CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205382Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	205382
Submission Date	12/18/2013
Proposed Brand Name	INCRUSE ELLIPTA
Generic Name	Umeclidinium Bromide
Clinical Pharmacology Reviewer	Jianmeng Chen, M.D., Ph.D.
Clinical Pharmacology Team Leader	Satjit Brar, Pharm.D., Ph.D.
Pharmacometrics Reviewer	Jianmeng Chen, M.D., Ph.D.
Pharmacometrics Team Leader	Liang Zhao, Ph.D.
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 (62.5 mcg) QD

1. Executive Summary

1.1   Recommendations

From the viewpoint of the Office of Clinical Pharmacology, NDA 205382 is acceptable.

1.2   Phase IV Commitments

None

1.3   Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

GSK has submitted NDA 205382 seeking the marketing approval for Umeclidinium bromide Inhalation Powder (UMEC) (INCRUSE ELLIPTA) for the treatment of chronic obstructive pulmonary disease (COPD). UMEC is an anticholinergic for oral inhalation to be administered from a Novel Dry Powder Inhaler (NDPI). UMEC is currently available in US as a component of UMEC/VI 62.5/25 mcg once daily oral inhalation (ANORO ELLIPTA, NDA203975) for the maintenance treatment of COPD.

This submission includes 7 Phase 3 studies to evaluate the efficacy and safety of UMEC, 3 Phase 2b studies to support dose selection of UMEC and 21 clinical pharmacology studies for UMEC or UMEC/VI combination.

Dose selection

Rationale for Dose and Dosing Frequency Selection
The proposed dose of UMEC is 62.5 mcg once daily. Two dosing regimens, once daily doses of UMEC 62.5 and 125mcg, 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.

Dose Selection
Results for different UMEC doses on trough FEV_1 from four Phase 2 dose-ranging studies in subjects with COPD are summarized in **Table 1**. Efficacy was observed with UMEC 62.5 mcg and near maximal efficacy with UMEC 125 mcg. Thus, the sponsor selected two doses of UMEC (62.5 and 125 mcg) for further evaluation in the COPD Phase 3 program.

Table 1: 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) [a]						
	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 →

Dosing Frequency
Study AC4115321 evaluated once and twice daily dosing for UMEC in subjects with COPD. The improvement of weighted mean FEV$_1$ (0-24h) was similar with UMEC 31.25 mcg twice daily and UMEC 62.5 mcg once daily dosing (**Figure 2**).

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

Following selection of doses and dosing frequency for UMEC, the sponsor evaluated the efficacy of UMEC 62.5 and 125 mcg in Phase 3 studies in COPD patients.

Morning vs. evening dosing
All Phase 2 and 3 studies employed morning dosing. The timing of dosing is not specified in the proposed label.

Dose selection based on Phase 3 trials

Page 5 of 91

In the application, the sponsor proposes 62.5 mcg only for approval, although the higher UMEC dose of 125 mcg showed numerically better results in trough FEV1 and several secondary endpoints in phase 3 studies. There is no clear safety concern related to the higher dose. The detailed primary assessment of the efficacy and safety results is summarized in the medical (Dr. Jennifer Pippins) and biostatistics (Dr. Gregory Levin) reviews.

PHARMACOKINETICS

Absorption
- The absolute systemic bioavailability for UMEC was about 12.8% (based on an earlier clinical formulation). However, the systemic bioavailability of UMEC was low after oral administration, on average <1%. Therefore, systemic exposures for inhaled UMEC 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 UMEC following oral inhalation administration.
- The accumulation of C_{max} after once-daily dosing of UMEC 125 µg was 1.3 fold for UMEC at Day 7. The assessment of accumulation of AUC is limited by low assay sensitivity.
- Systemic exposure increased in proportion to the dose in the dose range of 125 to 500 µg for UMEC (AUC_{tau}, C_{max}).

Distribution
- The *in vitro* plasma protein binding of UMEC is independent of concentration with average values of 89%.

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.
- UMEC is a substrate of P-glycoprotein (P-gp).
- Based on in vitro studies, the potential for UMEC 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.
- The effective half-life of UMEC following oral inhalation administration was about 11 h.

COPD vs. Healthy

- UMEC C_{max} was 50% lower and AUC_{0-24} was 29% higher in COPD patients as compared to healthy subjects.

POPULATION PHARMACOKINETIC ANALYSIS

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

SPECIAL POPULATIONS

Renal Impairment
The effect of renal function on the PK of UMEC was evaluated in Study DB2114636.

- Following administration of inhaled UMEC 125 μg, 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.
- 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.

- Systemic UMEC exposure in moderate hepatic impairment patients is comparable to that in healthy subjects. There was no evidence for reduced plasma protein binding of UMEC 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 UMEC when administered in combination compared with administration alone.

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

Effect of UMEC on exposure of co-administered drugs

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

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS FOR SAFETY

UMEC is administered by oral inhalation and efficacy is presumed to be driven by local effects in the lung. The systemic exposure of UMEC is considered more relevant for safety.

Effect of UMEC on QTc

QT effect for UMEC 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 supratherapeutic 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 500 mcg and placebo were below 10 ms, 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: *In Vitro* 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
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**. The PK profile of UMEC was evaluated in 9 Phase 1 studies (Studies AC4105209, AC4106889, AC4113377, DB2113208, DB2114636, DB2114637, DB2114635,

AC4110106, DB2113950) in healthy subjects, and 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) in COPD patients.

The PK of UMEC 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. All clinical studies by treatment are summarized briefly in **Table 2.1c**.

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) via 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) | Part 1/Single-dose
UMEC 100 mcg QD (N=16)
UMEC 500 mcg (N=16)
UMEC 1000 mcg (N=16)
Placebo (N=4)

Part 1/Repeat-dose
UMEC 500 mcg (N=8)
UMEC 1000 mcg (N=8)
Placebo (N=4)

Part 2/Single-dose
UMEC 100 mcg QD (N=6)
UMEC 500 mcg (N=12)
UMEC 1000 mcg (N=6)
Placebo (N=4)

Part 2/Repeat-dose
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: All Clinical Pharmacology Studies by Treatment.

Type of Study	Number of Studies	Studies
All Clinical Studies Contributing PK Data (21 studies total)		
UMEC	13	AC4105209, AC4105211, AC4110106, AC4106889, AC4108123, AC4112008, AC4113377, AC4115487, AC4112014, AC4113589, AC4115321, AC4113073, AC4115408
UMEC/VI [a]	8	DB2113208, DB2113950, DB2114635, DB2114636, DB2114637, DB2113120, DB2113361, DB2113373

Source: Table 1, Summary of Clinical Pharmacology

UMEC is an inhaled product delivered by the ELLIPTA dry powder inhaler (DPI). The INCRUSE ELLIPTA inhaler contains a foil strip with regularly distributed blisters containing umeclidinium bromide and excipients. The drug substance is a white powder with active ingredient (umeclidinium bromide) and excipients (magnesium stearate and lactose) blended together. 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**.

Table 2.1e: Formulations Used in the Clinical Trials.				
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

				PK results will be in the labeling
AC4112014	safety, tolerability, mass balance	solution	P22 Table 18	
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

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 is a small molecule drug. 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 $C_{29}H_{34}NO_2.Br$. UMEC is slightly soluble in water.

Drug Product

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

Table 2.2.1: Composition of Umeclidinium Inhalation Powder 62.5 mcg.			
Component	Quantity per 12.5 mg Blister[2]	Function	Reference to Standard
Umeclidinium Blister Strip			
Umeclidinium bromide micronised	74.2 mcg[3]	Active	GlaxoSmithKline[1]
Magnesium Stearate	75 mcg	(b) (4)	JP, Ph. Eur and USP/NF[4]
Lactose Monohydrate	to 12.5 mg		JP, Ph. Eur and USP/NF[4]

Notes:

mcg: microgram

1. Details of the specification of the active ingredient are provided in m3.2.S.4.1. Specification
2. A manufacturing overage of up to (b) (4) of the blend may be included.
3. 74.2 micrograms of umeclidinium bromide is equivalent to 62.5 micrograms of umeclidinium (b) (4)
4. 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, 2.3.P, Description and Composition of the Drug Product

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

Umeclidinium bromide (UMEC) Inhalation Powder is an orally inhaled muscarinic antagonist 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 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 INCRUSE ELLIPTA 62.5mcg 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
- β2 agonist:
  - long acting: salmeterol, formoterol, arformoterol, indacaterol etc.
  - short acting: salbutamol, albuterol, terbutaline etc.
- Anticholinergics:
  - long acting: tiotropium, aclidinium
  - short acting: ipratropium
- Combination:
  - albuterol+ipratropium (Combivent, Duoneb)
  - umeclidinium+vilanterol (Anoro)
- Methylxanthine: theophylline

(b) Corticosteroids
- ICS+LABA Combination:
  - salmeterol+fluticasone propionate (Advair)
  - formoterol+budesonide (Symbicort)
  - vilanterol+fluticasone furoate (Breo)

(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 included a full characterization (dose-ranging) of UMEC to establish the appropriate dose and dose interval, prior to proceeding to the Phase 3 studies. The phase 3 studies for UMEC were part of the factorial design phase 3 trials to support UMEC/VI (NDA203975) approval. The key studies supporting choice of dose and dosing interval are shown in **Table 2.3.1**.

Table 2.3.1: Studies to Select Dose Regimens of UMEC Phase 3 Trials in COPD patients.

Study Number	Study Objective(s)	Study Design	Duration	Treatment in mcg (once-daily or otherwise specified
AC4113589	Dose-ranging	R, DB, PG, PC	28 days	UMEC 125 UMEC 250 UMEC 500 PLA
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
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
AC4115408	Efficacy and safety	R, DB, PG, PC	12 weeks	UMEC 125 or 62.5, or PLA

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

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 used trough FEV_1 as the primary endpoint in all Phase 2 dose-ranging/regimen selection studies. Trough FEV1 was the primary endpoint for the primary Phase 3 studies (DB2113373, AC4115408, DB2113361 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 concentrations were measured. No metabolites were quantified because the metabolites of UMEC are not active and are not associated with efficacy or safety.

2.4 Exposure-Response
2.4.1 What are the characteristics of the exposure-response relationship for effectiveness?

For UMEC, it is presumed that the systemic plasma exposure is not directly related to clinical response (FEV1). There is evidence of a dose-response relationship with regard to the pertinent pulmonary endpoints. The doses explored included 15.6 mcg to 1000 mcg in COPD patients. A clear dose-response relationship is observed, with an increasing effect with increasing dose, for all endpoints evaluated (see question below). Please refer to pharmacometrics review (Appendix 4.1) for additional details.

2.4.2 Was the dosing of UMEC adequately explored?

Yes, four dose-ranging trials were conducted in COPD patients exploring daily doses from 15.6 mcg to 1000 mcg and different dosing intervals (**Figure 2.4.2 and Table 2.4.2**). As a result, two dosing regimens, UMEC 62.5 mcg and 125 mcg once daily, were agreed upon by the FDA for Phase 3 trials in COPD patients.

An overall dose response was observed for UMEC QD doses ranging from UMEC 15.6 mcg to 125 mcg, with no consistent additional benefit for UMEC doses above 125 mcg (**Figure 2.4.2 and Table 2.4.2**). Of all 1204 patients, 118 patients reported AEs. A total of 107 moderate or severe AEs were reported. The most frequently reported moderate or severe AEs were headache (n=24), common cold (n=8), cough (n=8), COPD exacerbation (n=5), hoarseness (n=4), sore throat (n=4), and sinusitis (n=4).

Dosing frequency with UMEC, QD versus BID (twice daily), was explored in patients with COPD (left two panels of **Figure 2.4.2**). In the randomized, double-blind, placebo-controlled, cross-over trial (AC4115321) in patients with COPD, the efficacy and safety were compared for UMEC 31.2 mcg BID, UMEC 62.5 mcg QD, and UMEC 125 mcg QD. Trough FEV1 effects following 62.5 mcg QD and 31.2 mcg BID appeared similar, whereas the dosing regimen of 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 2.4.2 and lower left panel of Figure 2.4.2**)

Figure 2.4.2. 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.
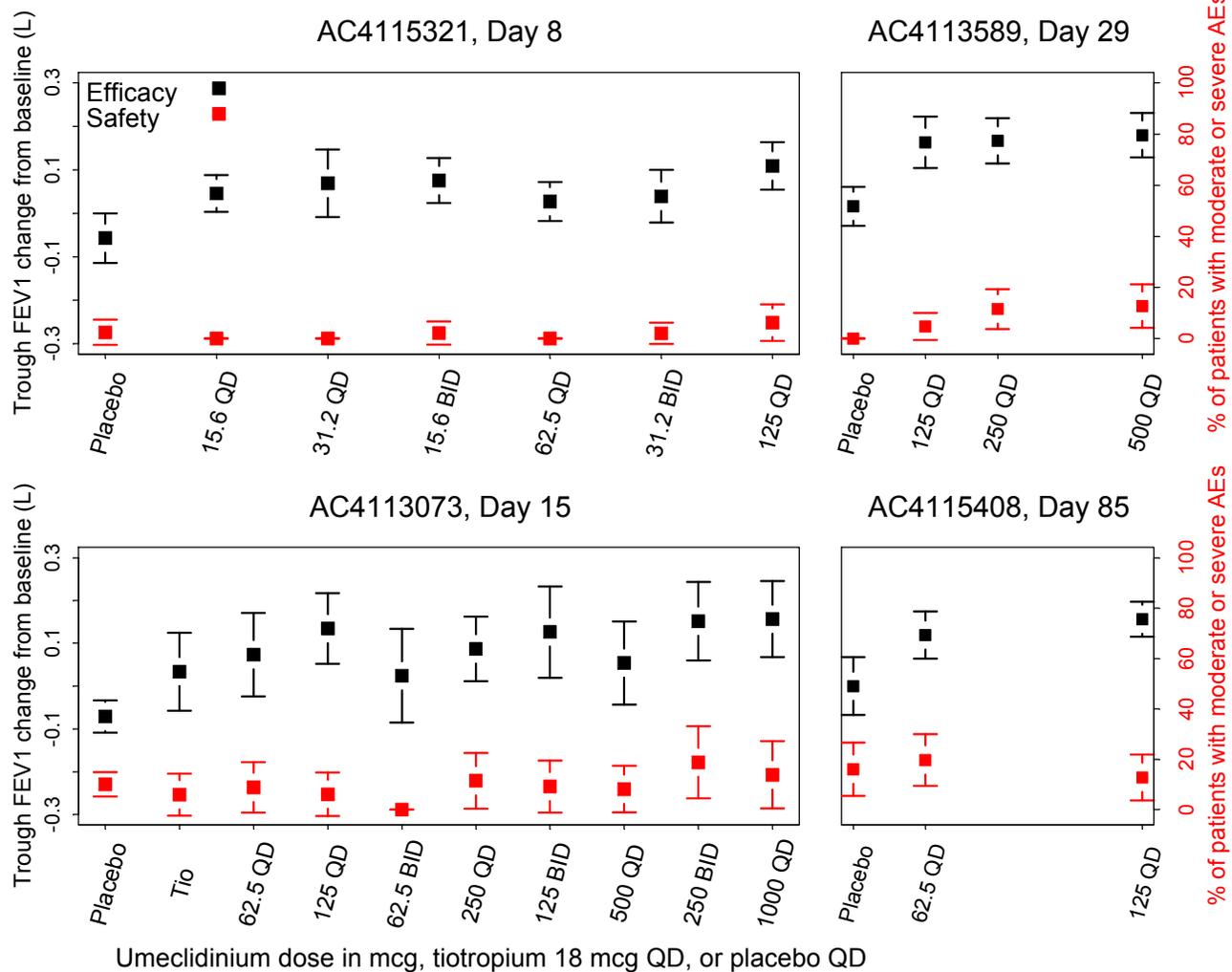
Table 2.4.2: Mean change from baseline in trough FEV1 (L) for umeclidinium once or twice daily doses.

Treatment	AC4115321 on Day 8 FEV1TRC ($CI_{95\ lo}$,$CI_{95\ hi}$)	N	AC4113073 on Day 15 FEV1TRC ($CI_{95\ lo}$,$CI_{95\ hi}$)	N	AC4113589 on Day 29 FEV1TRC ($CI_{95\ lo}$,$CI_{95\ hi}$)	N	AC4115408 on Day 85 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

2.4.3 Were there any significant covariate effects on the systemic exposure of UMEC that warrant dose adjustment?

No covariates found in the population PK of UMEC warrant dose adjustment. Based on pooled population PK data from Study DB2113361 and DB2113373, UMEC 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.

Weight, age and creatinine clearance were statistically significant covariates on apparent 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 V2/F increased by approximately 6% for every 10% increase in body weight from 70 kg. With every 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.

2.4.4 Does this drug prolong QT/QTc Interval?

QT effect for UMEC 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 supratherapeutic 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 500 mcg and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

For further details refer to QT/IRT review for NDA203975.

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 in healthy subjects with to-be-marketed formulation was characterized in study DB2114636. Study DB2114636 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 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.**
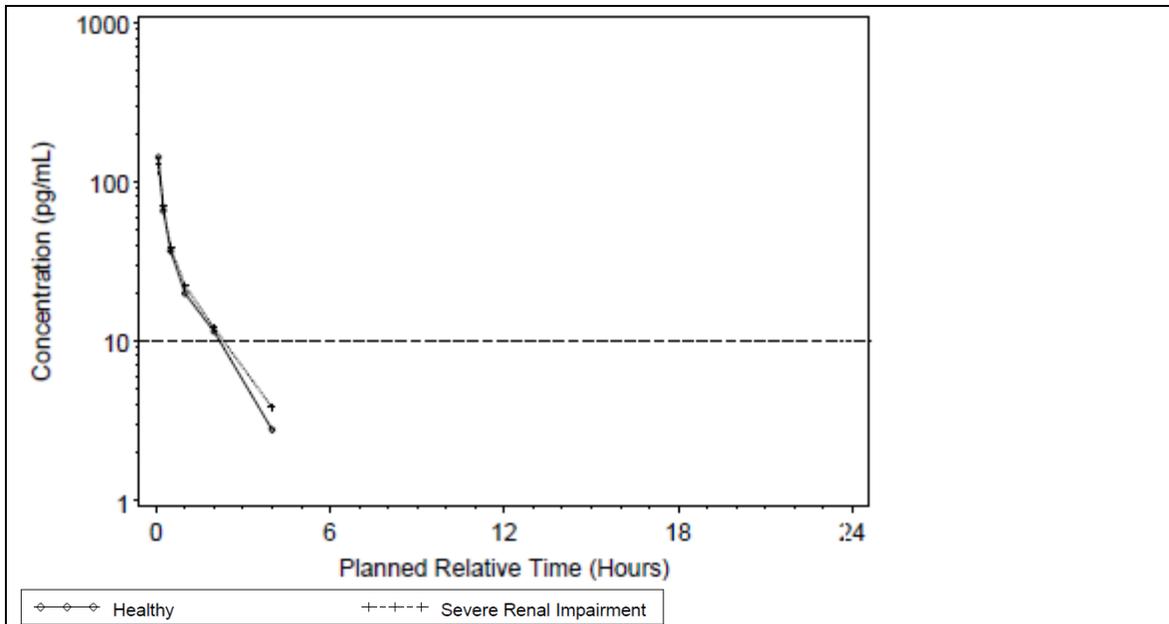
Source: Figure 10.3, db2114636 report

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
C_{max} (pg/mL)	127.6	57.1
T_{last} (h)*	2.00	NA
T_{max} (h)*	0.08	NA

Source: Table 8, db2114636 report

Multiple dose PK

The PK profile of UMEC 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.

Following repeat-dose administration of UMEC, UMEC was rapidly absorbed with median T_{max} values occurring at 6 minutes post-dose. The terminal phase $t\frac{1}{2}$ 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 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 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).
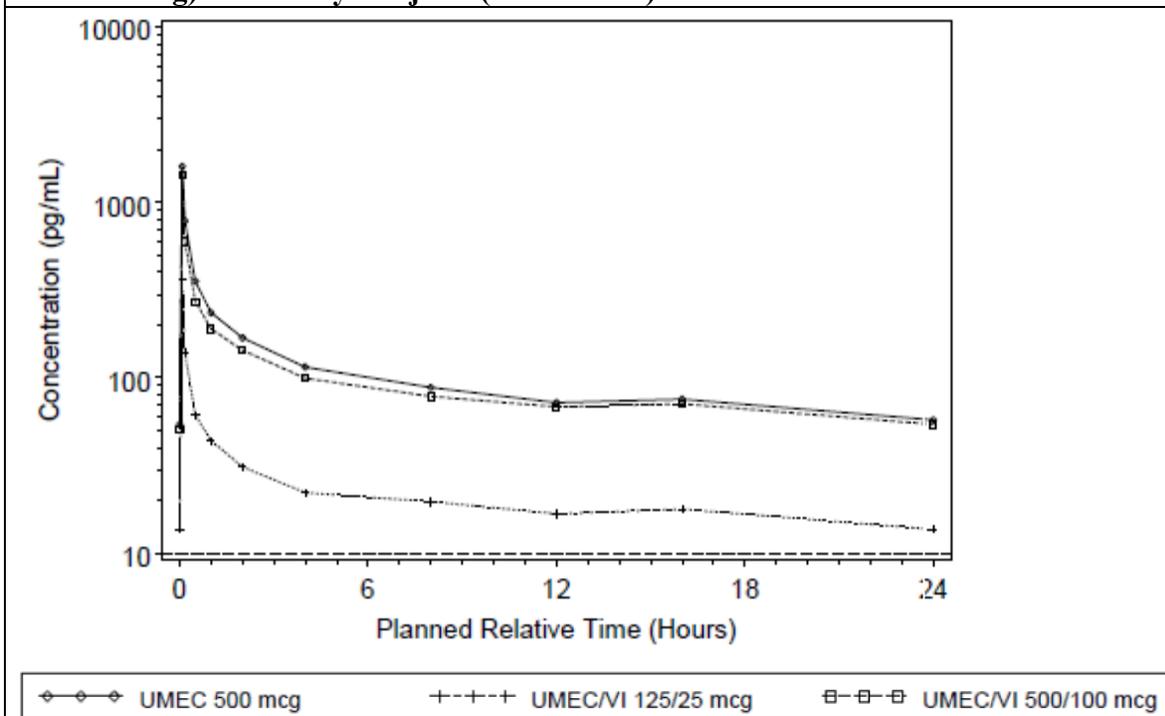
Source: Study DB2114635, Figure 11.2

Table 2.5.1c: Summary Statistics of Day 10 UMEC(500 mcg) PK Parameters (DB2114635).

Parameter	N	n	Geometric Mean	95% CI	%CVb
$AUC_{(0-\tau)}$ (h·pg/mL)	75	73	2444	2278, 2623	31.0
C_{max} (pg/mL)	75	73	1541	1412, 1682	38.8
t_{max} (h)[a]	75	73	0.10	0.08, 0.23	NA
$t_{\frac{1}{2}}$ (h)	75	47	25.9	23.7, 28.3	31.3
CL/F (L/h)	75	73	205	191, 220	31.0
V/F (L)	75	47	7749	6890, 8716	41.7

Source: Study DB2114635, Table 11.2

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

In subjects with COPD, UMEC C_{max} was approximately 50% lower while $AUC_{(0-24)}$ was 29% higher compared with healthy subjects (**Table2.5.2**).

Table 2.5.2: Comparison of Repeat-Dose UMEC PK Parameters between Healthy Subjects (NCA analysis) and Subjects with COPD (Population PK Analysis)

Analysis/Study Number/ N	Treatment Arm	$AUC_{(0-\tau)}$ (pg·h/mL) Geometric Mean (95%CI)	C_{max} (pg/mL) Geometric Mean (95%CI)
Pop PK DB2116975/ 406 (COPD)	UMEC/VI 125/25 mcg	628 (598, 659)	138 (132, 145)
Pop PK DB2116975/ 402 (COPD)	UMEC 125 mcg	623 (593, 653)	139 (132, 146)
NCA PK TQT DB2114635 / 74 (Healthy)	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 (Healthy)	UMEC 500 mcg	2444 (2278, 2623)	1541 (1412, 1682)
NCA PK TQT DB2114635/ 70 (Healthy)	UMEC/VI 500/100 mcg	2145 (1977, 2328)	1400 (1285, 1525)

Source: Summary of Clinical Pharmacology. Table 38

2.5.3   What are the characteristics of drug absorption?
UMEC absolute bioavailability following oral inhalation was ~12%. The oral bioavailability of UMEC was low, on average <1%, because of the extensive first pass metabolism.

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 inhalation 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 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.

2.5.4   What are the characteristics of drug distribution?
UMEC is widely distributed with Vss greater than total body water. 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.

2.5.5   Does the mass balance study suggest renal or hepatic as the major route of elimination?
Both hepatic and renal elimination pathways play a role in in the disposition of UMEC after IV dosing.

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.

What are the characteristics of drug metabolism?
UMEC is extensively metabolized. The main routes of metabolism in human for UMEC are O-dealkylation and hydroxylation by CYP2D6.

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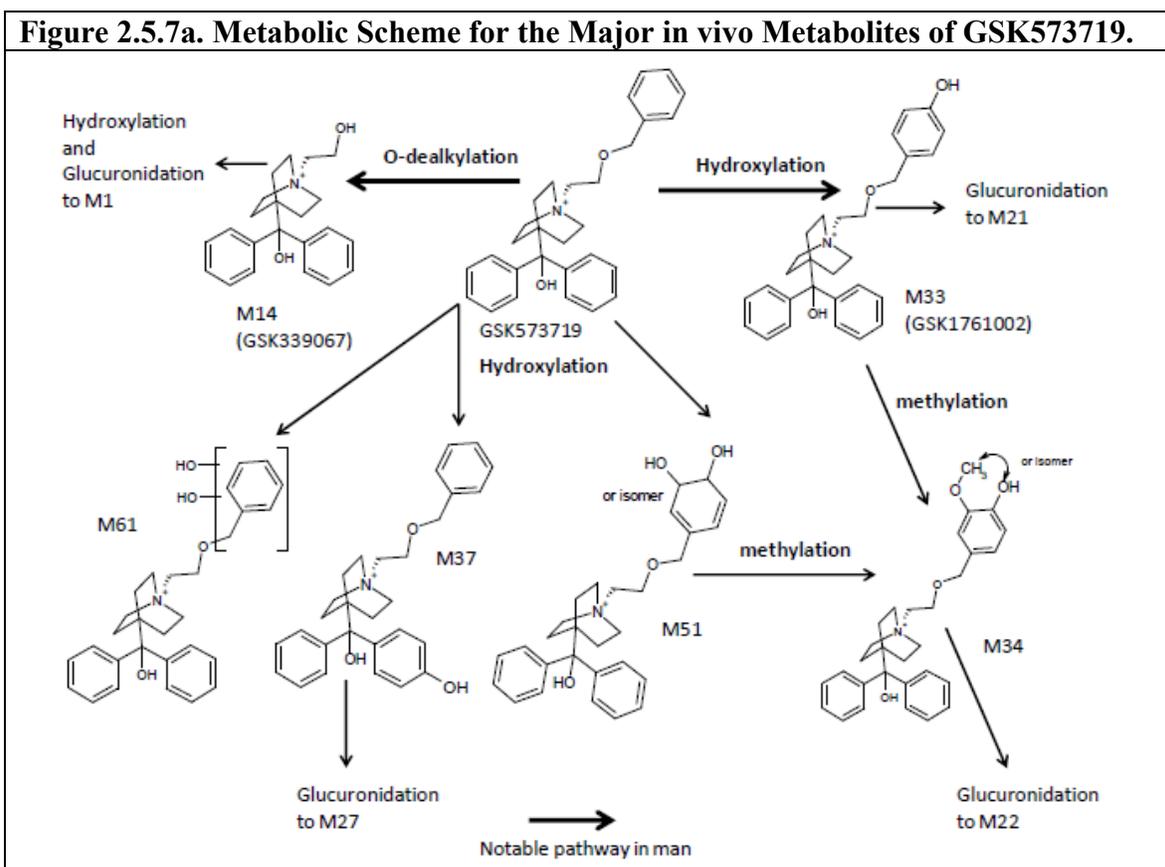
Source – adapted from Figure 3.1, Section 2.6.4, Pharmacokinetics Written Summary

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

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.

2.5.10 What are the characteristics of drug excretion in urine?

Mass balance study suggested that renal clearance constitutes 22% of UMEC elimination.

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

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	$AUC_{(0-\tau)}$ (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

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

There is no indication of time-dependent PK after multiple dosing for 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 125/25 mcg, followed by a 7- to 14-day washout and a subsequent second treatment period with 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 are similar between day 28 and day 84.

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

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 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 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.

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 for COPD. 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 (n=1635) were evaluated for an effect of race on the

PK of UMEC (DB2116975). No effect of race/ethnicity on PK was seen for UMEC.

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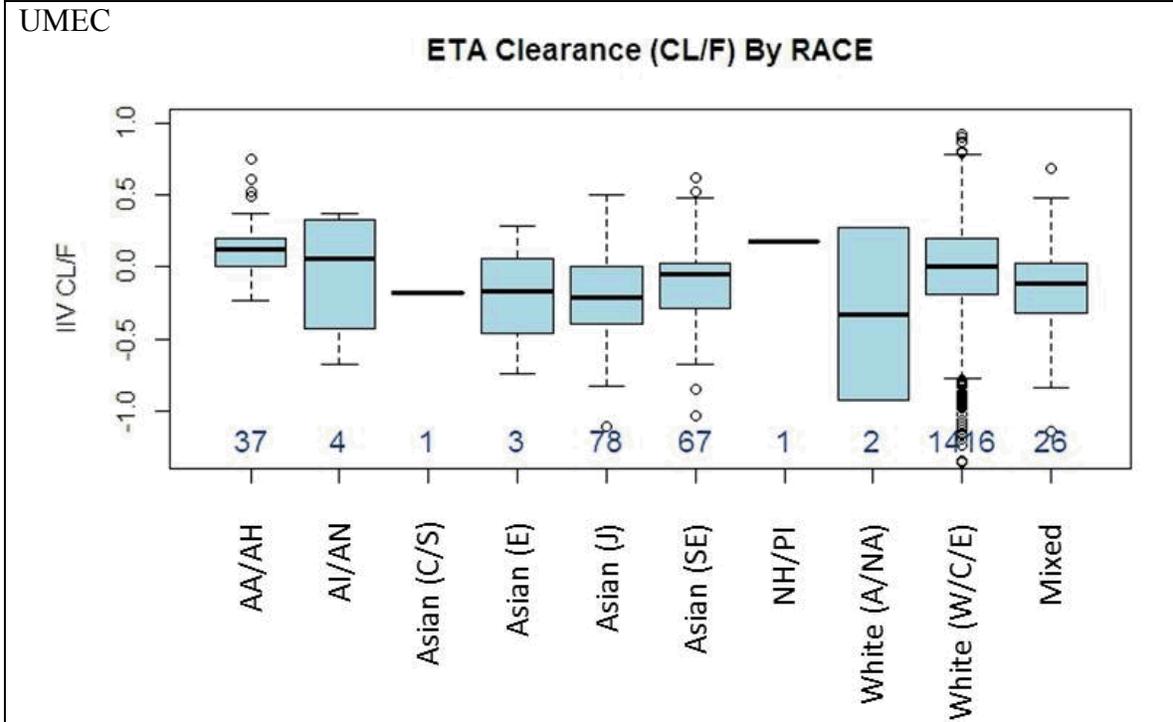
UMEC

Renal Impairment

Comparable exposure was observed for UMEC between healthy and severe renal impairment patients.

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 8, Study DB2114636 report

Hepatic Impairment

No dose adjustment for UMEC is needed in hepatic impairment patients as there is no change in exposure for UMEC in hepatic impairment patients.

The effect of hepatic impairment on the PK of UMEC was evaluated in DB2114637. 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 Hepatic Impairment / Healthy	1	74 / 87	0.85	(0.63, 1.15)
	UMEC 125		7	105 / 122	0.86	(0.64, 1.17)
	UMEC/VI 125/25		1	66 / 72	0.92	(0.68, 1.24)
$AUC_{(0-\tau)}$ (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 Hepatic Impairment / Healthy	1	165 / 220	0.75	(0.49, 1.14)
	UMEC 125		7	214 / 283	0.76	(0.50, 1.15)
	UMEC/VI 125/25		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 $AUC_{(0-\tau)}$.

Source: Table 10, study report DB2114637

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 interactions, because of induction or inhibition of CYP enzymes by UMEC, is less likely at the low concentrations achieved by the clinical doses. Please see sections 2.7.1 and 2.7.3 for further details.

2.7.1 Is the drug a substrate of CYP enzymes?

UMEC is a substrate for CYP2D6.

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

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

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

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.

2.7.4 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 in addition to those already discussed in sections 2.7.2 and 2.7.4

2.7.5 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 exposure has been evaluated, which is discussed under section 2.7.6 and 2.7.7. The differences in measured systemic exposures are not relevant for efficacy; however, it may have implications with respect to safety.

2.7.6 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 UMEC 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 changed 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 2.7.6: UMEC C_{max} 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

2.7.7 What are the drug-drug interactions?

There are no clinically meaningful drug-drug interactions for UMEC. No dose adjustment is needed for patients using concomitant CYP2D6 inhibitors or P-gp inhibitors.

In a clinical study conducted in healthy normal metabolizing status subjects and CYP2D6 poor metabolizer status subjects, there was no clinically significant difference in the systemic exposure to UMEC following 7 days of repeat dosing with inhaled 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 inhaled UMEC was evaluated in Study DB2113950. UMEC is a substrate of P-gp. 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 phase 3 program evaluated UMEC at 125 mcg, two times the proposed to-be-marketed UMEC dose. Therefore, no dose adjustment is needed for the use of P-gp transporter inhibitors with UMEC. It is noted that this study used earlier clinical formulation.

Table 2.7.7: 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.

2.7.8 Does the label specify co-administration of another drug?
The UMEC label does not mention specific co-administration with other drugs.
2.7.9 What other co-medications are likely to be administered to the target population?
All COPD patients are likely to take antibiotics and other bronchodilators. More severe COPD patients may take ICS.

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.

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

There is potential for an additive interaction with concomitantly used anticholinergic medications. It is therefore advised to avoid coadministration of INCRUSE ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

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?

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?

Phase 3 clinical supplies for UMEC monotherapy (1 blister strip) are identical to the to-be-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 and   (b) (4)   added to the formulation. (b) (4) was removed from the formulation and magnesium stearate added to produce a final blend composition of umeclidinium/lactose monohydrate/magnesium stearate which was used in all key clinical studies.

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 was not assessed. Since the oral bioavailability of UMEC is minimal, it is not likely that inhaled UMEC 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 mcg) is 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 in plasma samples involved solid phase extraction 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 9 analytical reports 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 UMEC was 10 pg/mL. At the proposed dose of UMEC (62.5 mcg), most plasma concentrations of UMEC were only above the LLOQ for a transient amount of time post-dose (~ 1-2 h). Many clinical pharmacology studies were conducted with supra-therapeutic doses of UMEC.

Table 2.9.1: Summary of Analytical Methods for Analysis of UMEC 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 mcL of human plasma by protein precipitation using acetonitrile containing an isotopically labeled internal standard (b) (4) 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 ([¹³C₁₀]-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 mcL) is diluted with acetonitrile containing an isotopically labeled internal standard ([¹³C₁₀]-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 mcL of human plasma by protein precipitation using acetonitrile containing an isotopically labeled internal standard ([¹³C₁₀]-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)	AC4115321ª AC4115408ª AC4115487ª DB2113361ª DB2113373ª DB2114635ª	GSK573719 and GW642444 are extracted from 200 mcL of human plasma using solid phase extraction using isotopically labeled ████████████████ (b) (4) 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 TurboIonSpray™ interface and multiple reaction monitoring.	
		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	AC4115321ª AC4115408 AC4115487ª	Human urine samples (1 mL) are diluted with acetonitrile containing an isotopically labeled internal standard ([¹³C₁₂]-GSK573719). Then an aliquot is further diluted with acetonitrile: water (1:1) prior to being analyzed by HPLC-MS/MS using a TurboIonSpray™ 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	DB2113120ª DB2113208 DB2113950ª	GSK573719 and GW642444 are extracted from 100 mcL of human plasma by protein precipitation using acetonitrile containing isotopically labeled internal standards ([¹³C₁₂]-GSK573719 and ([²H₁₂]-GW642444). Extracts are analyzed by HPLC-MS/MS using a TurboIonSpray™ 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	DB2114636ª DB2114637ª	GSK573719 and GW642444 are extracted from 250 mcL of human plasma using solid phase extraction using isotopically labeled ____ (b) (4) ____ Extracts are analyzed by HPLC-MS/MS using a TurboIonSpray™ 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	at least 4 hours at room temperature and on ice
		Processed Extract Stability	at least 144 hours at 4°C
2012N143619	DB2114636ª DB2114637ª	GSK573719 is extracted from 50 mcL human urine (treated with 20% Tween solution) using solid phase extraction using isotopically labeled [$^{13}C_{12}$]-GSK573719. 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 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

Source – Appendix Table 3, Section 2.7.1, Summary of Biopharmaceutic 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 2.9.1 presents a summary of analytical methods used for quantification of UMEC 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 10 to 2000 pg/mL in analytical report 2011N129207, the report with most studies including major studies (3361 and 3373) used in population PK analysis. A linear regression model, with weighting factor of 1/concentration^2 was used for the curve fitting for UMEC.

2.9.5.1 What are the lower and upper limits of quantitation?

LLOQ and ULOQ for UMEC were 10 pg/mL and 2000 pg/mL, respectively in report 2011N129207. A ten-fold dilution factor was also validated for concentrations above ULOQ.

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

The accuracy and precision of analytical methods for UMEC are listed in **Table 2.9.1**. The bias and imprecision in all validation reports were less than 15% and were within the acceptable range. For all analytical methods bias and imprecision for 10-fold dilution factor was less than 8%.

Page 35 of 91

The selectivity of 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 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.

3. Detailed Labeling Recommendations

The revised labeling language based on the preliminary review is as below. The revised label is consistent with the approved ANORO ELLIPTA (UMEC/VI) label.

(b) (4)
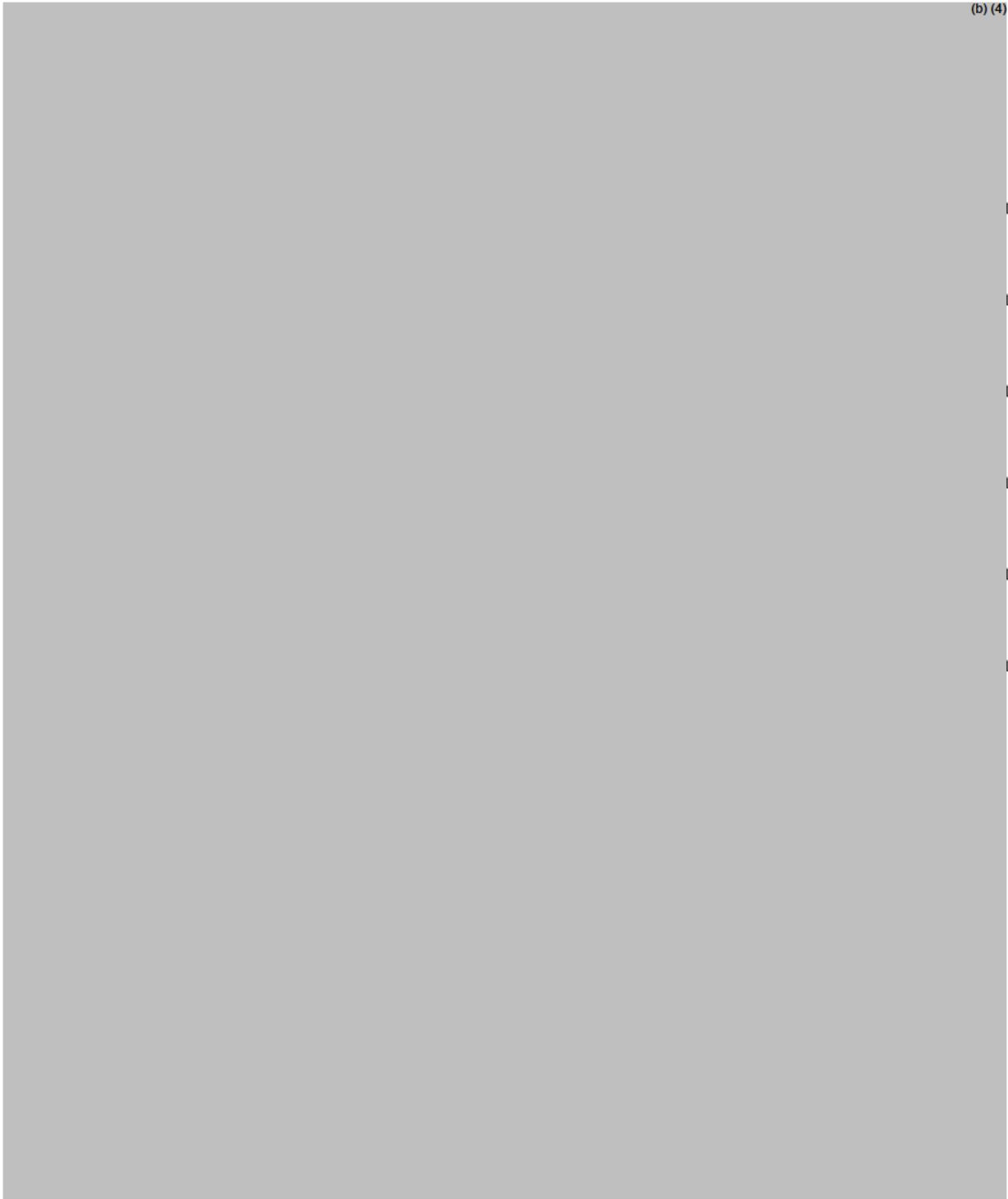
4. Appendix

4.1 PM Review

The same report DB2116975 on population PK analysis for UMEC has been submitted to support NDA203975. The same dose ranging studies AC4115321, AC4113073, AC4113589, and AC4115408 have been submitted to support the dose selection of UMEC for NDA 203975. These studies and reports have been reviewed under NDA 203975 (UMEC/VI) by Dr. Hongshan Li (DARRT date 08/16/2013). The previous review and conclusion is applicable to the current submission NDA205382 (UMEC), and the pertinent sections from previous review are attached below with minor revisions.

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

SUMMARY OF FINDINGS

Key Review Questions

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

Was the dosing of UMEC adequately explored?

Yes, four dose-ranging trials were conducted in COPD patients exploring daily doses from 15.6 mcg to 1000 mcg and different dosing intervals (**Table 1, Figure 1**). As a result, two dosing regimens, UMEC 62.5 mcg and 125 mcg once daily, were agreed upon by the FDA for Phase 3 trials in COPD patients.

An overall dose response was observed for UMEC QD doses ranging from UMEC 15.6 mcg to 125 mcg, with no consistent additional benefit for UMEC doses above 125 mcg (**Table 1, Figure 1**). Of all 1204 patients, 118 patients reported AEs. A total of 107 moderate or severe AEs were reported. The most frequently reported moderate or severe AEs were headache (n=24), common cold (n=8), cough (n=8), COPD exacerbation (n=5), hoarseness (n=4), sore throat (n=4), and sinusitis (n=4).

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 were compared for UMEC 31.2 mcg BID, UMEC 62.5 mcg QD, and UMEC 125 mcg QD. Trough FEV1 effects following 62.5 mcg QD and 31.2 mcg BID appeared similar, whereas the dosing regimen of 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**)

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.
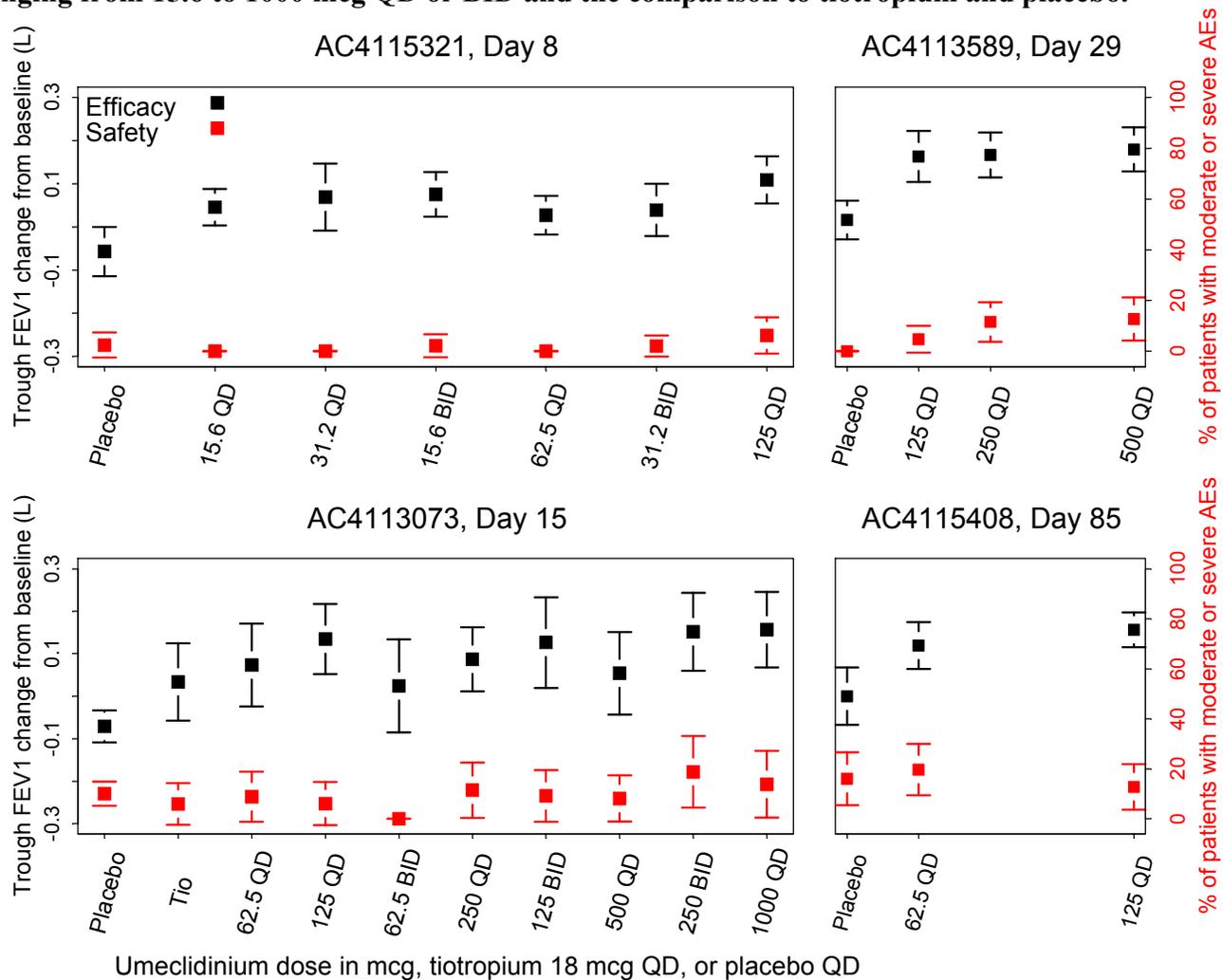
Table 1: Mean change from baseline in trough FEV1 (L) for umeclidinium once or twice daily doses.

Treatment	AC4115321 on Day 8 FEV1TRC ($CI_{95\ lo}$, $CI_{95\ hi}$)	N	AC4113073 on Day 15 FEV1TRC ($CI_{95\ lo}$, $CI_{95\ hi}$)	N	AC4113589 on Day 29 FEV1TRC ($CI_{95\ lo}$, $CI_{95\ hi}$)	N	AC4115408 on Day 85 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

In summary, the UMEC 62.5 mcg QD and UMEC 125 mcg QD carried forward for combination studies in the Phase 3 COPD program was supported by dose frequency and dose-ranging data of UMEC in COPD patients. The efficacy and safety data were collected from 7 Phase 3 clinical trials.

Reviewer's comments: The Pharmacometrics Reviewer defers efficacy and safety evaluation of UMEC in phase 3 pivotal studies to the reviews of DPARP Medical Officer (Jennifer Pippins, MD) and Biometrics Reviewer (Gregory Levin, Ph.D.).

Were there any significant covariate effects on the systemic exposure of UMEC that warrant dose adjustment?
No covariates found in the population PK of UMEC warrant further dose adjustment. As there was no apparent PK interaction with co-administration of UMEC with VI, UMEC PK data were pooled from both UMEC monotherapy arms and UMEC/VI arms. Based on pooled population PK data from Study DB2113361 and DB2113373, UMEC 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.

Weight, age and creatinine clearance were identified as statistically significant covariates on the apparent clearance (CL/F) and weight as significant covariate on the apparent volume of distribution (V_2/F). For every 10% increase in body weight from 70 kg, the CL/F increased approximately by 2% and the V2/F increased by approximately 6%. For every 10% increase in age from 60 years, the CL/F decreased by approximately 7%. For every 10% decrease in creatinine clearance from 110 mL/min, the CL/F decreased by approximately 3%. Overall, the changes in CL/F and V2/F due to variations of age, weight and creatinine clearance in their corresponding observed population ranges are marginal and do not warrant any dose adjustments.

Recommendations
The Pharmacometrics reviewer finds the application acceptable.

Label Statements
Labeling statements to be removed are shown in ~~blue strikethrough font~~ and suggested labeling to be included is shown in <u>underline red font</u>.
12.3   Pharmacokinetics

Special   Populations: (b) (4)

.

PERTINENT REGULATORY BACKGROUND
FDA approved UMEC/VI 62.5/25 mcg once daily oral inhalation (ANORO ELLIPTA, NDA203975) for the maintenance treatment of COPD on 12/18/2013. For ANORO ELLIPTA, GSK has demonstrated the effectiveness of UMEC 62.5 mcg and VI 25 mcg 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.

GSK met with the FDA on the following occasions to discuss the UMEC clinical development program:
- Pre IND Meeting held on May 26, 2009 (UMEC).
- End of Phase 2 Meeting held on October 29, 2010 (UMEC/VI).
- Pre-New Drug Application (NDA) Meeting held on January 18, 2012 (UMEC/VI).

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.

The studies that were conducted to support dose selection and dosing frequency for UMEC are outlined in **Table 2**. Consistent with the findings of the 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 2. Studies to Select Dose Regimens of UMEC 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
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; XO=cross-over a. Subjects' reversibility to salbutamol was used to stratify the randomization.					

b. Subjects' baseline FEV1 (≥40% to ≤65% and > 65% to ≤90% of predicted normal) was used to stratify the randomization.

The global clinical program for UMEC comprised a total of 50 clinical and clinical pharmacology studies, including 7 Phase 3 efficacy/safety studies in subjects with COPD. The phase 3 studies for UMEC were part of the factorial design phase 3 trials to support UMEC/VI approval as summarized in **Table 3**.

- Two 24-week placebo-controlled safety and efficacy studies (DB2113361 and DB2113373), and one 24-week TIO comparator study (DB2113374) which provide the majority of the efficacy and safety data
- One 12-week Phase 3 study to support the efficacy and safety of UMEC monotherapy (AC4115408).
- Two 12-week exercise endurance studies (DB2114417 and DB2114418) (hereafter referred to as Exercise studies).
- 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.

(b) (4)

nly UMEC/VI 62.5/25 mcg was approved as the fixed dose combination product. In this application, GSK only applied for the dose of 62.5 mcg once daily for UMEC monotherapy.

Table 3. Once Daily Dose Regimens for the 7 Phase 3 Efficacy and Safety Studies for UMEC in COPD Patients

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	✓		✓	✓		✓	
DB2113373	✓	✓		✓	✓		
DB2113360*				✓	✓	✓	✓
DB2113374			✓	✓		✓	✓
DB2114417	✓	✓	✓	✓	✓	✓	
DB2114418	✓	✓	✓	✓	✓	✓	
DB2113359	✓		✓			✓	
AC4115408	✓	✓	✓				

Abbreviations: PLA=placebo; Tio=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
*Not included in NDA205382 submission

Results of Sponsor's Analysis

Population PK Analysis for UMEC/VI in Subjects with COPD (DB2116975)

Purpose, Data and Methods

Purpose: The aim of the population PK analyses was to characterize the population pharmacokinetics (PK) of UMEC, used alone or in combination with VI 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 4**. Total 1635 subjects (406+402+417+410) contributed UMEC PK samples for 8498 UMEC observations. Plasma samples were analyzed for UMEC 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 in plasma was 10.0 pg/mL and the higher limit of quantification (HLQ) was 2000 pg/mL for UMEC.

Table 4. Plasma Samples for the Population PK Analysis of UMEC and VI		
Study	*Doses (mcg)*	Sampling Window (nominal)
DB2113361	☐UMEC/VI 125/25 (N=402) ☐UMEC 125 (N=406) ☐ 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.
DB2113373	☐UMEC/VI 62.5/25 (N=410) ☐UMEC 62.5 (N=417) ☐ 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 2**. This phenomenon was observed for UMEC across all treatment arms. As another case of outlier data, anomalous plasma concentration-time profiles were noted for 14-15 % of subjects in dataset. 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 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 2. Plasma concentration data for the population PK analysis of UMEC

(Higher than expected concentrations in the 23-24hr window for OCC 2 & 3)
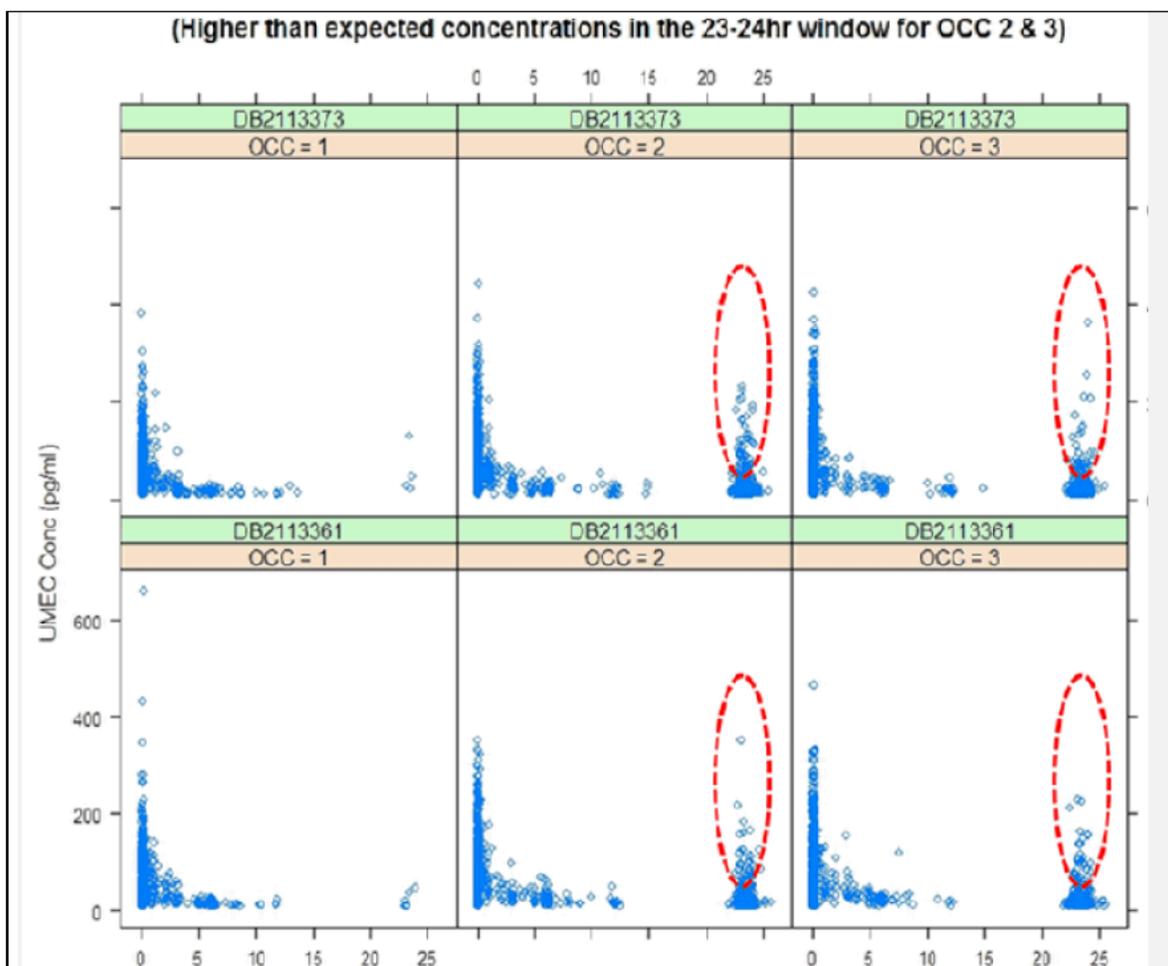
Handling Concentration Data for Unintended Analyte: About 1-2% of samples (in the analysis dataset) were for the analyte that was not administered to the individual subject. (For example, samples from UMEC mono treatment exhibiting VI concentration and vice versa). Every attempt was made to resolve this 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 UMEC. 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). 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 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 VI on UMEC PK, 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 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 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 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 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: 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 = Dose*F/CL). The C_{max} was obtained by simulating individual concentration – time profiles using the parameter and variability estimates from the final population PK model.

Results

The individual apparent inhaled clearance and apparent volume of distribution for UMEC in the final model are listed below.

$$(CL/F)_{ind} = (CL/F)_{pop} * (WT_{ind}/70)^{0.16} * (Age_{ind}/60)^{-0.731} * (CrCl_{ind}/110)^{0.271}$$
$$(V2/F)_{ind} = (V_2/F)_{pop} * (WT_{ind}/70)^{0.616}$$

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.

VPC: Visual predictive checks were performed by simulating the final model. The VPC displays 90% prediction intervals for UMEC concentrations at steady state over a dosing interval. The observed UMEC 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.

Conclusion

- UMEC 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). However, the magnitude of effect of these covariates on UMEC 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 PK parameters.
- There was no apparent trend between observed maximum heart rate and model predicted C_{max} (or highest observed concentrations) for UMEC.

Figure 3. Visual predictive check plots for UMEC

UMEC VPC Steady State – Final Model
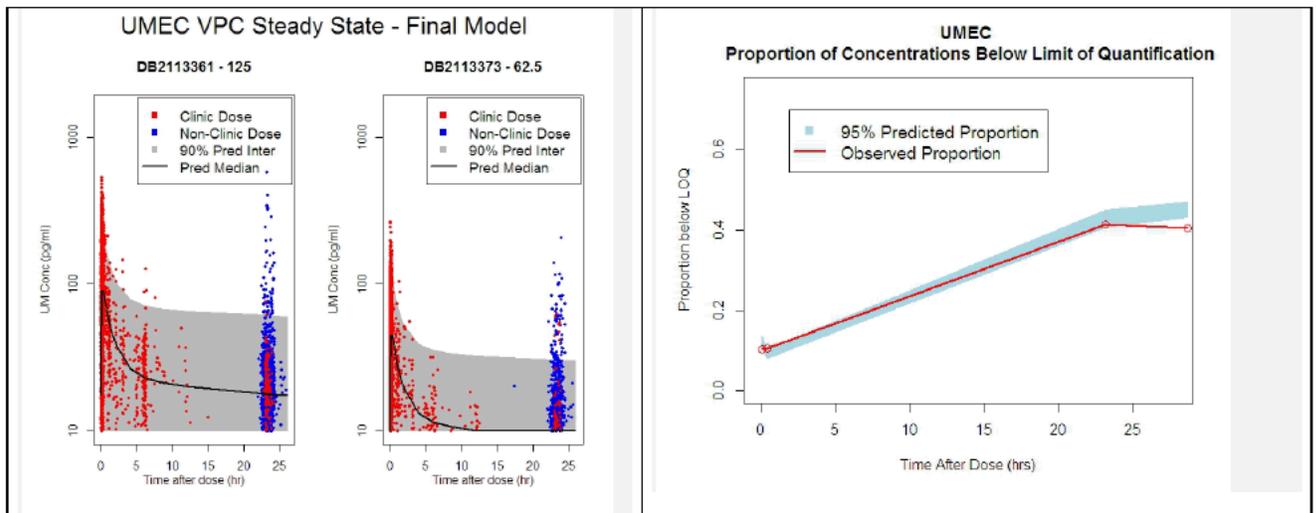
Figure 4. Goodness of Fit plots for the Final UMEC Population PK Model
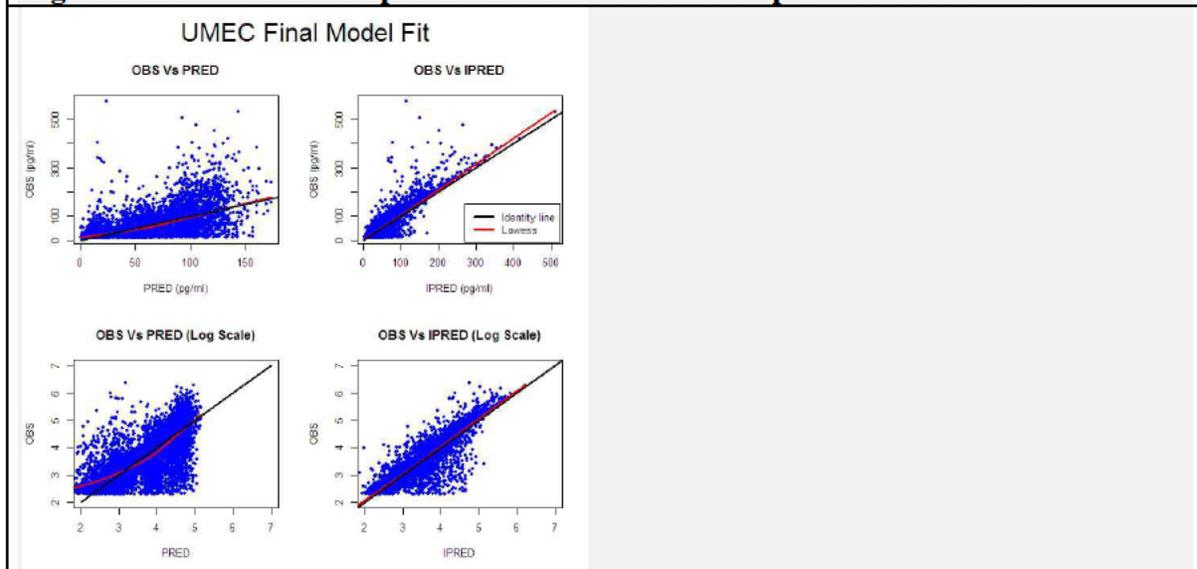
Reviewer's comments: A population PK analysis assessing the covariate effects on UMEC exposure was performed. Residual diagnostics based on the sponsor's analyses showed that the model reasonably fitted the data. Independent analysis from the reviewer was able to confirm the submitted population PK analysis results, especially the effect sizes of the identified covariates on drug exposure. See PM review by Dr. Hongshan Li on NDA203975 (DARRT date 8/16/2013) for more details.

4.2 Pharmacogenomics Review

Study AC4110106 investigated the impact of CYP2D6 phenotype on UMEC PK. This study has been reviewed under NDA 203975 (UMEC/VI) by Dr. Sarah Dorff. For brevity purposes, only key questions relevant to this current supplement NDA submission will be addressed. For additional information, please see the pharmacogenomics appendix of the clinical pharmacology review on the NDA 203975 by Dr. Sarah Dorff (DARRT date 08/16/2013).

4.2.1 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.

4.2.2 Label Recommendations

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

(b) (4)

4.3. Individual Study Review

Note – In this review, early development names GSK573719 is used to refer to Umeclidinium bromide (UMEC).

ADME In-Vitro STUDIES

Absorption and Transporters

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 analyzed 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 analyzed 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 of14C-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.

Distribution

Report #WD2008/00503

Title: Investigation of the plasma protein binding of GW573719 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.

Title: Investigation of the plasma protein binding of GW573719 and blood cell association of [14C]-GW573719 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 solid phase extraction 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.

In vitro Metabolism
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: [14C]-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. [14C]-GSK573719 was also incubated at concentrations of 0.01, 0.1 and 1μM in the presence of human liver microsomes for 1 hour. Additionally, [14C]-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 studies 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)} 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.

In vitro Enzyme Inhibition

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 (IC$_{50}$) of enzyme activity was calculated.

Results and Conclusion: GSK573719A demonstrated a marked direct inhibitor of CYP2D6 activity (IC$_{50}$ = 0.1 µM) and CYP3A4 (IC$_{50}$ = 1.0 µM for DEF and 8.0 for 7BQ) activities. GSK573719A did not demonstrate inhibition of CYP1A2, CYP2C19, and CYP2C9. The IC$_{50}$ values for miconazole (positive control) obtained in these studies were consistent with the IC$_{50}$ values typically observed for miconazole in these assays.

PHARMACOKINETICS

Mass Balance Study

Study # AC4112014

Title: An open-label, two period study to determine the excretion balance and pharmacokinetics of [$_{14}$C]-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
Cmax (pg/mL)	6	6	905.80 (70)	468.73, 1750.43
tlast (h)[1]	6	6	1.00 (0.8, 1.0)	NA
tmax (h)[1]	6	6	0.53 (0.5, 0.5)	NA
Vss (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
tlast (h)[1]	IV	6	6	168.0 (96.0, 168.0)	NA
	PO	6	6	168.0 (96.0, 168.1)	NA
tmax (h)[1]	IV	6	6	0.5 (0.5, 0.5)	NA
	PO	6	6	4.0 (3.0, 4.0)	NA
Vss (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 $AUC_{(0-\infty)}$ 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

Single dose rising

Trial # AC4105209

Title: A randomized 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 (FEV_1) 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 randomized, 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) 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 ████ (b) (4) per inhalation ██ (b) (4)% 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.

Multiple Dose Rising

Title: A single-center, randomized, 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-center, randomized, 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 randomized 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 randomized 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 t½ of GSK573719 following 14 day repeat dosing ranged from 26 to 28 h. Visual assessment of Cτ 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
Cmax (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
Cτ	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
tmax (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
t½ (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; Cmax=maximum observed plasma concentration; tmax=time of maximum observed plasma concentration; Cτ=trough concentration; t½=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 t½ based on the urine data were similar to plasma t½ and the means ranged from 28 to 33 h following single dosing and 25 to 35 h following repeat dosing.

PK Conclusions:

- The mean t½ of GSK573719 following 14 day repeat dosing ranged from 26 to 28 h. Visual assessment of Cτ 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 t½ based on the urine data were similar to plasma t½ 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 center, 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(%)
$AUC_{0-\tau}$ (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. $AUC_{0-\infty}$ 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 $AUC_{0-\tau}$ 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, AUC_{0-2} used for 500 µg and AUC_{0-8} used for 1000 µg) after repeat inhaled doses of GSK573719 250, 500 and 1000 µg are summarized 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

*: $AUC_{0-1.5}$, AUC_{0-2} and AUC_{0-8} 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.
- Accumulation was approximately 1.6 after 7-day repeat inhaled dosing of GSK573719 1000 µg. Accumulation 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 randomized, double-blind, placebo-controlled, dose ascending, 2-cohort, parallel group study to examine the safety, tolerability and pharmacokinetics of once daily
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 randomized, 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 summarized 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 t½ 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 randomized, 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-center, randomized, 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(%)
t½ (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.

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

Methods: This was a randomized, 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
		10	Single dose placebo oral tablet moxifloxacin
B	Moxifloxacin positive control	1–10	Single inhalation from matching placebo NDPI once daily
		10	Single dose oral tablet moxifloxacin (400 mg)
C	UMEC supra-therapeutic dose	1–10	Single inhalation from UMEC 500 mcg NDPI once daily
		10	Single dose placebo oral tablet moxifloxacin
D	UMEC/VI therapeutic dose	1–10	Single inhalation from UMEC/VI 125/25 mcg NDPI once daily
		10	Single dose placebo oral tablet moxifloxacin
E	UMEC/VI supra-therapeutic dose	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(%)
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
tlast (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
t½ (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
λz	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.

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.
- T_{half} for UMEC was 25 h.
- The systemic exposure of UMEC and VI was dose proportional based on AUC and C_{max}.

SPECIFIC POPULATION

Renal Impairment

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) 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-randomized 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 plasma pharmacokinetic parameters $AUC_{(0-t)}$, $AUC_{(0-t')}$, C_{max},

T_{max}, $AUC_{(0–24)}$, $AUC_{(0–\infty)}$, t_{last}, $t_{½}$, 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)	Healthy	9	9	1	56.5	(34.8, 91.6)	69.7
(h·pg/mL)	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)	Healthy	9	9	0	60.4	(44.6, 81.9)	41.1
(h·pg/mL)	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)	Healthy	9	9	1553	(998 , 2415)	62.6
(ng)	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)	Healthy	9	9	1627	(1186, 2232)	42.9
(ng)	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.

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 t½ in subjects with severe renal impairment was observed, suggesting efficient alternate disposition and elimination pathways for UMEC in these subjects. Overall urine t½ between the two groups were comparable
- Inhaled UMEC 125 mcg and UMEC/VI 125/25 mcg were well tolerated in healthy subjects and in subjects with severe renal impairment

- **Conclusions:**

No dose adjustment recommended for subjects with severe renal impairment.

Hepatic Impairment

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) 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 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-randomized 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
$AUC_{(0-\tau)}$ (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 $AUC_{(0-\tau)}$.

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
- 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

Conclusions:
No dose adjustment needed for subjects with hepatic impairment.

DRUG-DRUG INTERACTIONS

DDI with Verapamil

Trial # DB2113950

Title: A single-center, randomized, 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 GSK573719 in healthy subjects.

Study design and treatment schedule: Single center, 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 C_{max} 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 C_{max} 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.

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:**

UMEC pharmacokinetics was not affected by P-gp inhibition.

DDI in CYP2D6 Poor Metabolizers
Trial #AC4110106

Title: A single center, randomized, 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 metabolizers.

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 metabolizers).
• 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 metabolizers).
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 metabolizers (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 metabolizers).
• 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 metabolizers).
• 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 center, randomized, 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 randomized 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 randomized to Sequence 1, receiving 500 μg in the repeat dose period and 8 subjects were randomized to Sequence 2, receiving 1000 μg in the repeat dose period. Four subjects were randomized 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 randomized into Part 2, 8 in Cohort I (Sequences 1 and 2) and 8 in Cohort II (Sequences 3 and 4). Six CYP2D6 PM were randomized to Sequence 1 and 6 to Sequence 3. Two CYP2D6 PM were randomized 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)
Cmax (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

Absolute Bioavailability

Trial # AC4112008

Title: A single-center, 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%
$AUC_{(0-\infty)}$ (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
$AUC_{(0-t)}$ (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$_b$(%)
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
CLr (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 C_{max} 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.

PHARMACODYNAMICS

PKPD

Trial # DB2113208

Title: A single center, randomized, 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 center, double-blind, placebo-controlled, four-way crossover, randomized, 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 randomization 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 randomized 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.

Trial # AC4115487

Title: Randomized, double-blind, 5 period cross-over study assessing lung function in healthy volunteers following single inhalations of umeclidinium bromide (GSK573719) Inhalation Powder from two configurations of the Novel Dry Powder Inhaler.

Objectives:
Primary:
• To estimate the difference in bronchodilatory effect of single inhaled doses of UMEC administered to ipratropium responsive healthy volunteers via two configurations (1 strip vs 2 strip) of the Novel Dry Powder Inhaler (NDPI), using serial plethysmography over 24 hours.
Secondary:
• To estimate the difference in bronchodilatory effect of single inhaled doses of UMEC administered to ipratropium responsive healthy volunteers via two configurations(1 strip vs 2 strip) of the Novel Dry Powder Inhaler (NDPI), using serial plethysmography over 24 hours.
• To investigate the pharmacokinetics (PK) of single inhaled doses of UMEC administered via two configurations of the NDPI.

Reviewer's comment:
For anticholinergics, the bronchodilatory effect is small in normal airways in healthy subjects, but is greater in airways of patients with COPD.

Study design and treatment schedule:
This was a randomized, double-blind, cross-over study, with two different single doses of UMEC (62.5 mcg and 125 mcg), in two configurations (1 strip vs 2 strip) of the NDPI and placebo. The study consisted of a screening period, five treatment periods, and a follow-up visit.

Criteria for evaluation: APSD, PK and PD (FEV1)

Results:
APSD: The calculated percent difference in FPMass (sum of stages 3 to 5) of one strip configuration 62.5 mcg monotherapy product used in the study is 15% higher compared to two strip configuration.

QC release data for APSD of UMEC Inhalation Powder 62.5mcg supplied for AC4115487 (N = 1 batch)
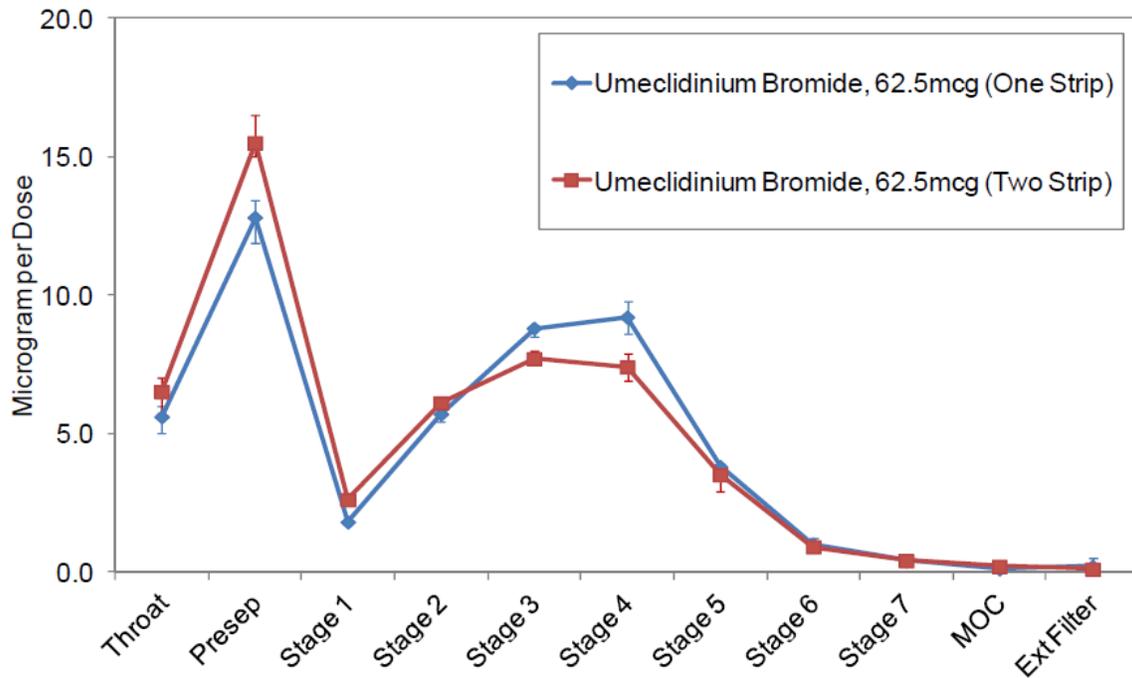
Source: Figure 5 from study report AC4115487

PK: Plasma UMEC PK parameter estimates are summarized by treatment in the table below. UMEC C_{max} is ~15% lower when administered with one strip NDPI compared to two strip NDPI. The AUC_{inf} is similar with the two configuration NDPIs.

Statistical Comparison of UMEC Plasma PK Parameters

Parameter	UMEC	Treatment Comparison (Test - Ref)	Adjusted Means Test/Reference	Ratio of Adjusted Means	90% CI of the Ratio
Cmax	62.5 mcg	one-strip – two-strip	97.038 / 113.365	0.856	(0.684, 1.071)
	125 mcg	one-strip – two-strip	226.147 / 257.123	0.880	(0.699, 1.106)
AUC(0-1)	62.5 mcg	one-strip – two-strip	32.067 / 35.370	0.907	(0.737, 1.115)
	125 mcg	one-strip – two-strip	ND	ND	ND
AUC(0-2)	62.5 mcg	one-strip – two-strip	ND	ND	ND
	125 mcg	one-strip – two-strip	104.941 / 112.383	0.934	(0.838, 1.041)
AUC(0-∞)	62.5 mcg	one-strip – two-strip	40.921 / 41.843	0.978	(0.791, 1.209)
	125 mcg	one-strip – two-strip	134.931 / 137.361	0.982	(0.795, 1.214)
AUC(0-1)*	62.5 mcg	one-strip – two-strip	35.617 / 35.694	0.998	(0.881, 1.130)
	125 mcg	one-strip – two-strip	NA	NA	NA
AUC(0-∞)*	62.5 mcg	one-strip – two-strip	45.431 / 41.615	1.092	(0.916, 1.302)
	125 mcg	one-strip – two-strip	133.754 / 139.033	0.962	(0.811, 1.141)

Source: Table 9 from study report AC4115487

PD: FEV1 values indicates similar change from baseline over time when comparing one-strip configuration and two-strip configuration for both UMEC doses, and a trend for slightly increased values across all time points when compared to placebo, as summarized in the table and figure below.

Summary of Results from Statistical Analysis of FEV1 (L) Weighted Mean and Maximal Change from Baseline (0-24 hours)

Parameter	UMEC	Treatment Comparison (Test - Ref)	Adjusted Means Test/Reference	Difference of Adjusted Means	90% CI of the Differences
FEV1 Maximal Change from Baseline (0-24 hours)	62.5mcg	one-strip – two-strip	0.241 / 0.269	-0.028	(-0.091, 0.035)
		one-strip - Placebo	0.241 / 0.215	0.026	(-0.036, 0.089)
		two-strip - Placebo	0.269 / 0.215	0.055	(-0.008, 0.117)
	125mcg	one-strip – two-strip	0.303 / 0.277	0.026	(-0.038, 0.090)
		one-strip - Placebo	0.303 / 0.215	0.089	(0.024, 0.153)
		two-strip - Placebo	0.277 / 0.215	0.062	(-0.00048, 0.125)

Source: Table 6 from study report AC4115487

Plot of Adjusted Geometric Mean of FEV1 (L) Time Profile and 95% CIs
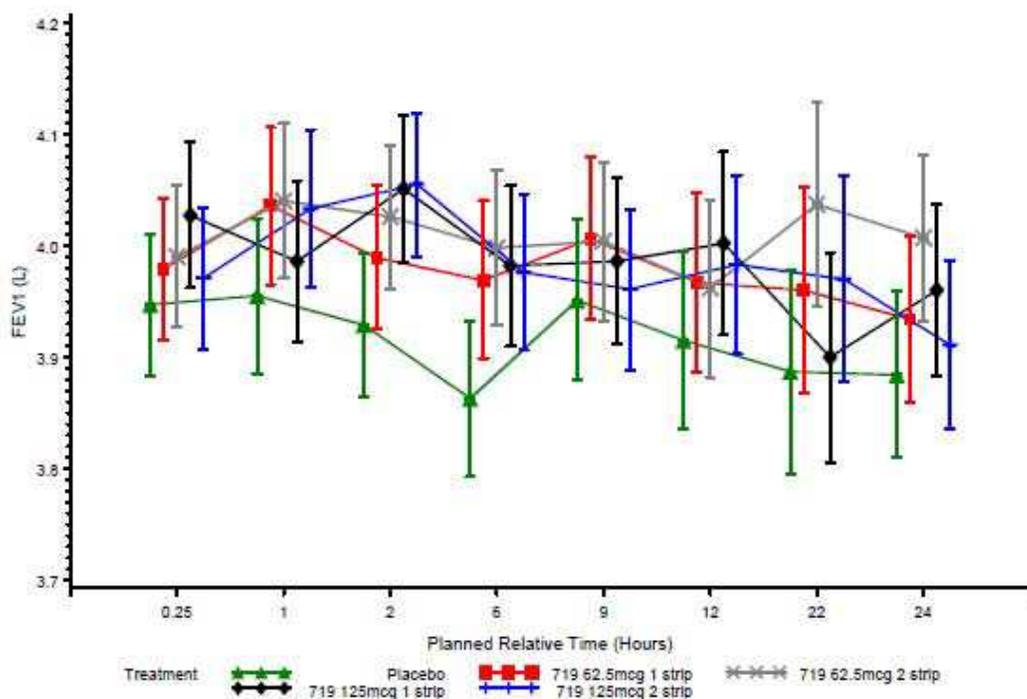
Source: Figure 2 from study report AC4115487

Reviewer's comment:

The phase 3 trials used the one-strip configuration for the UMEC monotherapy arm. As the phase 3 product is the same as the to-be- marketed product, no bridging study is required for NDA205382. In the CMC type B meeting on June 8, 2012, FDA commented on the use of one-strip configuration for UMEC monotherapy arm in the factorial design phase 3 trials based on the results of study AC4115487: "*While ultimately a review issue, the proposed approach for supporting the use of the one strip monotherapy products in the clinical program appears reasonable based on the available information.*"

4.4 New Drug Application Filing and Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	205382	**Brand Name**	**INCRUSE ELLIPTA**
OCP Division (I, II, III, IV, V)	II	**Generic Name**	**Umeclidinium Bromide Inhalation Powder**
Medical Division	Pulmonary, Allergy, and Rheumatology Products	**Drug Class**	**Inhaled anticholinergic**
OCP Reviewer	Liang Zhao, 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 (62.5 mcg) QD**
Date of Submission	4/30/2013	**Route of Administration**	**Oral Inhalation**
Estimated Due Date of OCP Review	1/3/2014	**Sponsor**	**GSK**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	4/30/2014		

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	1		AC4112014 (UMEC)
Isozyme characterization:	X			
Blood/plasma ratio:	X			
Plasma protein binding:	X			
Transporter specificity:	X			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		AC4105209 (UMEC, DISKUS) AC4115487 (UMEC, 1strip vs 2)
multiple dose:	X	3		DB2113208, AC4113377 (UMEC, Japanese) AC4106889 (UMEC)
Patients-				
single dose:	X	1		AC408123 (UMEC, COPD)

multiple dose:	**X**	**1**		AC4105211 (UMEC, 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**	**1**		DB2113950-Verapamil
In-vivo effects of primary drug:	**X**			Low systemic concentration
In-vitro:	**X**			
Subpopulation studies -				
ethnicity:	**X**			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**	**3**		UMEC dose ranging (AC4113589, AC4115321, AC4113073)
Phase 3:	**X**	**7**		UMEC dose ranging (IIIa)AC4115408 DB2113361, DB2113373, Active comparator: DB2113374, Exercise: DB2114417, DB2114418, Long term: 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**	**1**		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	**X**			
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		**24**		

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	205382	Brand Name	(b) (4) ELLIPTA
OCP Division (I, II, III, IV, V)	II	Generic Name	Umeclidinium Bromide Inhalation Powder
Medical Division	Pulmonary, Allergy, and Rheumatology Products	Drug Class	Inhaled LAMA
OCP Reviewer	Liang Zhao, 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 (62.5 mcg) QD
Date of Submission	4/30/2013	Route of Administration	Oral Inhalation
Estimated Due Date of OCP Review	1/3/2014	Sponsor	GSK
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	4/30/2014		

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	1		AC4112014 (UMEC)
Isozyme characterization:	X			
Blood/plasma ratio:	X			
Plasma protein binding:	X			
Transporter specificity:	X			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		AC4105209 (UMEC, DISKUS) AC4115487 (UMEC, 1strip vs 2)
multiple dose:	X	3		DB2113208, AC4113377 (UMEC, Japanese) AC4106889 (UMEC)
Patients-				
single dose:	X	1		AC408123 (UMEC, COPD)
multiple dose:	X	1		AC4105211 (UMEC, 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**	**1**		DB2113950-Verapamil
In-vivo effects of primary drug:	**X**			Low systemic concentration
In-vitro:	**X**			
Subpopulation studies -				
ethnicity:	**X**			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**	**3**		UMEC dose ranging (AC4113589, AC4115321, AC4113073)
Phase 3:	**X**	**7**		UMEC dose ranging (IIIa)AC4115408 DB2113361, DB2113373, Active comparator: DB2113374, Exercise: DB2114417, DB2114418, Long term: 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**	**1**		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	**X**			
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		**24**		

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__

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
- None

Information request to sponsor:
- Part of Figure 1 for hepatic and renal impairment population in the proposed label is based on UMEC PK data from the UMEC/VI combination arm. Please revise the figure using PK data associated with the UMEC monotherapy.

Jianmeng Chen and Liang Zhao
_____
Reviewing Clinical Pharmacologist   Date

Suresh Doddapaneni
_____
Team Leader/Supervisor   Date

<u>**Submission in brief:**</u>
Indication and mechanism of action
GSK has submitted the NDA 203975 seeking the marketing approval for Umeclidinium bromide Inhalation Powder (＿＿＿＿＿ (b) (4) 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 Inhalation Powder (hereafter referred to as UMEC) is not indicated for the prevention of exacerbation or the treatment of asthma.

UMEC is a novel long-acting muscarinic antagonist (LAMA) combination for oral inhalation to be administered from a Novel Dry Powder Inhaler (NDPI). Recommended dose is UMEC 62.5 mcg for the treatment of COPD. UMEC is a new molecular entities (NME). GSK has another pending NDA 203975 Umeclidinium Bromide/Vilanterol Inhalation Powder (ANORO ELLIPTA) for the treatment of COPD. The initial submission of UMEC/VI included two doses of 125/25 and 62.5/25 mcg. The ＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿ (b) (4) ＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿ .

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

EOP2-COPD (Oct 2010)	• 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 21 clinical pharmacology studies (Table 2), including 13 studies with UMEC monotherapy and 8 studies with UMEC/VI combination therapy. These are the same studies to support another NDA203975 (UMEC/VI). The clinical pharmacology information for UMEC 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 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 Studies Contributing PK Data (21 studies total)		
UMEC	13	AC4105209, AC4105211, AC4110106, AC4106889, AC4108123, AC4112008, AC4113377, AC4115487, AC4112014, AC4113589, AC4115321, AC4113073, AC4115408
UMEC/VI [a]	8	DB2113208, DB2113950, DB2114635, DB2114636, DB2114637, DB2113120, DB2113361, DB2113373

a. UMEC treatment arm included in study; may include UMEC/VI or VI arms.

Rationale for 62.5 mcg qd dose regimen selection

-Dose selection for UMEC

Results for different UMEC doses on trough FEV_1 from the four Phase 2 dose ranging studies in subjects with COPD are summarized in **Table 3**, which show substantial
efficacy with 62.5 mcg UMEC daily dose and near maximal efficacy with 125 mcg UMEC daily dose. Sponsor selected two doses of UMEC (62.5 and 125 mcg) for further evaluation 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) [a]						
	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 phase II dose ranging studies, sponsor evaluated the efficacy of UMEC 62.5 and 125 mcg in Phase III studies in COPD patients and demonstrated that both doses showed benefit in lung function over placebo(**Figure 2**) and lower the risk of a COPD exacerbation (**Figure 3**) in 24 weeks. The higher dose of UMEC 125 mcg conferred little additional benefit in lung function or exacerbation reduction compared with UMEC 62.5 mcg. Thus, sponsor seeks approval for UMEC 62.5 strength for the treatment of COPD.

**Fig 2. COPD; Trough FEV1 (L); Integrated Studies DB2113361, DB2113373, DB2113374 ITT Population**

Fig 3. COPD;First on treatment Exacerbation; Integrated Studies DB2113361, DB2113373, DB2113374 ITT Population
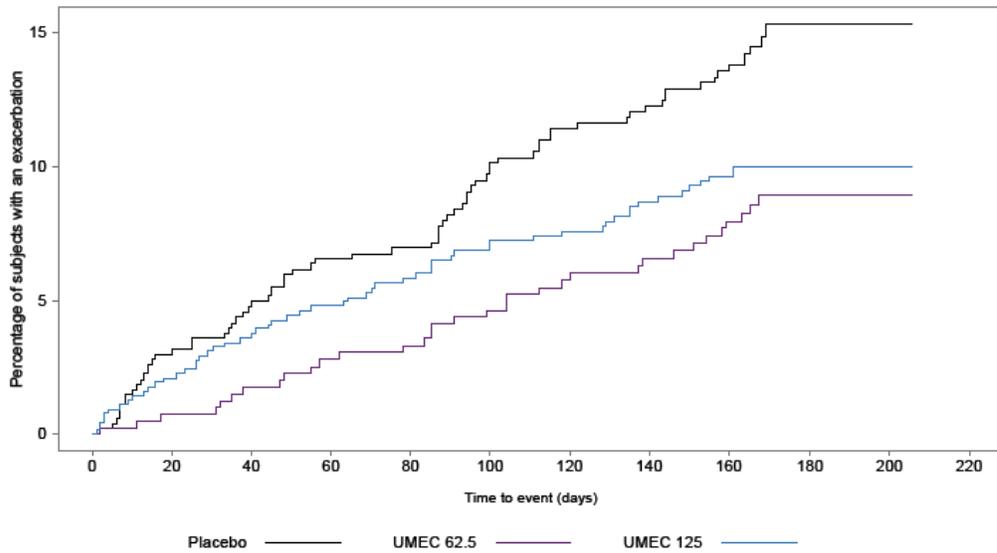
-Dosing Frequency:

Qd vs Bid: Study AC4115321 in subjects with COPD supported the comparability of once and twice daily dosing for UMEC (**Figure 4**).

Fig 4. COPD; Change from baseline FEV1 (L) on Day 7; study AC4115321
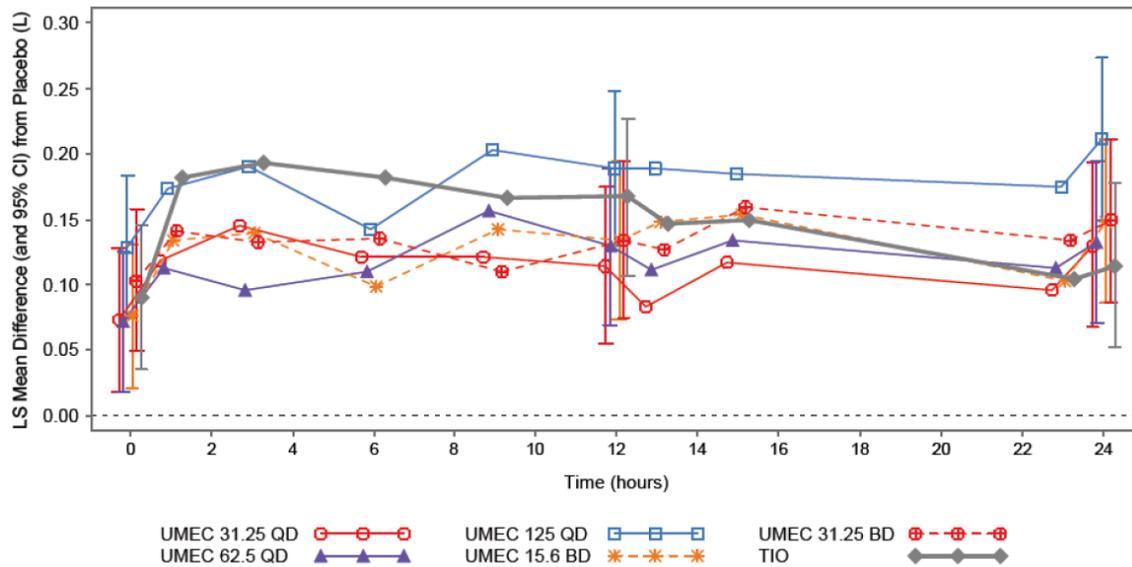
-Morning vs evening dosing

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 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 substate 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. For renal impairment, no dose adjustments are recommended. Systemic UMEC exposure is not increased in severe renal impairment patients. Co-administration with P-gp inhibitor verapamil did not significantly affect the PK of UMEC.

Effect on QT interval

As per sponsor's report, a thorough QT study (DB2114635) demonstrated a decreasing effect of QTc(F) at a supradose of 500 mcg UMEC for 10 days. The largest mean time-matched difference from placebo was -2.38 msec (90% CI: -3.82, -0.85) at the mean observed UMEC C_{max}.

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 for COPD.

Summary of PK

Oral bioavailability of both UMEC is low, on average <1%. Consequently, systemic exposure for inhaled UMEC is primarily due to absorption of the inhaled portion of the dose delivered to the lung. Following inhaled administration of UMEC in healthy subjects, C_{max} occurs at 5 to 15 minutes. The absolute bioavailability for UMEC (administered as UMEC/VI) is 13%. The apparent terminal phase elimination half-life of UMEC following inhaled UMEC/VI is on average 19 h.

UMEC is extensively distributed, with average volumes of distribution at steady-state of 86 L. *In vitro* plasma protein binding for UMEC is 89%.

UMEC is primarily metabolized by CYP2D6. UMEC is a P-gp substrate. In humans, UMEC is eliminated primarily by metabolism with metabolites excreting both in urine and feaces.

Steady-state for UMEC was achieved by day 10 with once-daily dosing. Based on $AUC_{(0-t)}$, accumulation ranged from 1.5 to 2 fold for UMEC. Population PK analysis of Phase III data showed plasma UMEC concentration time profiles following administration of UMEC was best described by a two-compartment model with first order absorption.

Summary of population based modeling analysis

UMEC is administered by oral inhalation and efficacy is presumed to be driven by topical effects in the lung. Systemic exposure of UMEC is considered more relevant for safety. Sponsor conducted population PK analysis to evaluate covariates, and several other population based

modeling analyses 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
Effect of co-administration of verapamil on UMEC exposure (AUC) and C_{max} was evaluated. Co-administration of repeat dose inhaled UMEC/VI (125/25 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}.

-Effect of UMEC on other drugs
With low systemic exposures for UMEC 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
06/18/2013

SURESH DODDAPANENI
06/18/2013