3.358	(2.843, 3.967)	26.7
	1000 µg	12	7.281	(6.133, 8.645)	27.5
C _{max} (ng/mL)	250 µg	11	0.695	(0.560, 0.863)	33.1
	500 µg	12	1.318	(1.007, 1.724)	44.3
	1000 µg	12	3.672	(3.166, 4.259)	23.6
Parameter	Dose	n	Median	Range	
t _{max} (h)	250 µg	11	0.08	(0.08, 0.08)	
	500 µg	12	0.08	(0.08, 0.08)	
	1000 µg	12	0.08	(0.08, 0.08)	
t _{last} (h)	250 µg	11	48.00	(8.00, 48.00)	
	500 µg	12	48.00	(48.00, 48.00)	
	1000 µg	12	48.00	(48.00, 48.00)	

CI: confidence interval

Dose proportionality was assessed using the Power Model. AUC and C_{max} parameters were log transformed prior to analysis. AUC_{0-∞} could not be computed due to a number of non-quantifiable values in the elimination phase of plasma concentration profiles. Therefore AUC_{0-1.5} and AUC_{0-τ} for Day 1 and Day 10, respectively, were derived and used in the dose proportionality analysis.

For the assessment of accumulation, the results of R[C_{max}] and Ro (AUC_{0-1.5} used for 250 µg, AUC₀₋₂ used for 500 µg and AUC₀₋₈ used for 1000 µg) after repeat inhaled doses of GSK573719 250, 500 and 1000 µg are summarised below.

Assessment of Accumulation after Dosing of GSK573719 250, 500 and 1000 µg

		n	Ratio of Adjusted Geometric Means (Day 10 vs Day 1)	90% CI
GSK573719 250 µg	R[C _{max}]	11	1.772	1.482, 2.119
	Ro*	11	1.862	1.687, 2.054
GSK573719 500 µg	R[C _{max}]	12	1.422	1.196, 1.690
	Ro*	12	2.012	1.830, 2.212
GSK573719 1000 µg	R[C _{max}]	12	1.483	1.247, 1.762
	Ro*	12	1.934	1.759, 2.127

*: AUC_{0-1.5}, AUC₀₋₂ and AUC₀₋₈ were used for calculation of Ro for 250 µg, 500 µg and 1000 µg, respectively.

PK Conclusions:

- GSK573719 was rapidly absorbed with median t_{max} values of 5 minutes after single inhaled dosing and after 7-day repeat inhaled dosing of GSK573719 250, 500 or 1000 µg.
- Plasma PK data suggested a slightly higher than dose proportional increase in systemic exposure following inhaled GSK573719 250 to 1000µg.
- Rs was approximately 1.6 after 7-day repeat inhaled dosing of GSK573719 1000 µg. Rs after 7-day repeat inhaled dosing of GSK573719 250 and 500 µg could not be calculated.
- Urine pharmacokinetic data for GSK573719 showed that, following single dose administration, approximately 1.3 to 2.0% of the total dose administered was excreted unchanged in urine.

- Following repeat dose administration, approximately 4.8 to 5.0% of the total GSK573719 dose administered was excreted unchanged in urine over the dosing interval.
- Renal clearance values ranged from 9.6 to 11.4 L/hr following repeat dose administration.
- For C_{max} and AUC following repeat dose administration a 1.4 to 2.0-fold accumulation of
- GSK573719 was observed for all doses. Based on Ae_{0-48} the observed accumulation ratio were approximately 2.8 to 4.7 for each dose group.

Reviewer's comments: The lowest dose investigated is 4-fold higher than the proposed dose of 62.5 µg.

Trial # AC4105211

Title: A randomised, double-blind, placebo-controlled, dose ascending, 2-cohort, parallel group study to examine the safety, tolerability and pharmacokinetics of oncedaily inhaled doses of GSK573719 formulated with the excipient Magnesium Stearate in COPD subjects for 7 days.

Objectives:

The primary objective was:

- To assess the safety and tolerability of repeat inhaled doses of GSK573719 (inhaled once daily (QD) for 7 days) in chronic obstructive pulmonary disease (COPD) subjects.

The secondary objective was:

- To assess the pharmacokinetics (PK) of GSK573719 following repeat inhaled doses (inhaled once daily for 7 days) in COPD subjects.

Study design and treatment schedule: This was a randomised, double-blind, placebo-controlled, dose ascending, 2-cohort, parallel group study to examine the safety, tolerability and pharmacokinetics of once daily inhaled doses (250 µg, 1000 µg or placebo) of GSK573719 formulated with the excipient magnesium stearate (MgSt) in COPD subjects for 7 days.

Criteria for evaluation: safety and PK

PK Results: Selected PK parameters are summarised in the tables below. Overall plasma data suggested that accumulation in GSK573719 systemic exposure following 7 days repeat dosing ranged between approximately 1.5 to 1.9 fold that of Day 1 systemic exposure.

Summary Statistics of Day 1 Dose GSK573719 PK Parameters

Parameter	Cohort	N	n	Geometric Mean	95% CI	CVb(%)
AUC(0-2) (h•ng/mL)	Cohort 1	8	8	0.1968	(0.1671, 0.2315)	19.7
	Cohort 2	9	9	0.0813	(0.0413, 0.1599)	108
	Cohort 3	9	9	0.9572	(0.3352, 2.7325)	233.2
AUC(0-8) (h•ng/mL)	Cohort 3	9	9	2.029	(1.250, 3.294)	69.8
AUC(0-t) (h•ng/mL)	Cohort 1	8	8	0.2607	(0.1902, 0.3573)	39.1
	Cohort 2	9	9	0.0361	(0.0057, 0.2256)	1707.8
	Cohort 3	9	9	0.9330	(0.1042, 8.3488)	5820.5
Cmax (ng/mL)	Cohort 1	8	8	0.2165	(0.1668, 0.2810)	32.0
	Cohort 2	9	9	0.0792	(0.0346, 0.1809)	147.6
	Cohort 3	9	9	1.5284	(1.0388, 2.2486)	53.6
tmax (h) ¹	Cohort 1	8	8	0.080	(0.08, 0.50)	NA
	Cohort 2	9	8	0.250	(0.08, 0.28)	NA
	Cohort 3	9	9	0.250	(0.08, 0.28)	NA
tlast (h) ¹	Cohort 1	8	8	4.000	(2.00, 8.12)	NA
	Cohort 2	9	8	2.000	(0.08, 4.00)	NA
	Cohort 3	9	9	8.000	(0.08, 8.00)	NA

1. Presented as median and range

NA : Not applicable

Summary Statistics of Repeat Dose GSK573719 PK Parameters (Day 7)

Parameter	Cohort	N	n	Geometric Mean	95% CI	CVb(%)
AUC(0-2) (h•ng/mL)	Cohort 1	8	6	0.3195	(0.1919, 0.5319)	51.6
	Cohort 2	9	8	0.1553	(0.0936, 0.2575)	66.5
	Cohort 3	9	6	1.9251	(1.3996, 2.6477)	31.1
AUC(0-8) (h•ng/mL)	Cohort 3	9	6	3.320	(2.362, 4.667)	33.3
AUC(0-t) (h•ng/mL)	Cohort 1	8	6	0.5551	(0.2140, 1.4400)	113.2
	Cohort 2	9	8	0.3053	(0.1306, 0.7133)	134.3
	Cohort 3	9	6	4.8620	(3.1620, 7.4759)	42.8
Cmax (ng/mL)	Cohort 1	8	6	0.3321	(0.1882, 0.5859)	58.3
	Cohort 2	9	8	0.1645	(0.0945, 0.2860)	74.2
	Cohort 3	9	6	2.7586	(1.5350, 4.9576)	60.5
tmax (h) ¹	Cohort 1	8	6	0.080	(0.02, 0.25)	NA
	Cohort 2	9	8	0.165	(0.08, 0.32)	NA
	Cohort 3	9	6	0.240	(0.07, 0.25)	NA
tlast (h) ¹	Cohort 1	8	6	6.000	(2.00, 27.05)	NA
	Cohort 2	9	8	6.015	(2.00, 24.00)	NA
	Cohort 3	9	6	24.010	(24.00, 24.48)	NA

1. Presented as median and range

NA : Not applicable

Overall, urine data suggested approximately 1.8 to 2.4 fold accumulation of unchanged GSK573719 following repeat dose administration for 7 days.

PK Conclusions:

- Due to the large amount of non-quantifiable data (40–61% of samples), plasma pharmacokinetic information obtained in this population was limited.

- Following single inhaled dose administration, GSK573719 was rapidly absorbed with a median t_{max} of 5–15 minutes.
- The plasma $t_{1/2}$ of GSK573719 ranged from on average 1–2 h for the 500 μg and 1000 μg dose levels. Half-lives estimated from the urine data were longer than those estimated from the plasma with on average 11–12 h across all dose levels examined.
- Both plasma and urine pharmacokinetic data suggested a greater than dose proportional increase in systemic exposure following inhaled GSK573719.
- Urine pharmacokinetic data for GSK573719 showed that on average about 1–1.3% of the total dose administered was excreted unchanged in urine over the 24-h period.
- Renal clearance values were estimated to be on average 5.32, 6.40, and 6.83 L/h for the GSK573719 250 μg , 500 μg and 1000 μg dose groups, respectively, following a single dose administration.

Reviewer's comments: The lowest dose investigated is 4-fold higher than the proposed dose of 62.5 μg .

Trial # AC4108123

Title: A randomised, double blind, placebo-controlled, double dummy, 4-way crossover, dose ascending study to assess the safety, tolerability, pharmacodynamics and pharmacokinetics of single inhaled doses of GSK573719 (250, 500 and 1000 μg) and tiotropium bromide (18 μg) via DPI in COPD patients.

Objectives:

Primary:

to investigate the safety and tolerability of single inhaled doses of GSK573719 in chronic obstructive pulmonary disorder (COPD) patients.

Secondary:

- To investigate the pharmacokinetics of single inhaled doses of GSK573719 in COPD patients.
- To investigate the bronchodilatory effect and duration of action of single inhaled doses of GSK573719, as measured by plethysmography (specific airway resistance, sGaw, airways resistance, Raw) and spirometry (forced expiratory volume in 1 second, FEV1) endpoints in COPD patients.
- To evaluate the safety and tolerability of single inhaled doses of tiotropium bromide in COPD patients.
- To investigate the bronchodilatory effect and duration of action of single inhaled doses of tiotropium bromide, as measured by plethysmography (sGaw, Raw) and spirometry (FEV1) endpoints in COPD patients.

Study design and treatment schedule: This was a multi-centre, randomised, double-blind, placebo-controlled, double-dummy, dose-ascending, four-way cross-over study, incomplete block design in ipratropium responsive subjects with COPD.

GSK573719 was presented as 250 µg/blister, to be administered via the DISKUS™ inhaler.

Criteria for evaluation: Safety, PK, PD

PK Results: A summary of selected plasma pharmacokinetic parameters is presented in the following table.

Parameter	Dose	N	n	n*	Geometric Mean	95% CI	CV(%)
AUC(0-2) (h*ng/mL)	250 µg	22	22	4	0.10264	(0.08059, 0.13072)	58.9
	500 µg	21	21	1	0.27099	(0.21170, 0.34689)	58.5
	1000 µg	13	13	0	0.71522	(0.62789, 0.81470)	21.8
AUC(0-t) (h*ng/mL)	250 µg	22	22	0	0.10271	(0.07763, 0.13589)	70.0
	500 µg	21	21	0	0.35491	(0.27070, 0.46531)	65.2
	1000 µg	13	13	0	0.96100	(0.81529, 1.13276)	27.7
Cmax (ng/mL)	250 µg	22	22	0	0.12615	(0.10494, 0.15164)	43.4
	500 µg	21	21	0	0.30389	(0.25430, 0.36314)	40.7
	1000 µg	13	13	0	0.83228	(0.72619, 0.95386)	22.9
tmax (h) ¹	250 µg	22	22	0	0.090	(0.08, 0.50)	NA
	500 µg	21	21	0	0.100	(0.07, 0.27)	NA
	1000 µg	13	13	0	0.250	(0.08, 0.28)	NA
tlast (h) ¹	250 µg	22	22	0	1.975	(0.47, 4.07)	NA
	500 µg	21	21	0	4.030	(1.00, 24.00)	NA
	1000 µg	13	13	0	6.000	(4.00, 15.95)	NA

Parameter	Dose	N	n	n*	Geometric Mean	95% CI	CV(%)
t _{1/2} (h)	250 µg	22	0	0	NA	NA	NA
	500 µg	21	19	0	1.31214	(1.06651, 1.61433)	45.1
	1000 µg	13	13	0	1.74653	(1.06456, 2.86539)	97.8

Reviewer's comments: The lowest dose investigated is 4-fold higher than the proposed dose of 62.5 µg.

VI

Trial # B2C108784

Title: A randomised, double-blind, placebo-controlled, parallel-group, 14 day repeat dose study to investigate the safety, tolerability, pharmacokinetics and extra-pulmonary pharmacodynamics of inhaled doses of GW642444M formulated with magnesium stearate in healthy subjects.

Objective:

Primary:

To evaluate the safety and tolerability of GW642444M (50, 200 and 400 µg)

administered once-daily for 14 days in healthy subjects.

Secondary:

- To evaluate the extra-pulmonary pharmacodynamic effects of GW642444M (50, 200 and 400 µg) administered once-daily for 14 days in healthy subjects.
- To evaluate the systemic pharmacokinetics of GW642444, GI179710 (triphenylacetate counter-ion) and the metabolites, GW630200 and GSK932009 following GW642444M (50, 200 and 400 µg) administered once-daily for 14 days in healthy subjects.
- To evaluate the systemic exposure-response relationship.

Study design and treatment schedule:

This was a single-centre, randomised, double-blind, placebo-controlled, parallel-group 14 day repeat dose study. Three sequential dose-ascending inhaled administrations of GW642444M were planned.

- Cohort 1: nine subjects (GW642444M 50 µg X 14d) + three subjects (placebo).
- Cohort 2: nine subjects (GW642444M 100 µg X 14d) + three subjects (placebo).
- Cohort 3: nine subjects (GW642444M 25 µgX 14d) + three subjects (placebo)

The product used in this study is GW642444M (to be marketed formulation) via a different device DISKUS™.

PK Sampling Schedule

- **Blood** – On day 1, 7 and 14, at pre-dose, 2, 5, 10, 15, 20, 30, 45 min and 1, 2, 4, 6, 8, 10, 12, and 24 hour after dosing.

Results

Summary PK parameters for VI are listed in table below.

Summary of Selected GW642444 Pharmacokinetic Parameters

	Day	N	AUC(0-t) (pg.h/mL) ¹	AUC(0-1) (pg.h/mL) ¹	AUC(0-4) (pg.h/mL) ¹	t _{last} (h) ²	C _{max} (pg/mL)	t _{max} (h) ²
25 µg	1	9	52 (31.2)	-	-	0.50 (0.35, 0.77)	193 (26.4)	0.08 (0.08, 0.22)
	7	9	105 (26.6)	103 (11.6) ³	-	1.02 (0.73, 2.00)	248 (20.9)	0.17 (0.08, 0.17)
	14	9	80 (32.8)	99.0 (8.76) ⁴	-	0.75 (0.50, 2.00)	246 (15.3)	0.08 (0.07, 0.17)
50 µg	1	9	160 (29.5)	168 (29.0) ³	-	1.00 (0.75, 2.00)	452 (32.8)	0.08 (0.08, 0.25)
	7	9	385 (32.5)	204 (22.2)	370 (18.8) ³	4.00 (2.00, 8.00)	567 (25.8)	0.08 (0.08, 0.17)
	14	9	274 (56.0)	174 (29.2) ⁵	336 (22.8) ⁶	4.00 (0.75, 8.00)	509 (44.0)	0.10 (0.08, 0.18)
100 µg	1	9	734 (37.2)	369 (26.2)	583 (24.4)	8.00 (4.00, 23.83)	929 (30.4)	0.17 (0.08, 0.22)
	7	9	1040 (47.0)	364 (23.5)	624 (18.6)	12.00 (4.00, 23.83)	932 (28.3)	0.08 (0.08, 0.17)
	14	9	913 (25.7)	357 (16.6)	587 (10.9)	10.00 (6.00, 24.00)	932 (17.9)	0.08 (0.08, 0.18)

(Source – Table 16, Study B2C108784 report)

On average, the maximum plasma concentrations of VI were achieved by 5-10 minutes post-dose for all treatments. The systemic exposure of VI as measured by AUC(0-t) increase in a greater than dose-proportional manner, and C_{max} increased in a dose-proportional manner. Based on AUC(0-t), there was 1.24 to 2.4 fold accumulation after repeated dosing, as presented in the following table.

Statistical Summary of GW642444 Accumulation Assessment

Comparison	Ratio of Adjusted Means (90% Confidence Interval of Ratio)			
	C _{max}	AUC(0-t)	AUC(0-1)	AUC(0-4)
25 µg Day 7 : Day 1	1.29 (1.10, 1.51)	2.00 (1.57, 2.55)	-	-
25 µg Day 14 : Day 1	1.27 (1.09, 1.49)	1.53 (1.20, 1.95)	-	-
25 µg Day 14 : Day 7	0.99 (0.85, 1.16)	0.77 (0.60, 0.98)	-	-
50 µg Day 7 : Day 1	1.25 (1.07, 1.47)	2.40 (1.88, 3.06)	1.20 (1.06, 1.35)	-
50 µg Day 14 : Day 1	1.13 (0.96, 1.32)	1.71 (1.34, 2.18)	0.98 (0.86, 1.11)	-
50 µg Day 14 : Day 7	0.90 (0.77, 1.05)	0.71 (0.56, 0.91)	0.82 (0.73, 0.92)	-
100 µg Day 7 : Day 1	1.00 (0.86, 1.17)	1.41 (1.11, 1.80)	0.99 (0.88, 1.10)	1.07 (0.95, 1.20)
100 µg Day 14 : Day 1	1.00 (0.86, 1.17)	1.24 (0.98, 1.59)	0.97 (0.87, 1.08)	1.01 (0.90, 1.13)
100 µg Day 14 : Day 7	1.00 (0.85, 1.17)	0.88 (0.69, 1.12)	0.98 (0.88, 1.09)	0.94 (0.84, 1.06)

(Source – Table 18, Study B2C108784 report)

Conclusion: The systemic exposure of VI, based on C_{max} was dose proportional, and the maximum accumulation is 2.4 fold based on AUC0-t.

Reviewer’s comment

This study was the first administration of this to be marketed GW642444 dry powder formulation (lactose, magnesium stearate, and GW642444 dry powder) in healthy subjects. (b) (4)

UMEC/VI

Trial # DB2114635

Title: A randomized, placebo-controlled, incomplete block, four period crossover, repeat dose study to evaluate the effect of the inhaled GSK573719/vilanterol combination and GSK573719 monotherapy on electrocardiographic parameters, with moxifloxacin as a positive control, in healthy subjects.

Objective: (PK related only)

- To characterise the pharmacokinetic profiles of UMEC and VI when administered in combination via novel dry powder inhaler (NDPI)
- To characterise the pharmacokinetic profile of supra-therapeutic dose of UMEC when administered as monotherapy via NDPI

Methods: This was a randomised, placebo-controlled, four period incomplete block crossover study in healthy adult male and female subjects.

Treatment Group	Days	Medication Regime
A Placebo	1-10	Single inhalation from matching placebo NDPI once daily
B Moxifloxacin positive control	10	Single dose placebo oral tablet moxifloxacin
	1-10	Single inhalation from matching placebo NDPI once daily
C UMEC supra-therapeutic dose	10	Single dose oral tablet moxifloxacin (400 mg)
	1-10	Single inhalation from UMEC 500 mcg NDPI once daily
D UMEC/VI therapeutic dose	10	Single dose placebo oral tablet moxifloxacin
	1-10	Single inhalation from UMEC/VI 125/25 mcg NDPI once daily
E UMEC/VI supra-therapeutic dose	10	Single dose placebo oral tablet moxifloxacin
	1-10	Single inhalation from UMEC/VI 500/100 mcg NDPI once daily
	10	Single dose placebo oral tablet moxifloxacin

NDPI=novel dry powder inhaler

Results: Summary Statistics of Day 10 UMEC Pharmacokinetic Parameters

Parameter	Treatment	N	n	Geometric Mean	95% CI	CVb(%)
C _{max} (pg/mL)	UMEC 500 mcg	75	73	1541	(1412, 1682)	38.8
	UMEC/VI 125/25 mcg	75	74	334	(294, 379)	59.1
	UMEC/VI 500/100 mcg	73	70	1400	(1285, 1525)	37.1
AUC _(0-τ) (h*pg/mL)	UMEC 500 mcg	75	73	2444	(2278, 2623)	31.0
	UMEC/VI 125/25 mcg	75	74	495	(431, 569)	65.6
	UMEC/VI 500/100 mcg	73	70	2145	(1977, 2328)	35.2
t _{max} (h)*	UMEC 500 mcg	75	73	0.10	(0.08, 0.23)	NA
	UMEC/VI 125/25 mcg	75	74	0.10	(0.08, 0.15)	NA
	UMEC/VI 500/100 mcg	73	70	0.10	(0.08, 0.12)	NA
t _{last} (h)*	UMEC 500 mcg	75	73	24.08	(23.98, 24.25)	NA
	UMEC/VI 125/25 mcg	75	74	24.08	(0.10, 24.25)	NA
	UMEC/VI 500/100 mcg	73	70	24.08	(24.08, 24.25)	NA
t _{1/2} (h)	UMEC 500 mcg	75	47	25.9	(23.7, 28.3)	0.1
	UMEC/VI 125/25 mcg	75	37	19.1	(12.6, 29.0)	110.9
	UMEC/VI 500/100 mcg	73	36	25.2	(22.4, 28.4)	0.2
CL/F (L/h)	UMEC 500 mcg	75	73	205	(191, 220)	31.0
	UMEC/VI 125/25 mcg	75	73	244	(216, 276)	56.9
	UMEC/VI 500/100 mcg	73	70	233	(215, 253)	35.2
V/F (L)	UMEC 500 mcg	75	47	7749	(6890, 8716)	41.7
	UMEC/VI 125/25 mcg	75	37	7857	(6225, 9918)	79.3
	UMEC/VI 500/100 mcg	73	36	8418	(7375, 9607)	40.6
λ _z	UMEC 500 mcg	75	47	0.027	(0.024, 0.029)	31.2
	UMEC/VI 125/25 mcg	75	37	0.036	(0.024, 0.055)	195.9
	UMEC/VI 500/100 mcg	73	36	0.027	(0.024, 0.031)	36.5

Source Data: [Table 11.2](#)

*Presented as median and range.

NA=not applicable; CVb=between-subject coefficient of variation.

Summary Statistics of Day 10 VI Pharmacokinetic Parameters

Parameter	Treatment	N	n	Geometric Mean	95% CI	CVb(%)
C _{max} (pg/mL)	UMEC/VI 125/25 mcg	75	74	340	(307, 376)	45.9
	UMEC/VI 500/100 mcg	73	70	1518	(1416, 1627)	29.8
AUC(0-τ) (h*pg/mL)	UMEC/VI 125/25 mcg	75	74	429	(379, 486)	57.6
	UMEC/VI 500/100 mcg	73	70	1824	(1728, 1924)	22.9
t _{max} (h)*	UMEC/VI 125/25 mcg	75	74	0.10	(0.08, 0.15)	NA
	UMEC/VI 500/100 mcg	73	70	0.10	(0.08, 0.22)	NA
t _{last} (h)*	UMEC/VI 125/25 mcg	75	74	16.02	(0.52, 24.25)	NA
	UMEC/VI 500/100 mcg	73	70	24.08	(24.08, 24.25)	NA
t _{1/2} (h)	UMEC/VI 125/25 mcg	75	55	10.52	(8.43, 13.12)	97.8
	UMEC/VI 500/100 mcg	73	62	19.22	(17.68, 20.90)	33.9
CL/F (L/h)	UMEC/VI 125/25 mcg	75	74	58.2	(51.4, 65.9)	57.6
	UMEC/VI 500/100 mcg	73	70	54.8	(51.9, 57.9)	22.9
V/F (L)	UMEC/VI 125/25 mcg	75	55	890	(783, 1010)	49.8
	UMEC/VI 500/100 mcg	73	62	1526	(1383, 1684)	40.2
λ _z	UMEC/VI 125/25 mcg	75	55	0.066	(0.053, 0.082)	97.8
	UMEC/VI 500/100 mcg	73	62	0.036	(0.033, 0.039)	33.9

Source Data: [Table 11.4](#)

*Presented as median and range.

NA=not applicable; CVb=between-subject coefficient of variation.

Conclusions:

- Exposure of UMEC is not affected by the presence of VI.
- Steady-state pharmacokinetic data in healthy subjects indicated rapid absorption for both UMEC and VI with high clearance and extensive distribution contributing to their disposition from systemic circulation.
- Thalf for UMEC was 25 h.
- Thalf for VI was 10-19 h.
- The systemic exposure of UMEC and VI was dose proportional based on AUC and C_{max}.

SPECIFIC POPULATION

Renal impairment

UMEC/VI

Trial # DB2114636

Title: A single-blind, non-randomized pharmacokinetic and safety study of single dose of GSK573719 and GSK573719 + GW642444 combination in healthy subjects and in subjects with severe renal impairment.

Objectives:

Primary objective

- To investigate the effect of severe renal impairment on the plasma pharmacokinetics of umeclidinium (UMEC, GSK573719) and vilanterol (VI, GW642444) following single dose administration of inhaled UMEC 125 mcg and single dose UMEC/VI (125/25 mcg), respectively

Secondary objectives

- To investigate the effect of severe renal impairment on the urine pharmacokinetics of UMEC following single dose administration of inhaled UMEC 125 mcg and single dose UMEC/VI (125/25 mcg), respectively
- To investigate the effect of severe renal impairment on safety and tolerability following single dose administration of UMEC 125 mcg and UMEC/VI (125/25 mcg), respectively

Methodology: This was a single-blind, non-randomised study that assessed the pharmacokinetics and safety of inhaled UMEC 125 mcg and UMEC/VI 125/25 mcg in healthy subjects and in subjects with severe renal impairment. Nine subjects with severe renal impairment were to be recruited along with matched healthy control subjects. All subjects were to receive a single dose of UMEC 125 mcg followed by a single dose of UMEC 125 mcg/VI 25 mcg, separated by a washout of at least 7 days.

Treatment administration: A single dose of UMEC 125 mcg via novel dry powder inhaler (NDPI) followed after a washout of at least 7 days by a single dose of UMEC 125 mcg/VI 25 mcg via NDPI. The PK blood sampling schedule was 0, 5, 15, 30, min, 1, 2, 4, 8, 12, 16, 24 hr. The urine sampling schedule was 0-4 hr, 4-8 hr, 8-12 hr, and 16-24 hr.

Analysis:

Primary endpoints

- UMEC and VI plasma pharmacokinetic parameters AUC(0-t), AUC(0-t'), C_{max}, t_{max}, AUC(0-24), AUC(0-∞), t_{last}, t_{1/2}, other pharmacokinetic parameters as data permitted

Secondary endpoints

- UMEC urine pharmacokinetic parameters
- General safety and tolerability endpoints: adverse events (AEs), blood pressure, heart rate, 12-lead electrocardiogram (ECG) and clinical laboratory safety tests

Results:

Summary statistics for plasma UMEC pharmacokinetic parameters are presented below.

Parameter	Group	N	n	n*	Geometric Mean	95% CI	CVb(%)
UMEC 125 mcg							
AUC(0-2) (h*pg/mL)	Healthy	9	9	1	56.5	(34.8, 91.6)	69.7
	Severe renal impairment	9	9	0	59.1	(40.5, 86.3)	52.3
Cmax (pg/mL)	Healthy	9	9	0	127.6	(84.8, 191.9)	57.1
	Severe renal impairment	9	9	0	113.2	(75.2, 170.4)	57.3
tlast (h)*	Healthy	9	9	0	2.00	(0.25, 4.00)	NA
	Severe renal impairment	9	9	0	2.00	(0.50, 4.00)	NA
tmax (h)*	Healthy	9	9	0	0.08	(0.08, 0.12)	NA
	Severe renal impairment	9	9	0	0.08	(0.08, 0.12)	NA
UMEC/VI 125/25 mcg							
AUC(0-2) (h*pg/mL)	Healthy	9	9	0	60.4	(44.6, 81.9)	41.1
	Severe renal impairment	9	9	0	66.3	(48.8, 90.1)	41.5
Cmax (pg/mL)	Healthy	9	9	0	152.4	(101.1, 229.7)	57.4
	Severe renal impairment	9	9	0	149.2	(104.2, 213.5)	49.3
tlast (h)*	Healthy	9	9	0	2.00	(0.50, 4.02)	NA
	Severe renal impairment	9	9	0	2.00	(0.50, 4.00)	NA
tmax (h)*	Healthy	9	9	0	0.08	(0.08, 0.12)	NA
	Severe renal impairment	9	9	0	0.08	(0.08, 0.12)	NA

*Presented as median and range.

NA=not applicable; n*=number imputed.

Summary statistics of UMEC urine pharmacokinetic parameters are presented below.

Parameter	Group	N	n	Geometric Mean	95% Confidence Interval	CVb(%)
UMEC 125 mcg						
Ae(0-24) (ng)	Healthy	9	9	1553	(998, 2415)	62.6
	Severe renal impairment	9	9	178	(100, 319)	87.4
CLr (L/h)	Healthy	9	2	13.041	(0.838, 202.849)	31.3
	Severe renal impairment	9	3	0.881	(0.229, 3.380)	58.4
Fe(0-24) (%)*	Healthy	9	9	1.4337	(0.4938, 3.1294)	NA
	Severe renal impairment	9	9	0.1878	(0.0686, 0.5362)	NA
t½ (h)	Healthy	9	5	9.66	(4.44, 20.99)	69.2
	Severe renal impairment	9	7	8.03	(6.49, 9.94)	23.3
UMEC/VI 125/25 mcg						
Ae(0-24) (ng)	Healthy	9	9	1627	(1186, 2232)	42.9
	Severe renal impairment	9	9	184	(104, 326)	86.1
CLr (L/h)	Healthy	9	1	12.917	ND**	ND
	Severe renal impairment	9	3	0.722	(0.053, 9.835)	142.2
Fe(0-24) (%)*	Healthy	9	9	1.3936	(0.5357, 2.4370)	NA
	Severe renal impairment	9	9	0.1891	(0.0492, 0.5031)	NA
t½ (h)	Healthy	9	3	11.34	(7.58, 16.97)	16.3
	Severe renal impairment	9	8	9.22	(6.54, 12.99)	42.9

* Arithmetic mean value (range).

**ND=not determined due to sample size =1; CLr=renal clearance; Fe=fraction of dose excreted unchanged in urine.

Summary statistics of plasma VI pharmacokinetic parameters are presented below.

Parameter	Group	N	n	Geometric Mean	95% CI	CVb(%)
AUC(0-1) (h*pg/mL)	Healthy	9	9	28.7	(20.6, 40.0)	45.3
	Severe renal impairment	9	9	34.8	(25.9, 46.6)	39.6
Cmax (pg/mL)	Healthy	9	9	74.8	(53.1, 105.4)	46.9
	Severe renal impairment	9	9	77.1	(56.9, 104.7)	41.3
t1/2 (h)*	Healthy	9	9	1.00	(0.50, 2.00)	NA
	Severe renal impairment	9	9	1.00	(1.00, 4.00)	NA
tmax (h)*	Healthy	9	9	0.08	(0.08, 0.12)	NA
	Severe renal impairment	9	9	0.12	(0.08, 0.25)	NA

*Presented as median and range.

Conclusions:

- There was no evidence of a clinically relevant increase in UMEC systemic exposure in subjects with severe renal impairment compared with healthy subjects following administration of UMEC 125 mcg and UMEC/VI 125/25 mcg
- Although urinary excretion of unchanged UMEC was considerably lower in subjects with severe renal impairment compared with healthy subjects for UMEC 125 mcg and UMEC/VI 125/25 mcg, no apparent increase in mean urine t_{1/2} in subjects with severe renal impairment was observed, suggesting efficient alternate disposition and elimination pathways for UMEC in these subjects. Overall urine t_{1/2} between the two groups were comparable
- There was no evidence of a clinically relevant increase in VI systemic exposure in subjects with severe renal impairment compared with healthy subjects
- Inhaled UMEC 125 mcg and UMEC/VI 125/25 mcg were well tolerated in healthy subjects and in subjects with severe renal impairment

FF/VI

Trial # HZA113970

Title: An open-label, non-randomized pharmacokinetic and safety study of repeat doses of fluticasone furoate and GW642444M combination in healthy subjects and in subjects with severe renal impairment

Objective:

Primary:

- To investigate the effect of severe renal impairment on the pharmacokinetics of fluticasone furoate (FF) and vilanterol (VI; GW642444) following repeat administration of FF/VI (200/25 mcg) via novel dry powder inhaler (NDPI)

Secondary:

- To investigate the effect of severe renal impairment on cortisol suppression, heart rate, and potassium following repeat administration of FF/VI (200/25 mcg) via NDPI
- To evaluate the safety and tolerability of FF/VI (200/25 mcg) via NDPI in subjects with severe renal impairment.

Study design: Open-label, non-randomised study. Healthy control subjects were matched to subjects with severe renal impairment by gender, ethnicity, age (± 5 years) and body mass index ($\pm 15\%$).

Treatment groups and sample size: Nine healthy subjects and nine subjects with severe renal impairment (CrCL<30mL/min calculated by Cockcroft-Gault equation).

Duration of Treatment: FF/VI 200/25 mcg once-daily every morning for 7 days.

PK Sampling Schedule

Blood – Day 1 at pre-dose, 5, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 6 and 8 hour after dosing; Day 7 at pre-dose, 5, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hour after dosing.

Results:

Pharmacokinetic results

Higher systemic VI exposure in severe renal impairment patients: Median plasma VI concentrations tended to be higher in subjects with severe renal impairment compared with healthy subjects after both single and repeat dose FF/VI. The summary of FF pharmacokinetic comparisons in renal impairment subjects and healthy subjects is presented in the following table. At day 7, subjects with severe renal impairment had 56% increase in VI AUC and similar VI C_{max}.

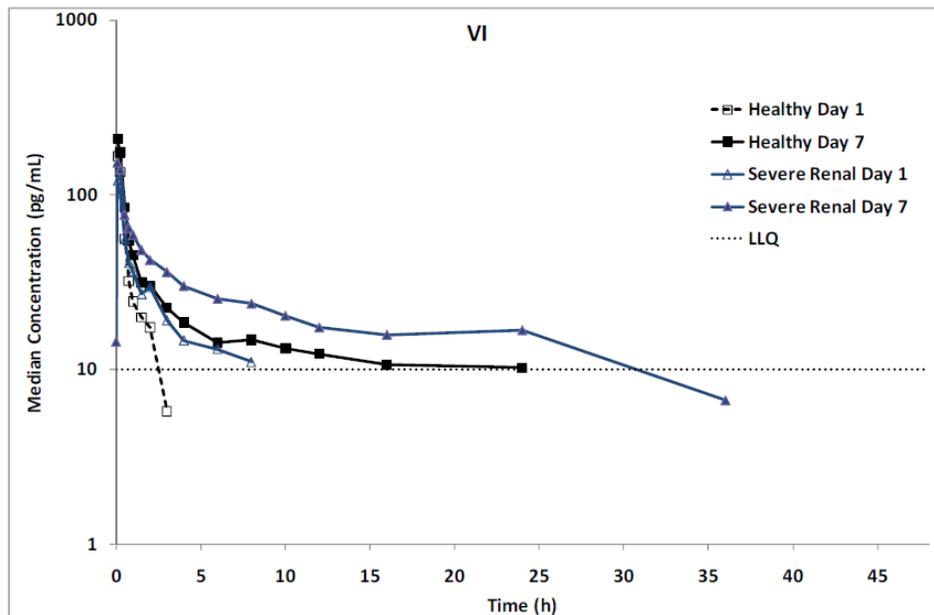
There was no evidence for reduced plasma protein binding of either FF or VI in plasma from subjects with severe renal impairment, compared with plasma from healthy subjects (>99.8% vs. >99.7% for FF and 90.1% vs. 95.4% for VI)

Because of low assay sensitivity for FF, PK parameters (AUC) and concentrations were imputed as a fixed value of ½ LLQ for several subjects. Therefore, the geometric mean ratio was close to 1, despite the lower median concentrations for FF in severe renal impairment patients. FF/VI is an oral inhalation drug intended for local action, and the systemic exposure is more related to safety rather than efficacy. Therefore, a lower systemic exposure of FF in the renal impairment population is not of concern.

VI Pharmacokinetic Parameters in Subjects with Severe Renal Impairment and Healthy Subjects After Single and Repeat Dose (7 Days) FF/VI (200/25 mcg) [HZA113970]

Parameter	Day	Group comparison	Adjusted geometric means	Ratio of adjusted geometric means	90% CI of the ratio
AUC(0–8)	1	Severe renal impairment / healthy	181.12 / 103.38	1.75	(1.00, 3.07)
AUC(0–24)	7	Severe renal impairment / healthy	604.26 / 386.35	1.56	(1.27, 1.92)
C _{max}	1	Severe renal impairment / healthy	126.70 / 107.80	1.18	(0.54, 2.56)
	7	Severe renal impairment / healthy	164.73 / 152.88	1.08	(0.49, 2.35)

(Source –Table 9, Study HZA113970 report)



Median VI Plasma Concentration-Time Profiles in Subjects with Severe Renal Impairment and Healthy Subjects After Single and Repeat Dose (7 Days) FF/VI (200/25 mcg) [HZA113970]
(Source –Figure 2, Study HZA113970 report)

Pharmacodynamic Results:

PD effect was assessed on day 7.

VI related: Maximum heart rate increased for 0.3 bpm in severe renal impairment patients compared to healthy subjects. Minimum serum potassium(0-4h) were on average 0.4 mmol/L higher. The increased PK exposure of VI did not result in significant heart rate increase or serum potassium decrease in severe renal impairment patients compared to healthy subjects.

• Conclusions:

No dose adjustment recommended for subjects with severe renal impairment.

Hepatic Impairment

UMEC/VI

Trial # DB2114637

Title: An open-label, non-randomized, pharmacokinetic and safety study of single dose GSK573719 + GW642444 (VI) combination and repeat doses of GSK573719 in healthy subjects and in subjects with moderate hepatic impairment

Objectives:

- **Primary objectives**
 - To investigate the effect of moderate hepatic impairment on the plasma pharmacokinetics of GSK573719 (umeclidinium, UMEC) and vilanterol (VI) following single dose administration of inhaled UMEC/VI (125 mcg/25 mcg)

- To investigate the effect of moderate hepatic impairment on the plasma pharmacokinetics of UMEC following single and repeat dose administration for 7 days of inhaled UMEC (125 mcg)
- **Secondary objectives**
 - To investigate the effect of moderate hepatic impairment on the urine pharmacokinetics of UMEC following single dose administration of inhaled UMEC/VI (125 mcg/25 mcg)
 - To investigate the effect of moderate hepatic impairment on the urine pharmacokinetics of UMEC following single and repeat dose administration for
 - 7 days of inhaled UMEC (125 mcg)
 - To investigate the effect of moderate hepatic impairment on safety and tolerability of UMEC and VI following single dose administration of inhaled UMEC/VI (125 mcg/25 mcg) and repeat dose administration (for 7 days) of inhaled UMEC (125 mcg), respectively

Methodology: This was an open-label, non-randomised study that assessed the pharmacokinetics and safety of single dose UMEC/VI and repeat daily administration for 7 days of UMEC in subjects with moderate hepatic impairment and matched healthy control subjects. Subjects took a single dose of UMEC/VI (125 mcg/25 mcg) followed by UMEC (125 mcg) once daily for 7 days, after a 7 to 14 day washout.

Data Analysis:

PK

Results:

Summary statistics for UMEC pharmacokinetic parameters on Day 1 and Day 7 are presented below.

UMEC Parameter Day 1	Group	N	n	Geometric Mean	95% CI	CVb(%)
UMEC 125 mcg						
AUC ₍₀₋₂₎ (h*pg/mL)	Healthy	9	9	87	(68, 112)	32.9
	Moderate Hepatic Impairment	9	9	74	(55, 100)	41.1
C _{max} (pg/mL)	Healthy	9	9	220	(151, 320)	51.9
	Moderate Hepatic Impairment	9	9	165	(108, 253)	60.0
t _{last} (h)*	Healthy	9	9	2.00	(2.00, 8.08)	NA
	Moderate Hepatic Impairment	9	9	2.00	(1.00, 4.00)	NA
t _{max} (h)*	Healthy	9	9	0.08	(0.08, 0.12)	NA
	Moderate Hepatic Impairment	9	9	0.08	(0.08, 0.12)	NA
UMEC/VI 125/25 mcg						
AUC ₍₀₋₂₎ (h*pg/mL)	Healthy	9	9	72	(48, 107)	55.4
	Moderate Hepatic Impairment	9	9	66	(52, 83)	30.5
C _{max} (pg/mL)	Healthy	9	9	190	(117, 309)	70.3
	Moderate Hepatic Impairment	9	9	160	(124, 207)	34.2
t _{last} (h)*	Healthy	9	9	2.00	(1.00, 4.03)	NA
	Moderate Hepatic Impairment	9	9	2.00	(1.00, 4.00)	NA
t _{max} (h)*	Healthy	9	9	0.08	(0.08, 0.10)	NA
	Moderate Hepatic Impairment	9	9	0.08	(0.08, 0.12)	NA

*=presented as median and range
CI=confidence interval; NA=not applicable

UMEC Parameter Day 7	Group	N	n	Geometric Mean	95% CI	CVb(%)
UMEC 125 mcg						
AUC ₍₀₋₂₎ (h*pg/mL)	Healthy	9	9	122	(101, 147)	24.9
	Moderate Hepatic Impairment	9	9	105	(76, 146)	44.9
AUC ₍₀₋₇₎ (h*pg/mL)	Healthy	9	9	482	(383, 607)	30.6
	Moderate Hepatic Impairment	9	9	438	(359, 536)	26.5
C _{max} (pg/mL)	Healthy	9	9	283	(220, 363)	33.3
	Moderate Hepatic Impairment	9	9	214	(126, 362)	77.5
t _{last} (h)*	Healthy	9	9	23.72	(8.00, 36.00)	NA
	Moderate Hepatic Impairment	9	9	36.00	(12.00, 36.00)	NA
t _{max} (h)*	Healthy	9	9	0.08	(0.08, 0.12)	NA
	Moderate Hepatic Impairment	9	9	0.08	(0.08, 0.12)	NA

*=presented as median and range

CI=confidence interval; NA=not applicable

As the dosing interval for UMEC is once-daily, AUC₍₀₋₂₄₎ corresponds to AUC₍₀₋₇₎.

Summary statistics for VI pharmacokinetic parameters are presented below.

VI Parameter	Group	N	n	Geometric Mean	95% CI	CVb(%)
AUC ₍₀₋₁₎ (h*pg/mL)	Healthy	9	9	46	(32, 66)	48.9
	Moderate Hepatic Impairment	9	9	36	(27, 46)	35.4
C _{max} (pg/mL)	Healthy	9	9	124	(87, 176)	48.6
	Moderate Hepatic Impairment	9	9	96	(70, 132)	42.7
t _{last} (h)*	Healthy	9	9	1.00	(0.50, 4.00)	NA
	Moderate Hepatic Impairment	9	9	1.00	(0.53, 2.00)	NA
t _{max} (h)*	Healthy	9	9	0.08	(0.08, 0.25)	NA
	Moderate Hepatic Impairment	9	9	0.08	(0.08, 0.12)	NA

*=presented as median and range

CI=confidence interval; NA=not applicable

Conclusions:

- There was no evidence of increased UMEC systemic exposure in subjects with moderate hepatic impairment compared with healthy subjects, following either single or repeat dose administration of UMEC 125 mcg, or single dose administration of UMEC/VI 125/25 mcg
- On average 1.3- to 1.4-fold accumulation based on both C_{max} and AUC was seen in both subject groups following repeat dosing with UMEC 125 mg. The degree of accumulation was similar between the two subject groups. Urine pharmacokinetic results for UMEC were consistent with plasma data with no evidence of an increased UMEC urine excretion in subjects with moderate hepatic impairment compared with healthy subjects
- There was no evidence of increased VI systemic exposure in subjects with moderate hepatic impairment compared with healthy subjects, following single dose administration of UMEC/VI 125/25 mcg
- Repeat dose inhaled UMEC 125 mcg and single dose inhaled UMEC/VI 125/25 mcg were well tolerated in subjects with moderate hepatic impairment and matched healthy controls

FF/VI

Trial # HZA111789

Title: An open-label, non-randomized, pharmacokinetic and safety study of repeat doses of fluticasone furoate and GW642444M combination in healthy subjects and in subjects with mild, moderate or severe hepatic impairment

Objective:

Primary:

- To investigate the effect of varying degrees of hepatic impairment on the pharmacokinetics of fluticasone furoate (FF) and vilanterol (VI; GW642444) following repeat administration of FF/VI (200/25 mcg) via novel dry powder inhaler (NDPI)

Secondary:

- To investigate the effect of varying degrees of hepatic impairment on cortisol suppression, heart rate, and potassium following repeat administration of FF/VI (200/25 mcg) via NDPI
- To evaluate the safety and tolerability of FF/VI (200/25 mcg) via NDPI in subjects with varying degrees of hepatic impairment.

Study design: Open-label, non-randomised study.

Treatment groups and sample size:

- healthy normal liver function (N=9)
- mild hepatic impairment (N=9)
- moderate hepatic impairment (N=9)
- severe hepatic impairment (N=8)

Duration of Treatment: FF/VI 200/25 mcg once-daily every morning for 7 days in healthy subjects and subjects with mild or moderate hepatic impairment. FF/VI 100/12.5 mcg once daily every morning for 7 days in severe hepatic impairment subjects.

PK Sampling Schedule

- **Blood – Day 1** at pre-dose, 5, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 6 and 8 hour after dosing; **Day 7** at pre-dose, 5, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hour after dosing

Pharmacogenomic evaluation

A whole blood sample was collected on a single occasion for future pharmacogenomic evaluation.

Results:

Pharmacokinetic results

No change of VI exposure in hepatic impairment patients: Subjects with various degrees of hepatic impairment had no significant change in AUC and C_{max} of VI compared to normal hepatic function. A higher extent of accumulation was seen for AUC(0–8) for subjects in all hepatic impairment groups, as presented in the following table.

There was no evidence for reduced plasma protein binding of either FF or VI in plasma from subjects with varying degrees of hepatic impairment, compared with plasma from healthy subjects.

Summary of Results of Dose-Normalised VI Pharmacokinetic Parameters in Subjects with Hepatic Impairment Compared with Healthy Subjects [HZA111789]

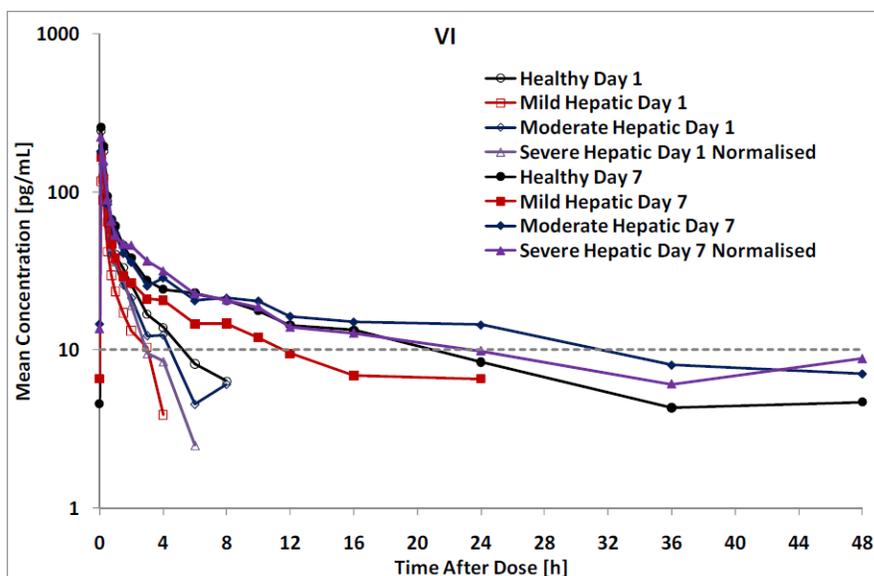
Parameter	Day	Group Comparison	Adjusted Geometric Means	Ratio of Adjusted Geometric Means	90% CI of The Ratio
AUC(0–8)	1	Hepatic Mild /Healthy	81.76 / 204.61	0.40	(0.26, 0.62)
		Hepatic Moderate /Healthy	189.74 / 204.61	0.93	(0.58, 1.48)
		Hepatic Severe /Healthy	118.17 / 204.61	0.58	(0.37, 0.91)
AUC(0–24)	7	Hepatic Mild /Healthy	335.74 / 511.10	0.66	(0.40, 1.08)
		Hepatic Moderate /Healthy	678.27 / 511.10	1.33	(0.78, 2.26)
		Hepatic Severe /Healthy	367.69 / 511.10	0.72	(0.43, 1.20)
Cmax	1	Hepatic Mild /Healthy	107.08 / 225.69	0.47	(0.33, 0.69)
		Hepatic Moderate /Healthy	167.93/ 225.69	0.74	(0.50, 1.11)
		Hepatic Severe /Healthy	167.02 / 225.69	0.74	(0.50, 1.09)
	7	Hepatic Mild /Healthy	154.51 / 246.82	0.63	(0.43, 0.91)
		Hepatic Moderate /Healthy	193.31/ 246.82	0.78	(0.52, 1.17)
		Hepatic Severe /Healthy	206.04 / 246.82	0.83	(0.57, 1.23)

(Source – Table 8, Study HZA111789 report)

Summary of results from statistical analysis of dose-normalised VI pharmacokinetic parameters to assess accumulation

Parameter	Group	Adjusted Geometric Means Day 7 / Day 1	Ratio of Adjusted Geometric Means	90% CI of the Ratio
AUC(0–8)	Healthy	306.17 / 204.61	1.50	(1.21, 1.85)
	Hepatic Mild	210.09 / 81.76	2.57	(2.07, 3.18)
	Hepatic Moderate	342.79 / 189.74	1.81	(1.42, 2.30)
	Hepatic Severe	257.12 / 118.17	2.18	(1.73, 2.73)
Cmax	Healthy	246.82 / 225.69	1.09	(0.89, 1.35)
	Hepatic Mild	154.51 / 107.08	1.44	(1.17, 1.78)
	Hepatic Moderate	193.31/ 167.93	1.15	(0.91, 1.46)
	Hepatic Severe	206.04 / 167.02	1.23	(0.99, 1.54)

(Source – Table 9, Study HZA111789 report)



Mean VI Plasma Concentration-Time Profiles Following Single and Repeat Dose (Once-Daily for 7 Days) FF/VI 200/25 mcg (Healthy, Mild and Moderate Hepatic) or FF/VI 100/12.5 mcg (Severe Hepatic)

(Source – Figure 2, Study HZA111789 report)

Pharmacodynamic Results:

Note that for severe hepatic impairment group, the dose is FF/VI (100/12.5 mcg). PD effect was assessed on day 7.

VI related: For maximum heart rate, the difference versus healthy subjects was less than 4 bpm across all hepatic impairment groups, as presented in the following table. Serum potassium was not consistently lower in the hepatic impairment subjects. The lack of PD changes in heart rate increase or serum potassium decrease was consistent with the similar PK exposure of VI in hepatic impairment patients compared to healthy subjects.

Summary of results from statistical analysis of maximum heart rate (0–4 h) (bpm) on Day 7

Group comparison	Adjusted means test/reference	Difference of adjusted means	90% CI of the difference
Hepatic mild / healthy	76.9 / 73.1	3.8	(-1.2, 8.8)
Hepatic moderate / healthy	76.3 / 73.1	3.2	(-1.7, 8.1)
Hepatic severe / healthy	70.7 / 73.1	-2.4	(-7.7, 3.0)

(Source – Table 10, Study HZA111789 report)

Summary of results from statistical analysis of minimum serum potassium (0–4 h) (mmol/L) on Day 7

7

Group comparison	Adjusted means test/reference	Difference of adjusted means	90% CI of the difference
Hepatic mild / healthy	3.88 / 3.84	0.04	(-0.19, 0.27)
Hepatic moderate / healthy	3.73 / 3.84	-0.11	(-0.34, 0.12)
Hepatic severe / healthy	3.99 / 3.84	0.15	(-0.10, 0.40)

(Source – Table 11, Study HZA111789 report)

Conclusions:

No dose adjustment needed for subjects with hepatic impairment.

DRUG-DRUG INTERACTIONS

DDI with Ketoconazole

VI

Trial # B2C112205

Title: A double-blind, placebo-controlled, randomised, 2-way crossover drug interaction study to investigate the pharmacokinetic and pharmacodynamic effects following coadministration of GW642444M with ketoconazole.

Objective:

- Primary: To determine whether co-administration of repeat dose ketoconazole with single dose inhaled GW642444M had an effect on the single dose systemic pharmacodynamics of GW642444M (supine heart rate and blood potassium levels).
- Secondary:
 - To determine whether repeat dose co-administration of ketoconazole with single dose VI inhalation powder had an effect on blood pressure, QTc duration and blood glucose levels.
 - To determine whether repeat dose co-administration of ketoconazole with single dose VI inhalation powder had an effect on the pharmacokinetics of VI.
 - To investigate the safety and tolerability of co-administration of VI inhalation powder and ketoconazole.

Study design and treatment schedule: This was a single centre, randomised, double-blind, placebo-controlled, two-way crossover study in healthy male and female subjects with two 7-day treatment periods. During each treatment period subjects received single doses of ketoconazole (400 mg) or placebo on the morning of days 1 to 6 with a single dose of GW642444M (25 µg) coadministered on the morning of Day 5.

Reviewer's comment:

The given schedule of ketoconazole 400 mg QD is sufficient in achieving the inhibition of CYP3A4 enzymes in liver and intestine at steady state. VI half-life is ~11 hrs. The inhibition of CYP3A4 would cover the majority of the elimination phase of VI. The product tested in this study (VI 25mcg in NDPI) is in the to-be marketed formulation.

PK Sampling Schedule

Blood –0, 2, 5, 10, 20, 30, 40, 60, 80, 100 min, 2, 3, 4, 6, 8, 12, 16, 24, 30, 36 and 48 hrs after VI administration.

Results:

Pharmacokinetic results

Higher systemic VI exposure with coadministration of ketoconazole: When co-administered with repeat dose ketoconazole 400 mg, single dose GW642444 C_{max} was comparable with, and AUC is 90% higher than, that observed following coadministration of GW642444M with repeat dose placebo.

PK parameters and statistical summary for comparison of plasma VI with and without ketoconazole

Parameter	Treatment Comparison	Adjusted Geometric Means	Ratio of Adjusted Geometric Means	90% CI of Ratio
AUC _(0-t) (h•pg/mL)	Ketoconazole + VI 25 mcg vs. Placebo + VI 25 mcg	304 / 160	1.90	1.37, 2.64
C _{max} (pg/mL)	Ketoconazole + VI 25 mcg vs. Placebo + VI 25 mcg	224 / 252	0.89	0.67, 1.18

(Source – Table 6 and 7, Study B2C112205 report)

Pharmacodynamic results

VI related: Co-administration of repeat dose ketoconazole and VI (25 mcg) had no significant effect on maximum heart rate, weighted mean heart rate, or minimum serum potassium. Maximum QTcF (0–4 h) was, on average 3.1 msec higher and maximum QTc(B)(0-4h) was 5.4 msec higher in the ketoconazole coadministration group.

Summary of statistical analysis of maximum and weighted QTcF (0–4 h) and QTcB(0-4h)

Day	Treatment	n	Adjusted Mean	Treatment Difference (90% Confidence Interval)
Change from Baseline in Maximum QTc(F) (0–4 h) (msec)				
4	Ketoconazole 400 mg	20	14.6	1.2 (-5.7, 8.1)
4	Placebo	19	13.4	
5	GW642444M 25 µg + ketoconazole 400 mg	19	17.9	3.1 (-2.8, 8.9)
5	GW642444M 25 µg + placebo	18	14.8	
Change from Baseline in Weighted Mean QTc(F) (0–4 h) (msec)				
4	Ketoconazole 400 mg	20	1.9	0.7 (-3.7, 5.0)
4	Placebo	18	1.2	
5	GW642444M 25 µg + ketoconazole 400 mg	19	4.7	4.7 (0.4, 8.9)
5	GW642444M 25 µg + placebo	18	0.0	
Change from Baseline in Maximum QTc(B) (0–4 h) (msec)				
4	Ketoconazole 400 mg	20	18.5	2.0 (-6.5, 10.5)
4	Placebo	19	16.5	
5	GW642444M 25 µg + ketoconazole 400 mg	19	26.9	5.4 (-4.2, 15.0)
5	GW642444M 25 µg + placebo	18	21.5	
Change from Baseline in Weighted Mean QTc(B) (0–4 h) (msec)				
4	Ketoconazole 400 mg	20	1.0	2.1 (-2.7, 6.9)
4	Placebo	18	-1.1	
5	GW642444M 25 µg + ketoconazole 400 mg	19	7.7	7.0 (1.3, 12.7)
5	GW642444M 25 µg + placebo	18	0.7	

(Source – Table 5, Study B2C112205 report)

Reviewer’s comment:

The increased PK exposure of VI did not result in significant heart rate increase or serum potassium decrease when VI is coadministered with ketoconazole.

Prolonged QT interval was observed with ketoconazole coadministration. While ketoconazole alone may be associated with QT increases, the increased VI exposure added to the magnitude of QT prolongation. The sponsor label misinterpreted this result and stated (line 713-715) “The increase in vilanterol exposure was not associated with an increase in beta-agonist–related systemic effects on heart rate, blood potassium, (b) (4). This statement about (b) (4) needs to be revised.

Conclusions:

When coadministered with ketoconazole, exposure for VI increased by 90% based on AUC(0-t). The changes in PK lead to 3.1 msec increase in QTcF and 5.4 msec increase in QTcB; therefore, we recommend use with caution with no dose adjustment.

FF/VI

Trial # HZA105548

Title: A double-blind, randomised, placebo-controlled, repeat dose, two-way crossover drug interaction study to investigate the pharmacokinetic and pharmacodynamic effects following administration of fluticasone furoate/GW642444M inhalation powder with

ketoconazole.

Objective:

- Primary:
 - To determine whether repeat dose co-administration of ketoconazole with fluticasone furoate (FF)/vilanterol (VI, GW642444) inhalation powder had an effect on heart rate, blood potassium levels and serum cortisol.
- Secondary:
 - To determine whether repeat dose co-administration of ketoconazole with FF/VI inhalation powder had an effect on blood pressure and QTcF (Fridericia's) duration.
 - To determine whether repeat dose co-administration of ketoconazole with FF/VI inhalation powder had an effect on the pharmacokinetics of FF and VI.
 - To investigate the safety and tolerability of co-administration of FF/VI inhalation powder and ketoconazole.

Study design and treatment schedule: single centre, randomised, double-blind (with respect to ketoconazole), two way crossover study (N=18). Eighteen healthy subjects received once daily oral ketoconazole 400 mg or placebo (Days 1–11) with co-administration of fluticasone furoate (FF)/vilanterol (VI, GW642444) inhalation powder (200/25 mcg) for the final 7 days (Days 5–11).

Study design for HZA105548.

Treatment Sequence	Regimen Code Period 1		Period 1		Regimen Code Period 2		Period 2	
	Days 1–4	Days 5–11	Days 1–4	Days 5–11	Days 1–4	Days 5–11	Days 1–4	Days 5–11
AB or BA	A B	Keto Placebo	Keto + FF/VI Placebo + FF/VI	B A	Placebo Keto	Placebo + FF/VI Keto + FF/VI		

Keto = ketoconazole.

(Source – Table 1, Study HZA105548 report)

Reviewer's comment:

The given schedule of ketoconazole 400 mg QD is sufficient in achieving the inhibition of CYP3A4 enzymes in liver and intestine at steady state. VI half-life is ~11hrs. The inhibition of CYP3A4 would cover the majority of the elimination phase of VI. The VI formulation tested in this study (FF/VI 200/25mcg in NDPI) is the same as the to be marketed product, therefore the information learned in this study could be extrapolated to the to-be-marketed product.

PK Sampling Schedule

Blood –0, 5, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36 and 48 hrs in Periods 1 (Days 5 and 6) and 2 (Days 11, 12 and 13)

Results:

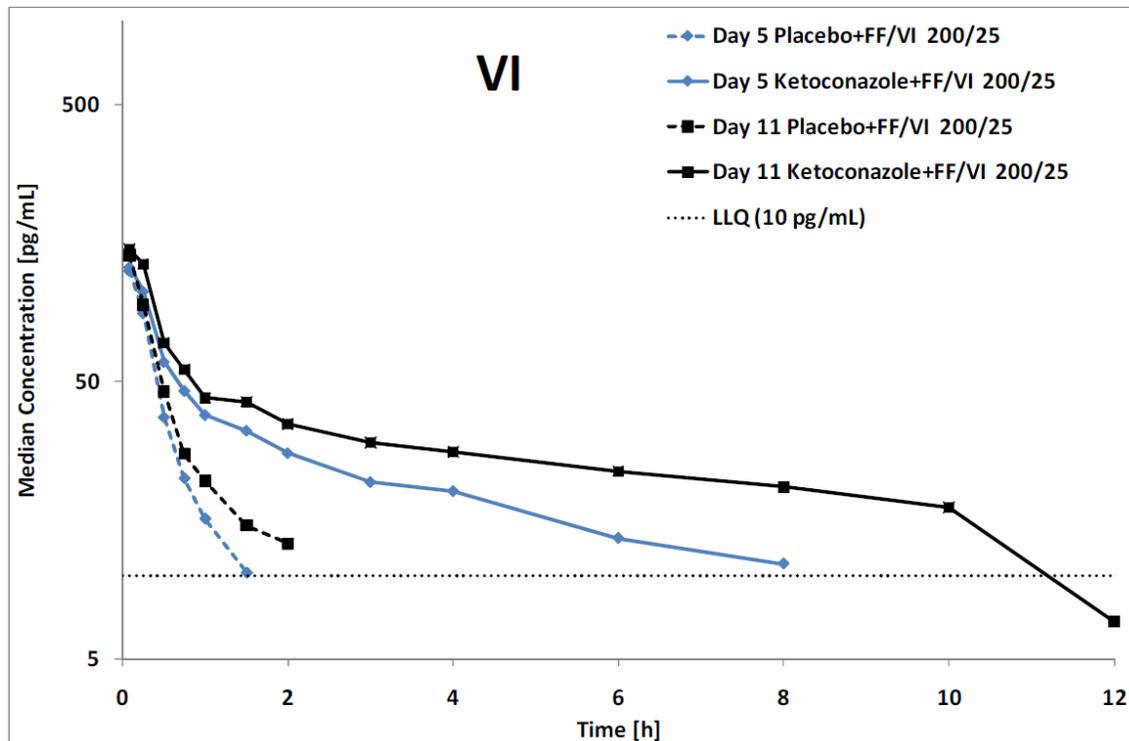
Pharmacokinetic results

Higher systemic VI exposure with coadministration of ketoconazole: Repeat dose co-administration of FF/VI (200/25 mcg) with ketoconazole in comparison with FF/VI (200/25 mcg) with placebo resulted in greater VI exposure. Mean VI AUC(0-t') and Cmax were increased by 65% (90% CI: 38% to 97%) and 22% (90% CI: 8% to 38%), respectively.

PK parameters and statistical summary for comparison of plasma VI with and without ketoconazole.

Parameter	Comparison	Ratio of Geometric Means	90% CI of the Ratio
AUC(0-t')	Ketoconazole + FF/VI 200/25 : Placebo + FF/VI 200/25	1.65	(1.38, 1.97)
Cmax	Ketoconazole + FF/VI 200/25 : Placebo + FF/VI 200/25	1.22	(1.08, 1.38)

(Source – Table 12, Study HZA105548 report)



Median VI Semi-log Concentration-time Profiles Following a Single (Day 5) and Repeated (Day 11) Inhaled Administration of FF/VI (200/25 mcg) with Placebo or Ketoconazole

(Source – Figure 4, Study HZA105548 report)

Pharmacodynamic results

VI related: Co-administration of repeat dose ketoconazole and FF/VI (200/25 mcg) had no significant effect on maximum heart rate, blood pressure, or minimum serum

potassium (0-4h). Maximum QTcF (0–4 h) was, on average 7.55 msec higher in the ketoconazole coadministration group, as presented in the following table.

Summary of statistical analysis of minimum diastolic blood pressure, maximum systolic blood pressure and maximum QTcF (0–4 h) on Day 11

Treatment comparison	Parameter	Adjusted means test/ reference	Difference of adjusted means	90% CI of difference
Ketoconazole + FF/VI 200/25 mcg – placebo + FF/VI 200/25 mcg	Minimum diastolic blood pressure (0–4 h) (mmHg)	57.8 / 59.8	-2.0	(-4.4, 0.3)
	Maximum systolic blood pressure (0–4 h) (mmHg)	114.9 / 115.0	-0.1	(-2.7, 2.5)
	Maximum QTcF (0–4 h) (msec)	425.96 / 418.41	7.55	(4.51, 10.60)

(Source – Table 8, Study HZA105548 report)

Reviewer’s comment:

The increased PK exposure of VI did not result in significant heart rate increase or serum potassium decrease when FF/VI is coadministered with ketoconazole.

Conclusions:

When coadministered with ketoconazole, exposure for VI increased. The changes in PK lead to 7.6msec increase in QTcF; therefore, we recommend use with caution with no dose adjustment.

7. DDI with Verapamil

UMEC/VI

Trial # DB2113950

Title: A single-centre, randomised, open-label study to evaluate the effects of steady-state verapamil, a moderate P-glycoprotein and CYP3A4 inhibitor, on the pharmacokinetics of GSK573719 and GSK573719 in combination with GW642444.

Objective: To assess the effects of verapamil 240 mg once daily on the steady-state pharmacokinetics of inhaled GW642444 in combination with inhaled GSK573719 in healthy subjects.

Study design and treatment schedule: Single centre, randomized, open label design. For this NDA, only data from cohort 2 was relevant and reviewed. Sixteen subjects were randomized to cohort 2.

Cohort 2, Period 1: GSK573719 (500 mcg) QD and GW642444 (25 mcg) QD for 8 days, immediately followed by Period 2: 5 days of GSK573719 (500 mcg) QD, GW642444 (25 mcg) QD and verapamil 240 mg QD.

Reviewer’s comment:

Verapamil is a combined P-gp inhibitor/ CYP3A4 inhibitor. The given schedule of verapamil 240 mg QD is sufficient in achieving the inhibition of P-gp and CYP3A4 at steady state. VI half-life is ~3 hrs. The inhibition of CYP3A4 would cover the majority of the elimination phase of UMEC and VI.

Notably throughout the study report, the dose of GSK573719 and GW642444 are 500 mg, and 25 mg respectively, instead of mcg. We assume it's a typing error.

PK Sampling Schedule

Blood –0, 5, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36 and 48 hrs in Periods 1 (Days 5 and 6) and 2 (Days 11, 12 and 13)

Results:

Pharmacokinetic results

UMEC PK results are shown in the table below. The analysis showed that the ratio of adjusted geometric means of Cmax showed no evidence of a difference when GSK573719 500 mg was administered in presence or absence of verapamil or in combination with GW642444 (25 mg). The treatment ratios were close to 1 for Cmax for both cohorts. For the 719 cohort (ratio=1.05, 90% CI; 0.90 to 1.22) and for the 719/444 cohort (ratio=0.89, 90% CI; 0.73 to 1.07). However, in the analysis of AUC(0-t), the ratio of adjusted geometric means showed evidence of a verapamil effect with the treatment ratio for the monotherapy group being 1.39 (90% CI; 1.18 to 1.64) and 1.37 (90% CI: 1.29 to 1.46) for the combination therapy, thereby indicating ~40% higher GSK573719 systemic exposure in terms of AUC when co-administered with verapamil.

Table 7 Summary of Analysis of Derived Plasma GSK573719

Parameter	Ratio of Adjusted Geometric Means		
	Treatment	Ratio	90% CI of the Ratio
AUC(0-0.25)	719 + V vs 719	1.06	(0.93, 1.21)
	719/444 + V vs 719/444	0.93	(0.78, 1.12)
AUC(0-2)	719 + V vs 719	1.15	(1.03, 1.28)
	719/444 + V vs 719/444	1.07	(0.95, 1.21)
AUC(0-t)	719 + V vs 719	1.39	(1.18, 1.64)
	719/444 + V vs 719/444	1.37	(1.29, 1.46)
Cmax	719 + V vs 719	1.05	(0.90, 1.22)
	719/444 + V vs 719/444	0.89	(0.73, 1.07)

Source Data: [Table 12.4](#)

CI = confidence interval; V = verapamil; AUC(0-x) = area under the plasma concentration-time curve from time zero to a fixed time x (h); AUC(0-t) = AUC over the dosing interval; Cmax = maximum observed plasma concentration.

Plasma GW642444 pharmacokinetic parameter estimates are summarized by treatment in the table below. GSK573719/VI co-administration with verapamil (240 mg once daily for five days) did not affect the VI C_{max} or AUC.

Summary of Analysis of Derived VI Pharmacokinetic Parameters Following Repeated Inhaled Administration of GSK573719/VI With and Without Verapamil in Healthy Subjects

Parameter	Ratio of Adjusted Geometric Means		
	Treatment	Ratio	90% CI of the Ratio
AUC _(0-0.25)	719/VI + V vs 719/VI	1.08	(0.93, 1.27)
AUC _(0-0.5)	719/VI + V vs 719/VI	1.02	(0.90, 1.15)
AUC ₍₀₋₂₎	719/VI + V vs 719/VI	1.14	(0.94, 1.37)
C _{max}	719/VI + V vs 719/VI	1.05	(0.90, 1.22)

CI = confidence interval; V = verapamil; C_{max} = maximum observed plasma concentration; AUC_(0-x) = area under the plasma concentration-time curve from time zero to a fixed time x (h).

(Source – Table 14, Study DB2113950 report)

Summary Statistics of Day 8 GW642444 Pharmacokinetic Parameters when used in combination of GSK 573719

Parameter	Treatment	N	n	Geometric Mean	95% CI	CVb(%)
AUC(0-0.25) (h•pg/mL)	719 500mg/444 25mg	16	15	38.895	(29.448, 51.372)	53.6
AUC(0-0.5) (h•pg/mL)	719 500mg/444 25mg	16	15	53.921	(36.311, 80.073)	81.5
AUC(0-2) (h•pg/mL)	719 500mg/444 25mg	16	15	78.328	(52.168, 117.608)	84.5
AUC(0-t) (h•pg/mL)	719 500mg/444 25mg	16	15	63.934	(40.156, 101.792)	101.2
C _{max} (pg/mL)	719 500mg/444 25mg	16	15	229.948	(174.813, 302.471)	52.7
t _{max} (h)*	719 500mg/444 25mg	16	15	0.0833	(0.0833, 0.1000)	NA
t _{last} (h)*	719 500mg/444 25mg	16	15	0.5333	(0.2500, 2.0000)	NA

(Source – Table 12, Study DB2113950 report)

Pharmacodynamic results

Maximum heart rate increased by 0.4 bpm with co-administration of repeat dose verapamil, as presented in the table below. Weighted mean (0-4h) heart rate was 0.61 bpm higher. Maximum QTcF was 7.67 msec longer. Minimum potassium (0-4h) was 0.13mmol/L lower. The clinical implication of these changes is not clear, and the interpretation of the PD change is complicated by the presence of another drug GSK573719.

- Heart rate ↑
- QT↑
- Plasma potassium↓

Summary of Analysis of Maximum Heart Rate (0–4 h) (bpm)

Treatment Comparison	Adjusted Means		Difference	90% CI of Difference
	Test (+V)	Reference		
719 v 719+V	69.07	63.33	5.74	(-3.25, 14.73)
719/444 v 719/444+V	70.87	70.47	0.40	(-3.04, 3.84)

(Source – Table 18, Study DB2113950 report)

Summary of Analysis of Maximum QTcF (0–4 h) (msec)

Treatment Comparison	Adjusted Means		Difference	90% CI of Difference
	Test (+V)	Reference		
719 v 719+V	410.9	402.0	8.96	(4.75, 13.16)
719/444 v 719/444+V	407.0	399.3	7.67	(3.74, 11.59)

(Source – Table 24, Study DB2113950 report)

Summary of Analysis of Minimum Potassium (0–4 h) (mmol/L)

Treatment Comparison	Adjusted Means		Difference	90% CI of Difference
	Test (+V)	Reference		
719 v 719+V	3.93	4.03	-0.10	(-0.19, -0.01)
719/444 v 719/444+V	3.92	4.05	-0.13	(-0.23, -0.04)

(Source – Table 28, Study DB2113950 report)

• **Conclusions:**

VI pharmacokinetics was not affected by P-gp inhibition. Drug interaction trials with a specific P-gp inhibitor and fluticasone furoate have not been conducted.

Reviewer's comment:

VI exposure is similar with the addition of verapamil.

The PD changes might be related to the effect of GSK573719 and verapamil. The PD changes may not be statistically significant for some endpoints, but the long term impact on safety is uncertain.

8. DDI between UMEC and VI

Trial #AC4110106

Title: A single centre, randomised, double-blind, dose ascending, placebo-controlled study, in two parts, to evaluate the safety, tolerability and pharmacokinetics of escalating single and repeat inhaled doses of GSK573719 and placebo formulated with the excipient magnesium stearate, in healthy subjects and in a healthy population of Cytochrome P450 Isoenzyme 2D6 poor metabolisers.

Objective:

Part 1

- To evaluate the safety and tolerability of GSK573719 administered as single inhaled doses of 100 µg, 500 µg and 1000 µg in healthy subjects (extensive, intermediate or ultra-rapid CYP2D6 metabolisers).
- To evaluate the safety and tolerability of GSK573719 administered once daily by inhalation of 500 µg and 1000 µg doses for seven days in healthy subjects (extensive, intermediate or ultra-rapid CYP2D6 metabolisers).

Part 2

- To evaluate the safety and tolerability of GSK573719 administered as single inhaled doses of 100 µg, 500 µg and 1000 µg in a healthy population of CYP2D6 poor metabolisers (PM).
- To evaluate the safety and tolerability of GSK573719 administered as repeat daily

dose at 100 µg, 500 µg and 1000 µg for 7 days in a healthy population of CYP2D6 PM.

Secondary:

Part 1

- To evaluate the pharmacokinetics (PK) of GSK573719 administered as single inhaled doses of 100 µg, 500 µg and 1000 µg in healthy subjects (extensive, intermediate or ultra-rapid CYP2D6 metabolisers).
- To evaluate the PK of repeat inhaled doses of GSK573719 administered once daily by inhalation of doses of 500 µg and 1000 µg doses for seven days in healthy subjects (extensive, intermediate or ultra-rapid CYP2D6 metabolisers).
- To explore any relevant relationship between dose and concentration of GSK573719 versus systemic effects [including heart rate (HR)].

Part 2

- To evaluate the PK of GSK573719 administered as single inhaled doses of 100 µg, 500 µg and 1000 µg in a healthy population of CYP2D6 PM.
- To evaluate the PK of repeat inhaled doses of GSK573719 administered once daily by inhalation of doses of 100 µg, 500 µg and 1000 µg for seven days in healthy population of CYP2D6 PM.
- To explore any relevant relationship between dose and concentration of GSK573719 versus systemic effects (including HR).

Study design and treatment schedule: This was a single centre, randomised, double-blind, placebo-controlled study, in two parts, to evaluate the safety, tolerability and pharmacokinetics of escalating single doses and repeat doses of inhaled GSK573719 (100 µg, 500 µg and 1000 µg) formulated with the excipient magnesium stearate (MgSt) and placebo in healthy subjects and in a healthy population of Cytochrome P450 Isoenzyme CYP2D6 PM. Drug was administered using a novel dual strip dry powder device.

Twenty subjects were randomised into Part 1 of the study. The ratio of subjects receiving active: placebo drug was 4:1. Thus, 16 healthy subjects received ascending doses of GSK573719. Eight subjects were randomised to Sequence 1, receiving 500 µg in the repeat dose period and 8 subjects were randomised to Sequence 2, receiving 1000 µg in the repeat dose period. Four subjects were randomised to Sequence 3 and received Placebo for all four periods.

Randomisation Sequence for Part 1

Sequence	Period 1 SD	Period 2 SD	Period 3 SD	Period 4 RD
1 (8 subjects)	100 µg	500 µg	1000 µg	500µg
2 (8 subjects)	100 µg	500 µg	1000 µg	1000 µg
3 (4 subjects)	Placebo	Placebo	Placebo	Placebo

SD= Single dose; RD= Repeat Dose

Sixteen CYP2D6 PM subjects were randomised into Part 2, 8 in Cohort I (Sequences 1 and 2) and 8 in Cohort II (Sequences 3 and 4). Six CYP2D6 PM were randomised to Sequence 1 and 6 to Sequence 3. Two CYP2D6 PM were randomised to Sequence 2 and

2 to Sequence 4. Thus, 12 CYP2D6 PM in total received ascending doses of GSK573719 and 4 subjects received placebo for all periods.

Randomisation Sequence for Part 2

Cohort	Sequence	Period 1 SD	Period 2 RD	Period 3 SD	Period 4 RD	Period 5 SD	Period 6 RD
I	1 (6 subjects)	100 µg	100 µg	500 µg	500 µg	X	X
	2 (2 subjects)	Placebo	Placebo	Placebo	Placebo	X	X
II	3 (6 subjects)	X	X	500 µg	500 µg	1000 µg	1000 µg
	4 (2 subjects)	X	X	Placebo	Placebo	Placebo	Placebo

SD= Single dose; RD= Repeat Dose

PK Results and Conclusions:

The ratio of the adjusted geometric means and corresponding 90% CIs showed no clear evidence of a difference in systemic exposure between HVT and PM populations.

Statistical Analysis of Derived Plasma Parameters to Assess Differences in Exposure between PM and HVT

Parameter	Treatment Comparison PM vs HVT	Day	Ratio of Adj. Geo. Means	90% CI
AUC _(0-0.25) (h•ng/mL)	GSK573719 100 µg	1	1.261	(0.955, 1.663)
AUC ₍₀₋₄₎ (h•ng/mL)	GSK573719 500 µg	1	1.076	(0.862, 1.342)
AUC ₍₀₋₂₄₎ (h•ng/mL)	GSK573719 1000 µg	1	1.093	(0.831, 1.439)
AUC _(0-τ) (h•ng/mL)	GSK573719 500 µg	7	1.029	(0.789, 1.343)
	GSK573719 1000 µg	7	1.331	(0.978, 1.811)
C _{max} (ng/mL)	GSK573719 100 µg	1	1.277	(0.936, 1.743)
	GSK573719 500 µg	1	1.212	(0.942, 1.558)
	GSK573719 1000 µg	1	1.040	(0.764, 1.416)
	GSK573719 500 µg	7	0.800	(0.594, 1.078)
	GSK573719 1000 µg	7	1.072	(0.761, 1.511)

BIOPHARMACEUTICS

9. Absolute Bioavailability

UMEC

Trial # AC4112008

Title: A single-centre, open-label, sequential, cross-over study to examine the safety, tolerability and pharmacokinetics of three ascending single intravenous doses, a single 1000 µg oral dose and a single 1000 µg inhaled dose of GSK573719 in healthy male volunteers.

Objectives:

Primary objective:

- To establish a safe and well-tolerated intravenous (IV) dose of

GSK573719 for administration in the subsequent radiolabel study.

Secondary objectives:

- To evaluate the pharmacokinetics of ascending single IV doses, a single oral dose and a single inhaled dose of GSK573719, in healthy male subjects.
- To determine the bioavailability of GSK573719 following single oral and single inhaled administration.

Methods: The treatments in Study AC4112008 were as follows:

- Single IV doses of umeclidinium 20, 50, and 65 microgram: Umeclidinium solution for infusion (20 microgram/mL) was provided in 10 mL vials. Intravenous infusion delivered in 20 mL 0.9% w/v sodium chloride over 30 minutes.
- A single oral dose of umeclidinium 1000 microgram: Umeclidinium solution for infusion (20 microgram/mL) was provided in 10 mL vials and administered as a single 50 mL oral bolus dose followed by an additional 100 mL of water.
- A single IH dose of umeclidinium 1000 microgram (2x500 microgram strips in inhaler) inhalation powder administered as a single oropharyngeal inhalation.

Subjects: 10 subjects will be enrolled. Healthy non-smoking male subjects aged 18–65 years with a body mass index within the range 18–30 kg/m², inclusive.

Criteria for evaluation: Safety tolerability, plasma PK and urine PK

Results:

Safety: GSK573719 was well tolerated. There were no serious adverse events (SAEs) and no AEs leading to withdrawal. There were no AEs that appeared to increase in frequency with increasing IV dose (GSK573719 20–65 µg). All AEs were of mild intensity; there were no AEs of moderate or severe intensity.

PK: Following a single inhaled dose administration, umeclidinium was rapidly absorbed with the C_{max} values occurring at approximately 5 to 15 minutes post-dose. Plasma concentrations declined rapidly following the occurrence of C_{max}. Plasma concentrations of umeclidinium following single oral dose administration were all non-quantifiable (NQ; Lower Limit of Detection, bioanalytical assay LLQ was 0.02 ng/mL). Absolute bioavailability of umeclidinium following inhaled administration was calculated using plasma data following 1000 microgram inhalation which averaged 12.8% (95% CI: 9.0%, 18.2%). Absolute bioavailability of umeclidinium following oral administration using plasma data was reported as negligible (<1%) since all plasma concentrations of umeclidinium were non-quantifiable following oral administration.

Selected plasma GSK573719 pharmacokinetic parameters are shown below:

Summary of Selected Umeclidinium Pharmacokinetic Parameters Following a Single Dose Administration in Healthy Subjects (Study AC4112008)

Parameter	Dose	N	n	Geometric Mean	95% CI	CV%
AUC _(0-∞) (h•ng/mL)	20 mcg IV	10	10	0.132	0.087, 0.201	64.3
	50 mcg IV	9	8	0.525	0.416, 0.661	28.2
	65 mcg IV	9	9	0.543	0.277, 1.067	108
	1000 mcg IH	9	9	1.33	1.08, 1.65	28.3
AUC ₍₀₋₁₎ (h•ng/mL)	65 mcg IV	9	9	0.688	0.550, 0.860	29.7
	1000 mcg IH	9	9	0.615	0.525, 0.720	20.8
C _{max} (ng/mL)	20 mcg IV	10	10	0.377	0.305, 0.465	30.3
	50 mcg IV	9	8	1.14	0.99, 1.33	18.0
	65 mcg IV	9	9	1.55	1.22, 1.98	32.4
	1000 mcg IH	9	9	1.67	1.18, 2.35	47.2
t _{max} (h) ^a	20 mcg IV	10	10	0.48	0.33, 0.53	-
	50 mcg IV	9	8	0.48	0.48, 0.53	-
	65 mcg IV	9	9	0.48	0.33, 0.48	-
	1000 mcg IH	9	9	0.083	0.08, 0.25	-
F (%)	1000 mcg IH	9	8	12.82	9.04, 18.17	43.7

Urine GSK573719 pharmacokinetic parameters

Parameter	Dose	N	n	Geometric Mean	95% Confidence Interval	CV _g (%)
Ae(0-12) (ng)	20 µg IV	10	10	2297.2	(1826.4, 2889.3)	32.9
	50 µg IV	9	8	5267.5	(4629.0, 5994.0)	15.5
	65 µg IV	9	9	8908.6	(7681.2, 10332.2)	19.5
	1000 µg IH	9	9	14062.7	(10646.9, 18574.3)	37.4
Ae(0-24) (ng)	20 µg IV	10	10	2326.5	(1842.3, 2938.0)	33.5
	50 µg IV	9	8	5383.4	(4733.7, 6122.2)	15.5
	65 µg IV	9	9	9677.5	(8323.8, 11251.4)	19.8
	1000 µg IH	9	9	16598.6	(12648.6, 21782.0)	36.5
Ae(0-36) (ng)	20 µg IV	10	10	2326.5	(1842.3, 2938.0)	33.5
	50 µg IV	9	8	5428.3	(4782.1, 6161.9)	15.2
	65 µg IV	9	9	10423.1	(8950.7, 12137.6)	20.0
	1000 µg IH	9	9	18518.0	(14065.3, 24380.4)	37.0
Ae(0-48) (ng)	20 µg IV	10	10	2326.5	(1842.3, 2938.0)	33.5
	50 µg IV	9	8	5502.6	(4846.7, 6247.2)	15.3
	65 µg IV	9	9	11126.5	(9513.4, 13013.1)	20.6
	1000 µg IH	9	9	20153.9	(15249.8, 26635.1)	37.5
Fe(0-4)(%) ^a	20 µg IV	10	10	10.5571	(8.2952, 12.8550)	NC
	50 µg IV	9	8	9.3942	(8.0317, 10.7568)	NC
	65 µg IV	9	9	11.8088	(9.9433, 13.6743)	NC
	1000 µg IH	9	9	1.0749	(0.8061, 1.3437)	NC
Fe(0-12)(%) ^a	20 µg IV	10	10	11.9791	(9.5784, 14.3797)	NC
	50 µg IV	9	8	10.6460	(9.2595, 12.0325)	NC
	65 µg IV	9	9	13.9202	(12.0288, 15.8117)	NC
	1000 µg IH	9	9	1.4861	(1.0983, 1.8739)	NC
Fe(0-24)(%) ^a	20 µg IV	10	10	12.1465	(9.6986, 14.5943)	NC
	50 µg IV	9	8	10.8792	(9.4697, 12.2887)	NC
	65 µg IV	9	9	15.1297	(13.0383, 17.2210)	NC
	1000 µg IH	9	9	1.7502	(1.3007, 2.1996)	NC
Fe(0-36)(%) ^a	20 µg IV	10	10	12.1465	(9.6986, 15.5943)	NC
	50 µg IV	9	8	10.9661	(9.5786, 12.3535)	NC
	65 µg IV	9	9	16.2988	(14.0458, 18.5519)	NC
	1000 µg IH	9	9	1.9547	(1.4501, 2.4592)	NC
Fe(0-48)(%) ^a	20 µg IV	10	10	12.146	(9.699, 14.594)	NC
	50 µg IV	9	8	11.116	(9.707, 12.526)	NC
	65 µg IV	9	9	17.413	(14.967, 19.859)	NC
	1000 µg IH	9	9	2.130	(1.577, 2.682)	NC
CL _r (L/h)	1000 µg IH	9	9	10.427	(8.870, 12.257)	21.3
F (%)	1000 µg IH	9	9	13.066	(10.456, 16.326)	29.6
AUER (0-30) (ng)	20 µg IV	10	7	1567.4	(1212.6, 2026.1)	28.3
	50 µg IV	9	8	3556.4	(3187.3, 3968.3)	13.2
	65 µg IV	9	9	7067.5	(6123.5, 8157.1)	18.8
	1000 µg IH	9	9	14206.3	(10742.3, 18787.3)	37.6
AUER (0-42) (ng)	20 µg IV	10	7	1570.2	(1214.0, 2030.9)	28.4
	50 µg IV	9	8	3648.7	(3275.5, 4064.4)	13.0
	65 µg IV	9	9	7786.7	(6699.5, 9050.4)	19.8
	1000 µg IH	9	7	15680.8	(10776.2, 22817.7)	42.3

a. Arithmetic mean (95% confidence interval).

NC = not calculated; Ae = amount of drug excreted unchanged in urine, Fe = fraction of dose excreted unchanged in urine.

Source: page 6 from synopsis of AC4112008

Conclusions:

- Following administration of inhaled GSK573719 at 1000 µg, rapid absorption was observed with C_{max} values for individual subjects occurring at approximately 5–15 minutes post-dose.

- Plasma concentrations of GSK573719 were all NQ following oral administration of GSK573719 1000 µg.
- Bioavailability of GSK573719 following inhaled GSK573719 at 1000 µg averaged 13% based on both plasma and urine data.
- Urine pharmacokinetic data showed that on average 2% of the total inhaled dose administered was excreted unchanged in urine (Fe) over 48 h post dose, and on average approximately 11% to 17% of the total IV dose administered was excreted unchanged in urine (Fe) over 48 h post dose.
- Plasma pharmacokinetic data suggested a dose proportional increase in AUC and Cmax as dose increased from 20 µg to 65 µg following IV administration of GSK573719; however, urine Ae(0-48) data suggested a more than dose proportional increase as dose increased from 20 µg to 65 µg.

VI

Trial # B2C106180

Title: A single-centre, open-label, sequential, dose-ascending study to examine safety, tolerability, pharmacodynamics and pharmacokinetics of single intravenous and oral doses of GW642444 in healthy male subjects.

Objective:

To determine the PK and safety of GW642444 (vilanterol, VI) when administered as IV, oral, or inhalation powder from novel dry powder inhaler in healthy subjects.

Study design and treatment schedule:

open-label, ascending single dose study in nine healthy male volunteers divided into two groups, Group 1 (n=3) and Group 2 (n=6). The study design is presented in the table below. The treatment periods were separated by a washout period of at least 7 days and no more than 14 days.

Study period	Treatment given (single dose)	Subject numbers
1	GW642444 2.5 µg IV	1 to 3
2	GW642444 20 µg IV	1 to 3
3	GW642444 55 µg IV	1 to 9
4	GW642444M/MgSt 100 µg inhaled	1 to 9
5	None – Period 5 cancelled	Not applicable
6	GW642444 200 µg oral	1 to 3
	GW642444 500 µg oral	4 to 9

Source: Table 1, study report b2c106180

PK Sampling Schedule

Blood – IV at pre-dose, 30, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24 and 48 hour after dosing; **Inhaled dosing at** pre-dose, 2, 5, 10, 20, 30 min, 1, 2, 3, 4, 6, 8, 10, 12, 24 and 48 hour after dosing; **Oral dosing at** pre-dose, 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hour after dosing;

Results and Conclusions

The absolute bioavailability of VI following oral inhalation administration was about 30%, as calculated from the ratio of AUCs to a common time point after IV administrations. The estimated absolute bioavailability based on urinary excretion data is 26% for VI.

Individual Inhaled Bioavailability Estimated from Urinary Excretion of Unchanged GW64244 (0-48h)

STUDYID	SUBJID	PATRTGRP	PCTYP	PARAMETER	ESTIMATE	UNITS
B2C106180	1	444M 100mcg Inh	Urine	F_inhaled_urine	25.6	%
B2C106180	2	444M 100mcg Inh	Urine	F_inhaled_urine	32.4	%
B2C106180	3	444M 100mcg Inh	Urine	F_inhaled_urine	24.1	%
B2C106180	4	444M 100mcg Inh	Urine	F_inhaled_urine	13.9	%
B2C106180	5	444M 100mcg Inh	Urine	F_inhaled_urine	24.2	%
B2C106180	6	444M 100mcg Inh	Urine	F_inhaled_urine	16.8	%
B2C106180	7	444M 100mcg Inh	Urine	F_inhaled_urine	25.9	%
B2C106180	8	444M 100mcg Inh	Urine	F_inhaled_urine	27.0	%
B2C106180	9	444M 100mcg Inh	Urine	F_inhaled_urine	31.7	%

(Source – Table 13.0, Study B2C106180 report)

PD study

12. PKPD

Trial # DB2113208

Title: A single centre, randomised, placebo-controlled, four-way cross over study to assess the safety, tolerability, pharmacodynamics and pharmacokinetics of single inhaled doses of GSK573719 and GW642444 as monotherapies and concurrently in healthy Japanese subjects.

Objectives:

Primary:

- To evaluate the safety and tolerability of GSK573719 500 µg and GW642444 50 µg administered as single inhaled doses and in combination (GSK573719 500 µg and GW642444 50 µg) in healthy Japanese subjects.

Secondary:

- To evaluate the pharmacokinetics (PK) of GSK573219 500 µg and GW642444 50 µg administered as single inhaled doses and concurrently (GSK573719 500 µg and GW642444 50 µg) in healthy Japanese subjects.

Exploratory:

- To evaluate the effect of GSK573719 500 µg and GW642444 50 µg administered as single inhaled doses and concurrently (GSK573719 500 µg and GW642444 50 µg) in healthy Japanese subjects on lung function parameters.

Study design and treatment schedule:

This was a single centre, double-blind, placebo-controlled, four-way crossover, randomised, single dose study in healthy Japanese subjects.

All subjects attended the unit for Screening within 30 days of their first dosing period. Each subject was admitted to the unit in the day prior to Day 1 of each of the treatment period and remained resident until all the 24 h assessments had been completed. The GSK573719 and GW642444 products were delivered using 2 monotherapy devices (one GSK573719 and GW642444 device). Therefore, each subject received a total of two devices; the second device was a Placebo (lactose monohydrate) except when both GSK573719 and GW642444 were administered. Each subject received the following treatments once only.

- Placebo and Placebo
- GSK573719 500 µg and Placebo
- GW642444 50 µg and Placebo
- GSK573719 500 µg and GW642444 50 µg

The order in which these treatments were administered was in accordance with the randomisation schedule, and there was a minimum washout period of 7 days between doses. All subjects attended the unit for a Follow-up visit 5 to 10 days following their final dose. The maximum duration of the study for each randomised subject was about 10 weeks (Screening to Follow-up inclusive).

Criteria for evaluation: PK and PD (FEV1)

Results: Following a single dose administration of either GSK573719 alone or combination of GSK573719 and GW642444, GSK573719 was rapidly absorbed with all of the C_{max} values occurring at 5 min following which plasma concentrations declined rapidly.

Parameter	Treatment	N	n	n*	Geometric Mean	95% CI	CVb(%)
AUC(0-0.25) (h•pg/mL)	GSK573719 500 µg	15	15	2	126.519	(82.969, 192.928)	88.7
	GSK573719 500 µg /GW642444 50 µg	15	15	0	179.603	(140.326, 229.873)	46.9
AUC(0-2) (h•pg/mL)	GSK573719 500 µg	15	15	2	312.130	(194.090, 501.959)	104.3
	GSK573719 500 µg /GW642444 50 µg	15	15	0	413.471	(315.589, 541.712)	51.8
AUC(0-4) (h•pg/mL)	GSK573719 500 µg	15	15	2	377.787	(226.444, 630.280)	116.2
	GSK573719 500 µg /GW642444 50 µg	15	15	0	513.611	(380.274, 693.702)	58.5
AUC(0-t) (h•pg/mL)	GSK573719 500 µg	15	15	2	374.225	(213.422, 656.186)	134.0
	GSK573719 500 µg /GW642444 50 µg	15	15	0	537.640	(380.159, 760.359)	69.2
AUC(0-∞) (h•pg/mL)	GSK573719 500 µg	15	15	3	368.704	(196.798, 690.770)	161.7
	GSK573719 500 µg /GW642444 50 µg	15	15	0	617.322	(434.415, 877.242)	70.4
C _{max} (pg/mL)	GSK573719 500 µg	15	15	2	578.301	(224.078, 1492.478)	421.3
	GSK573719 500 µg /GW642444 50 µg	15	15	0	1289.384	(991.659, 1676.496)	50.2
t _{1/2} (h)	GSK573719 500 µg	15	12	3	1.563	(1.288, 1.897)	31.2
	GSK573719 500 µg /GW642444 50 µg	15	15	0	1.776	(1.166, 2.703)	88.2
t _{max} (h) ¹	GSK573719 500 µg	15	13	2	0.080	(0.08, 0.13)	NA
	GSK573719 500 µg /GW642444 50 µg	15	15	0	0.080	(0.08, 0.08)	NA
t _{last} (h) ¹	GSK573719 500 µg	15	13	2	4.000	(1.00, 8.00)	NA
	GSK573719 500 µg /GW642444 50 µg	15	15	0	5.000	(1.00, 16.00)	NA

Plasma GW642444 PK parameter estimates are summarised by treatment in the table below. Following a single dose administration of either GW642444 alone or combination of GSK573719 and GW642444, GW642444 was rapidly absorbed with most of the C_{max} values occurring at 5 min following which plasma concentrations declined rapidly.

Parameter	Treatment	N	n	n*	Geometric Mean	95% CI	CV(%)
AUC(0-1) (h*pg/mL)	GW642444 50 µg	16	16	0	207.995	(171.502, 252.254)	37.4
	GSK573719 500 µg/ GW642444 50 µg	15	15	1	225.337	(177.127, 286.669)	45.6
AUC(0-t) (h*pg/mL)	GW642444 50 µg	16	16	0	234.342	(183.621, 299.074)	48.3
	GSK573719 500 µg/ GW642444 50 µg	15	15	1	271.343	(204.657, 359.759)	54.4
AUC(0-∞) (h*pg/mL)	GW642444 50 µg	16	16	1	233.768	(176.956, 308.819)	56.0
	GSK573719 500 µg/ GW642444 50 µg	15	15	1	315.562	(237.212, 419.791)	55.2
Cmax (pg/mL)	GW642444 50 µg	16	16	0	495.929	(396.693, 619.989)	43.8
	GSK573719 500 µg/ GW642444 50 µg	15	15	0	499.298	(330.787, 753.651)	85.9
t½ (h)	GW642444 50 µg	16	15	1	0.422	(0.361, 0.493)	28.9
	GSK573719 500 µg/ GW642444 50 µg	15	14	1	0.707	(0.515, 0.971)	59.3
tmax (h) ¹	GW642444 50 µg	16	16	0	0.080	(0.08, 0.10)	NA
	GSK573719 500 µg/ GW642444 50 µg	15	15	0	0.080	(0.08, 0.08)	NA
tlast (h) ¹	GW642444 50 µg	16	16	0	1.500	(1.00, 4.00)	NA
	GSK573719 500 µg/ GW642444 50 µg	15	15	0	2.000	(0.08, 5.00)	NA

13. PK Assessment in Efficacy/Safety Trials

The following briefly summarizes the study design of the efficacy/safety trials with PK assessment.

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route ¹ ; Duration)	Total No. of Subjects by Group Entered ² / Completed
DB2113120 (YM2010/00171)	Evaluate safety and tolerability	R, DB, PC, PG	COPD subjects ≥40 years with post-bronchodilator FEV ₁ ≤80% of predicted and FEV ₁ /FVC ratio ≤0.70	UMEC/VI 500/25 QD Placebo QD IH 28 days	42/35 9/9
DB2113361 (2011N130134)	Evaluate efficacy and safety over 24 weeks	R, DB, PG, PC	COPD subjects ≥40 years with post-bronchodilator FEV ₁ ≤70% predicted and FEV ₁ /FVC <0.70 mMRC dyspnea score ≥2	UMEC/VI 125/25 QD UMEC 125 QD VI 25 QD Placebo QD IH 24 weeks	403/325 407/312 404/298 275/183
DB2113373 (2011N130136)	Evaluate efficacy and safety over 24 weeks	R, DB, PG, PC	COPD subjects ≥40 years with post-bronchodilator FEV ₁ ≤70% predicted and FEV ₁ /FVC <0.70 mMRC dyspnea score ≥2	UMEC/VI 62.5/25 QD UMEC 62.5 QD VI 25 QD Placebo QD IH 24 weeks	413/332 418/324 421/318 280/204

AC4113589 (RM2010/00314)	Dose ranging	R, DB, PC, PG	COPD subjects ≥ 40 to ≤ 80 years with post-bronchodilator FEV ₁ $\geq 35\%$ to $\leq 70\%$ of predicted and FEV ₁ /FVC ratio ≤ 0.70	UMEC 125 QD UMEC 250 QD UMEC 500 QD Placebo QD IH 28 days	71/65 72/68 71/64 71/67
AC4115321 (2011N124430)	Dose ranging	R, DB, PC, XO	COPD subjects ≥ 40 to ≤ 80 years with post-bronchodilator FEV ₁ $\geq 35\%$ to $\leq 70\%$ of predicted and FEV ₁ /FVC ratio < 0.70	Total UMEC 15.6 QD UMEC 31.25 QD UMEC 62.5 QD UMEC 125 QD UMEC 15.6 BID UMEC 31.25 BID TIO 18 QD Placebo QD IH 7 days	163/147 58 ^a 56 ^a 59 ^a 58 ^a 55 ^a 56 ^a 56 ^a 59 ^a
AC4113073 (RM2009/00680)	Dose ranging and dose-interval	R, DB, PC, XO	COPD subjects ≥ 40 to ≤ 80 years with post-bronchodilator FEV ₁ $\geq 35\%$ to $\leq 70\%$ of predicted and FEV ₁ /FVC ratio ≤ 0.70	Total UMEC 62.5 QD UMEC 125 QD UMEC 250 QD UMEC 500 QD UMEC 1000 QD UMEC 62.5 BID UMEC 125 BID UMEC 250 BID TIO 18 QD Placebo QD IH 14 days	176/135 34 ^a 33 ^a 35 ^a 37 ^a 29 ^a 32 ^a 33 ^a 32 ^a 34 ^a 152 ^a
AC4115487 (2011N120469)	Relative pharmacodynamics	R, DB, PC, XO, SD	Healthy subjects	UMEC IH: 62.5 active/no strip 62.5 active/placebo 125 active/no strip 125 active/placebo 0 placebo/placebo Single dose	15/15 15/15 15/14 15/15 15/15
AC4106889 (GM2008/00043)	Safety, tolerability, PK, PD	R, DB, PC, PG, 14-day repeat dose ascending	Healthy subjects	UMEC IH: DISKUS 250 QD 750 QD 1000 QD Placebo 14 days	36/9 36/9 36/9 36/9

4.3. Appendix – New Drug Application Filing and Review Form

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information about the Submission</u>				
	Information		Information	
NDA/BLA Number	203975	Brand Name	ANORO ELLIPTA	
OCP Division (I, II, III, IV, V)	II	Generic Name	Umeclidinium Bromide/Vilanterol Inhalation Powder	
Medical Division	Pulmonary, Allergy, and Rheumatology Products	Drug Class	Inhaled LAMA/ LABA	
OCP Reviewer	Ping Ji, Ph.D. Jianmeng Chen MD, Ph. D	Indication(s)	COPD	
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Inhalation powder administered from NDPI	
Pharmacometrics Reviewer	Hongshan Li, Ph.D.	Dosing Regimen	UMEC/VI (62.5/25 and 125/25 mcg) QD	
Date of Submission	12/18/2012	Route of Administration	Oral Inhalation	
Estimated Due Date of OCP Review		Sponsor	GSK	
Medical Division Due Date		Priority Classification	Standard	
PDUFA Due Date	12/17/2013			
<i>Clin. Pharm. and Biopharm. Information</i>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	2		AC4112014 (UMEC) B2C106181 (VI)
Isozyme characterization:	X			
Blood/plasma ratio:	X			
Plasma protein binding:	X			
Transporter specificity:	X			
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	5		AC4105209 (UMEC, DISKUS) AC4115487 (UMEC, 1strip vs 2) B2C106180 (VI) DB1112017 (VI, Japanese) B2C10001 (VI, DISKUS)
multiple dose:	X	3		AC4113377 (UMEC, Japanese) AC4106889 (UMEC) B2C108784 (VI)
Patients-				
single dose:	X	2		AC408123 (UMEC, COPD) B2C110165 (VI, COPD)

multiple dose:	X	2		AC4105211 (UMEC, COPD) DB2113120 (UMEC/VI, COPD)
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2		B2C112205- Ketoconazole DB2113950-Verapamil
In-vivo effects of primary drug:	X	1		Low systemic concentration Combination rule-DB2113208
In-vitro:	X			
Subpopulation studies -				
ethnicity:	X			Japanese/non-Japanese studies Pop PK
gender:	X			Pop PK
pediatrics:				
geriatrics:	X			Pop PK
renal impairment:	X	1		DB2114636
hepatic impairment:	X	1		DB2114637
PD -				
Phase 2:	X	6		UMEC dose-rangings (AC4113589, AC4115321, AC4113073, AC4115408) VI dose-rangings (B2C111045, B2C 109575)
Phase 3:	X	7		DB2113360,, DB2113361, DB2113373, DB2113374, DB2114417, DB2114418, DB2113359
PK/PD -				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:	X			DB2113361, DB2113373,
Population Analyses -				
Data rich:				
Data sparse:	X			DB2116975 (pop PK for phase IIIa DB2113361 &DB2113373)
II. Biopharmaceutics				
Absolute bioavailability	X	2		HZA102934 AC4112008 (UMEC)
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	X	1		AC4110106
QT studies	X	1		DB2114635
Chronopharmacokinetics				
Pediatric development plan				Full waiver request
Literature References	X			
Total Number of Studies		40		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JIANMENG CHEN
08/16/2013

PING JI
08/16/2013

HONGSHAN LI
08/16/2013

SARAH E DORFF
08/16/2013

SATJIT S BRAR
08/16/2013

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 203-975 (000)	Reviewer: Sandra Suarez Sharp, Ph.D	
Division:	DPARP		
Applicant:	GlaxoSmithKline	Biopharmaceutics Team Leader: Angelica Dorantes, Ph.D	
Trade Name:	ANORO ELLIPTA	Acting Supervisor: Richard Lostritto, Ph.D	
Generic Name:	Umeclidinium/Vilanterol Inhalation Powder	Date Assigned:	January 10, 2013
Indication:	Treatment of subjects with chronic obstructive pulmonary disease (COPD).	Date of Review:	Aug 02, 2013
Formulation/strengths	Inhalation Powder		
Route of Administration	Oral Inhalation		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date		Date of informal/Formal Consult	Primary review due date
December 18, 2012		January 10, 2013	08/16/13
Type of Submission:	Original NDA		
Review focus:	-Clinical relevance of differences in solubility between [REDACTED] (b) (4) content		
<p>REVIEW SUMMARY:</p> <p>Umeclidium (UMEC)/Vilanterol (VI) Inhalation Powder is a pre-dispensed multi dose dry powder for oral inhalation being proposed for the once a day maintenance treatment of Chronic Obstructive Pulmonary Disease (COPD). UMEC/VI Inhalation Powder is a novel fixed-dose combination of UMEC, a long acting muscarinic antagonist (LAMA) and vilanterol (VI), a long-acting beta2-agonist (LABA) with sustained duration of effect in the lung. When actuated, the inhaler delivers the contents of a single blister simultaneously from each of the two blister strips. The product will be available in two strengths, 62.5/25 microgram and 125/25 microgram.</p> <p>Currently, dissolution testing is not being implemented as part of the quality control tests of orally inhaled products (OIPs). Nevertheless, the Applicant used a developmental method to test the dissolution of some batches representative of clinical trials batches. Although dissolution was implemented for some batches of the proposed product, this test was not carried on to the clinical batches or the release and stability batches. There is currently no established methodology for the in vitro dissolution testing of inhaled products. This Reviewer acknowledges that dissolution testing is not currently being implemented as part of the quality control testing of orally inhaled products (OIPs) and therefore, it is not a required parameter for QC purposes.</p> <p>During the review cycle (e.g. filing meeting), this Reviewer informed the CMC team of the solubility differences between the [REDACTED] (b) (4) forms of UMEC and VI and recommended the</p>			

monitoring of these forms upon batch release and on stability as follows:

- We recommend that the amount of [REDACTED] (b) (4) for both UMEC and VI in the drug product be controlled and monitored at release and throughout the stability program to assure a consistent drug product quality. Alternatively, we recommend the implementation of a control strategy that ensures that the ratio of [REDACTED] (b) (4) throughout the product's shelf life is consistent and similar to the ratio observed in the clinical batches.
- Our overall recommendations are based on the following:
 - Solid state form was classified as a CQA by the Applicant.
 - There are differences in solubility for the [REDACTED] (b) (4) forms which may have an impact on the mean residence time in the lungs and/or the rate and extent of absorption from the lungs.
 - According to the Applicant, no [REDACTED] (b) (4) above the detection limit has been observed in the micronized drug substances. However, the limit of detection needs to be qualified.
 - UMEC and VI are potent drugs and the in vivo impact (PK/efficacy/safety) of differences in the content of [REDACTED] (b) (4) has not been determined.

RECOMMENDATION:

ONDQA-Biopharmaceutics has reviewed NDA 203-975 (000) submitted on December 18, 2012. From the Biopharmaceutics perspective, NDA 203975 for UMEC/VI Inhalation Powder is recommended for APPROVAL.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

c.c. RLostritto

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDRA SUAREZ
08/15/2013

ANGELICA DORANTES
08/15/2013

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	203975	Brand Name	ANORO ELLIPTA
OCP Division (I, II, III, IV, V)	II	Generic Name	Umeclidinium Bromide/Vilanterol Inhalation Powder
Medical Division	Pulmonary, Allergy, and Rheumatology Products	Drug Class	Inhaled LAMA/ LABA
OCP Reviewer	Ping Ji, Ph.D. Jianmeng Chen MD, Ph. D	Indication(s)	COPD
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Inhalation powder administered from NDPI
Pharmacometrics Reviewer	Hongshan Li, Ph.D.	Dosing Regimen	UMEC/VI (62.5/25 and 125/25 mcg) QD
Date of Submission	12/18/2012	Route of Administration	Oral Inhalation
Estimated Due Date of OCP Review		Sponsor	GSK
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	12/17/2013		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	2		AC4112014 (UMEC) B2C106181 (VI)
Isozyme characterization:	X			
Blood/plasma ratio:	X			
Plasma protein binding:	X			
Transporter specificity:	X			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	5		AC4105209 (UMEC, DISKUS) AC4115487 (UMEC, 1strip vs 2) B2C106180 (VI) DB1112017 (VI, Japanese) B2C10001 (VI, DISKUS)
multiple dose:	X	3		AC4113377 (UMEC, Japanese) AC4106889 (UMEC) B2C108784 (VI)
Patients-				
single dose:	X	2		AC408123 (UMEC, COPD) B2C110165 (VI, COPD)

multiple dose:	X	2		AC4105211 (UMEC, COPD) DB2113120 (UMEC/VI, COPD)
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2		B2C112205- Ketoconazole DB2113950-Verapamil
In-vivo effects of primary drug:	X	1		Low systemic concentration Combination rule-DB2113208
In-vitro:	X			
Subpopulation studies -				
ethnicity:	X			Japanese/non-Japanese studies Pop PK
gender:	X			Pop PK
pediatrics:				
geriatrics:	X			Pop PK
renal impairment:	X	1		DB2114636
hepatic impairment:	X	1		DB2114637
PD -				
Phase 2:	X	6		UMEC dose ranging (AC4113589, AC4115321, AC4113073, AC4115408) VI dose ranging (B2C111045, B2C 109575)
Phase 3:	X	7		DB2113360,, DB2113361, DB2113373, DB2113374, DB2114417, DB2114418, DB2113359
PK/PD -				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:	X			DB2113361, DB2113373,
Population Analyses -				
Data rich:				
Data sparse:	X			DB2116975 (pop PK for phase IIIa DB2113361 &DB2113373)
II. Biopharmaceutics				
Absolute bioavailability	X	2		HZA102934 AC4112008 (UMEC)
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	X	1		AC4110106
QT studies	X	1		DB2114635
Chronopharmacokinetics				
Pediatric development plan				Full waiver request
Literature References				
Literature References	X			
Total Number of Studies		40		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	full waiver request
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	full waiver request
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			

19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		
----	---	--	---	--	--

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- None

Jianmeng Chen and Ping Ji

Reviewing Clinical Pharmacologist

Date

Suresh Doddapaneni

Team Leader/Supervisor

Date

Submission in brief:

Indication and mechanism of action

GSK has submitted the NDA 203975 seeking the marketing approval for Umeclidinium bromide /Vilanterol Inhalation Powder (ANORO ELLIPTA), to be used as “*the long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.*” Umeclidinium bromide /Vilanterol Inhalation Powder (hereafter referred to as UMEC/VI) is not indicated for the prevention of exacerbation or the treatment of asthma.

UMEC/VI is a novel long-acting muscarinic antagonist (LAMA) /long-acting beta₂ agonist (LABA) combination for oral inhalation to be administered from a Novel Dry Powder Inhaler (NDPI). Recommended dose is UMEC/VI (62.5/25 and 125/25 mcg) for the treatment of COPD. Both UMEC and VI are new molecular entities (NME). GSK has another pending NDA 204275 Fluticasone Furoate/Vilanterol Inhalation Powder (BREO ELLIPTA) for the treatment of COPD.

There have been several interactions between Agency and Sponsor to discuss dosing for the proposed product as listed in Table 1.

Table 1. Summary of Regulatory history relevant to dose regimen

Type C (Mar 2010)	<ul style="list-style-type: none"> Agreed that 25 mcg VI is reasonable for Phase 3 trials for COPD, but not asthma Agreed that once daily dosing of VI appeared reasonable
EOP2-COPD (Oct 2010)	<ul style="list-style-type: none"> FDA suggested to explore lower doses (<125 mcg) for UMEC to establish a dose response curve. FDA acknowledged that the data is supportive of once daily dosing for UMEC, but concerned that it might be the result of a nominal dose that’s higher than necessary. Confirmation of the dosing interval should be preceded by adequate dose-ranging In post meeting communications, FDA agreed that two different doses of LAMA (62.5 and 125 mcg) be evaluated in the safety and efficacy trials
PNDA (Jan 2012)	Comment on dose/ dose interval selection is pending on dose ranging study data

Summary of information submitted

NDA 203975 consists of 40 clinical pharmacology studies (Table 2), including 8 studies with UMEC/VI combination drugs, 13 studies with UMEC, and 19 studies with VI. The clinical pharmacology information for UMEC/VI is mainly derived from Phase 1 studies as well as in vitro studies evaluating plasma protein binding, role of transporters, and potential for CYP 450 metabolic enzymes inhibition and induction. Population based modeling analyses including population pharmacokinetics analysis were performed to assess the effect of covariates on pharmacokinetics (PK) and to understand the time course of toxicities and their association with dose or exposure.

Table 2. Summary of clinical pharmacology studies

Type of Study	Number of Studies	Studies
All Clinical Pharmacology Studies (40 studies total)		
UMEC/VI ^a	8	DB2113208, DB2113950, DB2114635, DB2114636, DB2114637, DB2113120, DB2113361, DB2113373
UMEC	13	AC4105209, AC4105211, AC4110106, AC4106889, AC4108123, AC4112008, AC4113377, AC4115487, AC4112014, AC4113589, AC4115321, AC4113073, AC4115408
VI (including GW642444H) ^b	19	B2C10001, B2C106180, B2C106181, B2C108784, B2C110165, B2C112205, DB1112146, DB1111509/AC2111509, DB1112017, HZA102934, HZA102936, HZA102940, HZA105548, HZA105871, HZA111789, HZA113970, HZC111348, HZC110946, B2C104604

a. UMEC/VI treatment arm included in study, may also have included UMEC or VI monotherapy arms.

b. GW642444H is the H salt of GW642444 (VI is the M salt of GW642444).

Contribution of UMEC and VI to combination -PK

The comparison of systemic PK for UMEC or VI following administration in combination from the NDPI vs. administration as mono product is shown in Table 3. UMEC C_{max} is higher in the UMEC/VI treatment arm compared with UMEC alone (30% (90% CI: 4%, 64%)). VI AUC is higher in the UMEC/VI treatment arm compared with VI alone (21% (90% CI: 2%, 44%)). The higher systemic exposures in combination drugs are more relevant to safety rather than efficacy.

Table 3. Geometric mean ratios and 90% CI for comparison of systemic PK from combination product vs. mono products

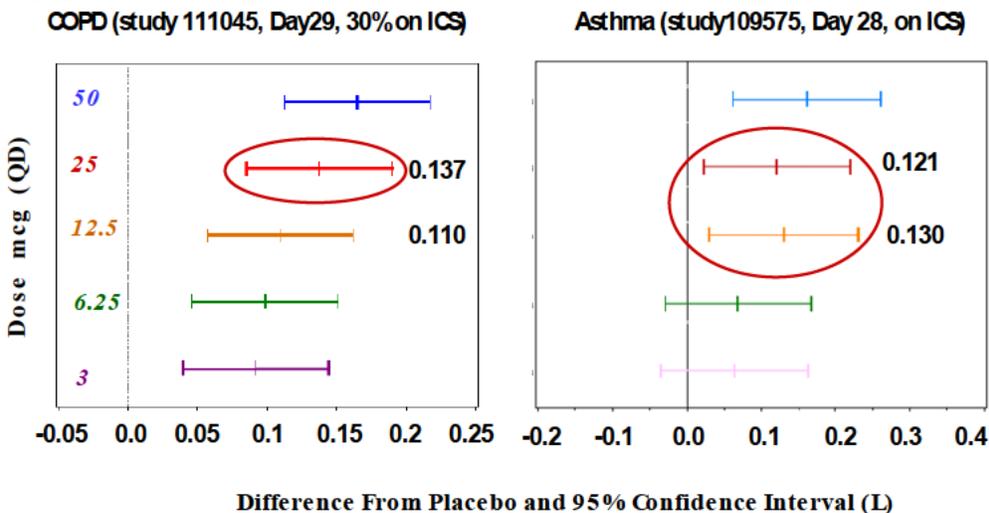
Parameter	Treatment Comparison	Adjusted Geometric Means	Ratio of Adjusted Geometric Means	90% CI of Ratio
AUC ₍₀₋₁₎ (h*pg/mL)	UMEC/VI 500/50 mcg vs. VI 50 mcg	252 / 208	1.21	1.02, 1.44
C_{max} (pg/mL)	UMEC/VI 500/50 mcg vs. VI 50 mcg	500 / 496	1.01	0.70, 1.45
AUC _(0-∞) (h*pg/mL)	UMEC/VI 500/50 mcg vs. UMEC 500 mcg	624 / 576	1.08	0.74, 1.59
C_{max} (pg/mL)	UMEC/VI 500/50 mcg vs. UMEC 500 mcg	1299 / 996	1.30	1.04, 1.64

Rational for 62.5/25 and 125/25 qd dose regimen selection

-Dose for VI

The 25 mcg dose of VI was selected on the basis of results from a Phase 2 dose-ranging study in subjects with COPD (Study B2C111045), which tested a range of VI doses (3, 6.25, 12.5, 25 and 50 mcg once daily). Based upon the primary endpoint trough FEV₁ (**Figure 1**) and secondary endpoint weighted mean FEV₁ as well as the safety profile, 25 mcg was the appropriate dose. The 25 mcg dose was also supported by study B2C109575 in patients with asthma.

Fig 1. Effect of VI on lung function (trough FEV₁) across doses ranging from 3 mcg to 50 mcg QD



-Dose for UMEC

Results for different UMEC doses on trough FEV₁ from the four Phase 2 dose ranging studies in subjects with COPD are summarized in **Table 3**, which show substantial efficacy with UMEC 62.5 and near maximal efficacy with UMEC 125. Sponsor selected two doses of UMEC (62.5 and 125 mcg) for further evaluation in combination with VI in the COPD phase III program.

Table 3. Difference from Placebo for LS Mean Change from Baseline in Trough FEV₁ (L) (95% CI)

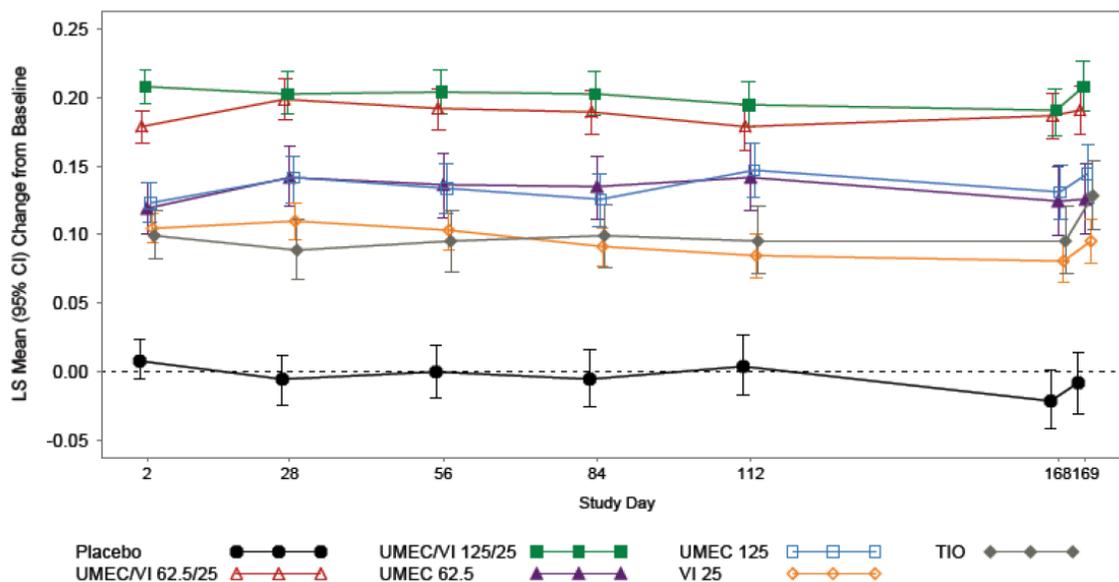
Study	Difference from Placebo for LS Mean Change from Baseline in Trough FEV ₁ (L) (95% CI) by once daily UMEC dose (mcg) *						
	15.6	31.25	62.5	125	250	500	1000
AC4115321 at Day 8	0.113 (0.058, 0.168)	0.101 (0.045, 0.158)	0.124 (0.068, 0.179)	0.183 (0.127, 0.239)			
AC4113073 at Day 15			0.128 (0.060, 0.196)	0.147 (0.077, 0.216)	0.095 (0.027, 0.162)	0.140 (0.074, 0.205)	0.186 (0.113, 0.259)
AC4113589 at Day 29				0.159 (0.088, 0.229)	0.168 (0.099, 0.238)	0.150 (0.080, 0.220)	
AC4115408 at Day 85			0.127 (0.052, 0.202)	0.152 (0.076, 0.229)			

← Limited efficacy

→ toxicity

Following selection of doses for individual components of UMEC and VI, sponsor evaluated the efficacy of UMEC/VI 62.5/25 and 125/25 mcg in Phase III studies in COPD patients and demonstrated that both doses showed benefit in lung function over placebo (**Figure 2**). Sponsor reported that UMEC/VI 125/25 conferred some additional lung function and symptom benefit compared with UMEC/VI 62.5/25 in the salbutamol reversible subgroup. UMEC/VI 62.5/25 was reported to be less efficacious than UMEC/VI 125/25 in some symptomatic endpoints. Thus, sponsor seeks approval for both UMEC/VI 62.5/25 and 125/25 strength for the treatment of COPD.

Fig 2. COPD; Trough FEV1 (L); Integrated Studies DB2113361, DB2113373, DB2113360, DB2113374 ITT Population



Dosing Frequency:

Qd vs Bid: Study AC4115321 in subjects with COPD supported the comparability of once and twice daily dosing for UMEC (**Figure 3**). HZA113310 in subjects with persistent asthma demonstrated that the improvement of weighted mean FEV1 (0-24h) was similar with VI 6.25 mcg twice daily and VI 12.5 mcg once daily dosing (**Figure 4**).

Fig 3. COPD; Change from baseline FEV1 (L) on Day 7; study AC4115321

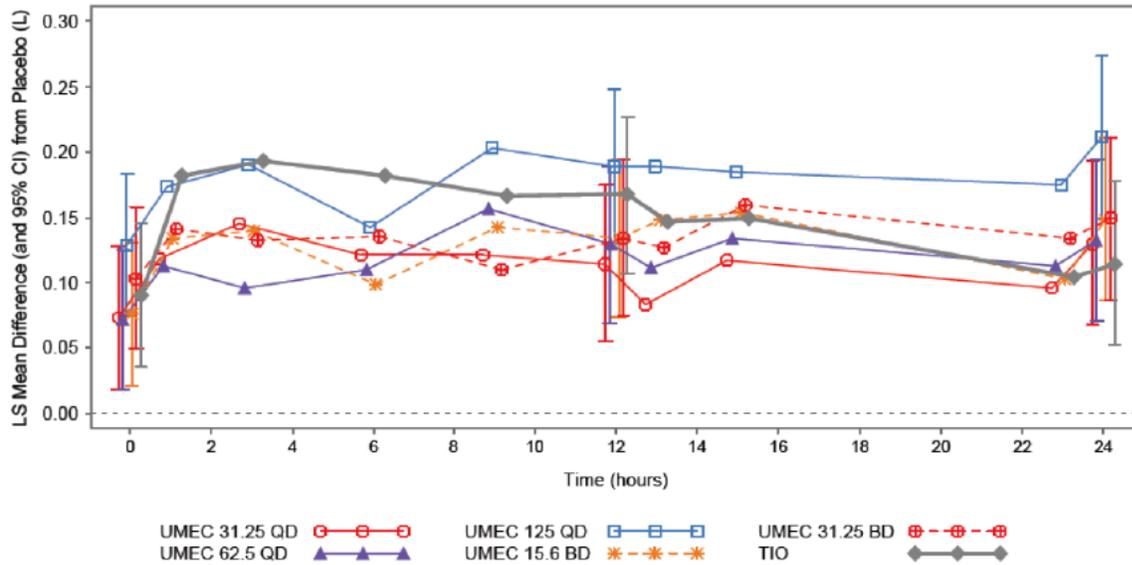
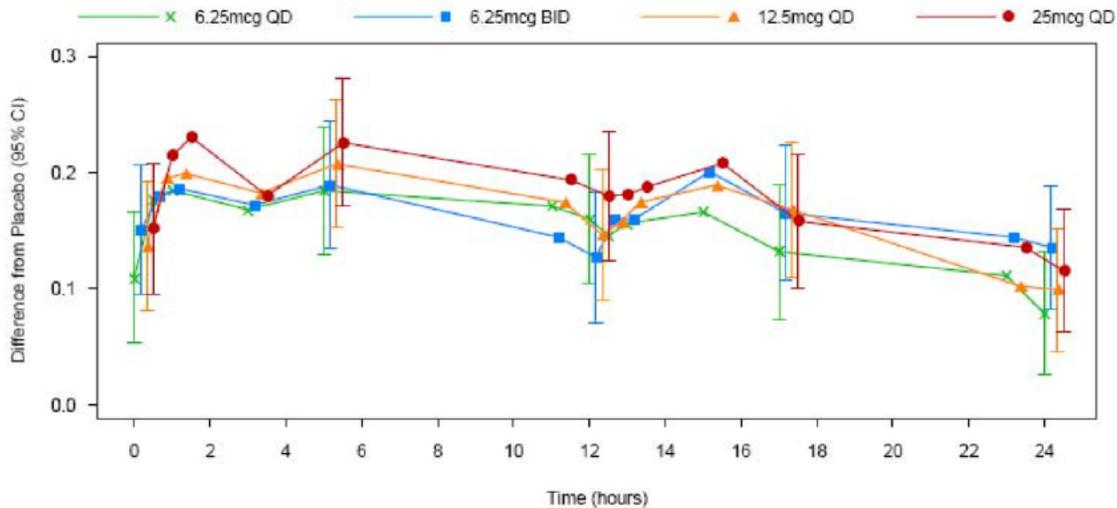


Fig 4. Effect of VI dosing on FEV1 in subjects with persistent asthma (study HZA113310)

Change from Baseline FEV1 (L) Over Time on Day 7



Morning vs evening dosing

All phase II and III studies used morning dosing. The timing of dosing is not specified in the proposed label.

Effect of intrinsic/extrinsic factors on dose

Food effect study was not conducted because the oral bioavailability for UMEC/VI is low. No dose adjustments have been proposed based on studied intrinsic and extrinsic factors such as weight, age, gender, and race. UMEC is a substrate for CYP2D6. No clinically significant increase in exposure was observed in CYP2D6 poor metabolizers. In patients with moderate or severe hepatic impairment, no dose adjustment is recommended. In subjects with moderate

hepatic impairment, UMEC systemic exposure is not increased compared with healthy subjects. There was no effect of hepatic impairment on VI systemic exposure. For renal impairment, no dose adjustments are recommended. Systemic UMEC exposure is not increased and systemic VI exposure is higher in severe renal impairment patients. The increased exposure of VI did not increase heart rate or decrease serum potassium. Co-administration with ketoconazole (CYP3A4 inhibitor) showed modest increases in VI systemic exposure and did not result in an increased effect on heart rate or blood potassium. P-gp inhibitor verapamil did not significantly affect the PK of UMEC or VI.

Effect on QT interval

As per sponsor's report, a thorough QT study (DB2114635) demonstrated the lack of effect of UMEC/VI at therapeutic dose (125/25 mcg) on the QTcF interval as compared with placebo after 10 days dosing. At a supradose of 500/100 mcg for 10 days, there was an effect on QTcF during the first hour after dosing. The largest mean time-matched difference from placebo was 8.2 msec (90% CI: 6.2, 10.2) at 30 minutes after dosing.

Pediatrics development plan

Since COPD is a disease of adults and has no pediatric correlate, sponsor has requested a full waiver from the requirement to conduct pediatric research with UMEC/VI for COPD.

Summary of PK

The PK characteristics of UMEC/VI are summarized in **Figure 5**.

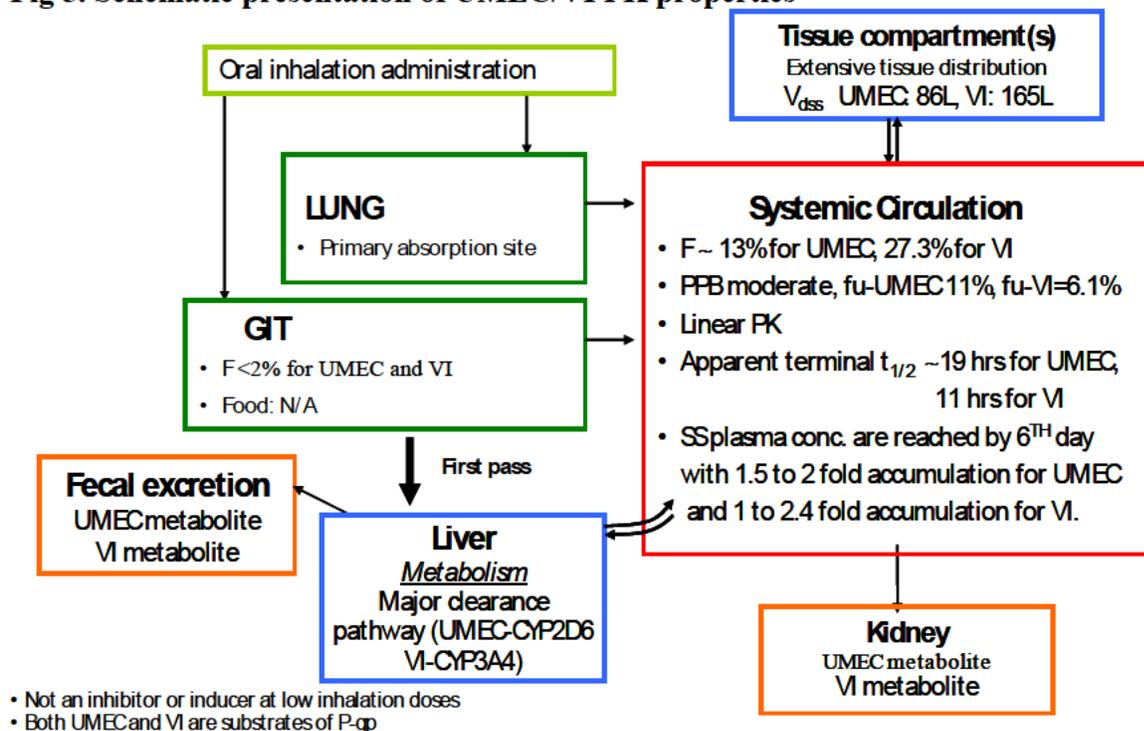
Oral bioavailability of both UMEC and VI is low, on average <1% and <2% respectively. Consequently, systemic exposure for both inhaled UMEC and VI is primarily due to absorption of the inhaled portion of the dose delivered to the lung. Following inhaled administration of UMEC or VI in healthy subjects, C_{max} occurs at 5 to 15 minutes. The absolute bioavailability for UMEC and VI (administered as UMEC/VI) is 13% and 27.3%, respectively. The apparent terminal phase elimination half-life of UMEC and VI following inhaled UMEC/VI is on average 19 h and 11 h respectively.

UMEC and VI are extensively distributed, with average volumes of distribution at steady-state of 86 L and 165 L, respectively. *In vitro* plasma protein binding for UMEC and VI is 89% and 94%, respectively.

UMEC is primarily metabolized by CYP2D6. VI is primarily metabolized BY CYP3A4 . Both UMEC and VI are P-gp substrates. In humans, UMEC/VI is eliminated primarily by metabolism with metabolites excreting both in urine and feaces.

Steady-state for UMEC and VI was achieved by day 10 and day 6 with once-daily dosing. Based on $AUC_{(0-t)}$, accumulation ranged from 1.5 to 2 fold for UMEC and 2.4 fold for VI. Population PK analysis of Phase III data showed plasma UMEC and VI concentration time profiles following administration of UMEC/VI was best described by a two-compartment model with first order absorption.

Fig 5. Schematic presentation of UMEC/VI PK properties



Summary of population based modeling analysis

UMEC/VI is administered by oral inhalation and efficacy is presumed to be driven by topical effects in the lung. Systemic exposures of UMEC and VI are considered more relevant for safety. Sponsor conducted population PK analysis to evaluate covariates, and several other population based modeling analysis to evaluate the association of exposure/dose with safety (heart rate) and the association of dose with efficacy endpoint (trough FEV1).

Summary of drug-interaction studies

Effect of other drugs on UMEC/VI

Effect of co-administration of ketoconazole and verapamil on UMEC/VI exposure (AUC) and C_{max} was evaluated. Co-administration of repeat dose inhaled VI (25 mcg once daily) and the strong CYP3A4 and potent P-gp inhibitor ketoconazole (400 mg once daily), resulted in increases in mean VI AUC_(0-∞) by 90% and no change in VI C_{max} . Co-administration of repeat dose inhaled UMEC/VI (25 mcg once daily) with the moderate P-gp inhibitor verapamil resulted in 1.4 fold higher UMEC systemic exposure(AUC) with no effect on C_{max} . Co-administration of verapamil did not affect the VI C_{max} or AUC.

Effect of UMEC/VI on other drugs

With low systemic exposures for both UMEC and VI after oral inhalation administration, potential for inhibition and induction of metabolic enzymes is negligible.

Mid-Cycle Deliverables

Following are the Mid-Cycle Deliverables;

- Any approvability issues
- Dose Selection
- Exposure-Response Evaluation for Safety
- Drug-drug Interaction and Extrinsic/Intrinsic Factors
- Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JIANMENG CHEN
01/31/2013

SURESH DODDAPANENI
02/01/2013