CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206038Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	206038
Submission Date	11/5/2014
Brand Name	ORKAMBI
Generic Name	Lumacaftor/Ivacaftor
Clinical Pharmacology Reviewer	Jianmeng Chen, M.D., Ph.D.
Pharmacometrics Reviewer	Anshu Marathe, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Clinical Pharmacology Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor/Authorized Applicant	Vertex
Submission Type; Code	505(b)(1); priority review
Formulation; Strength(s)	Tablet (200/125 mg)
Indication	CF patients with F508del homozygous mutations, 12 years and above
Dosage Regimen	400/250 BID

Note –
In this review, early development name VX809 is also used to refer to lumacaftor(LUM), and VX770 is also used to refer to ivacaftor (IVA).

---

1. Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 206038 and recommends approval from a clinical pharmacology perspective.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Vertex pharmaceuticals, Inc. has submitted NDA 206038 seeking the marketing approval for lumacaftor/ivacaftor, for the indication of "*treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene.*" If approved, this will be the first drug to treat the underlying defect in F508del CFTR protein for cystic fibrosis (CF) patients who are homozygous for the F508del mutation in the CFTR gene.

Lumacaftor (LUM) is an F508del CFTR protein stabilizer and ivacaftor is a CFTR potentiator. Recommended dose is two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours (lumacaftor 800 mg/ivacaftor 500 mg total daily dose) with fat containing food. Ivacaftor (IVA, KALYDECO, NDA203188) has been previously approved for the treatment of CF in subjects 2 years and older who possess at least one copy of one of the ten mutations (G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or R117H) in the CFTR gene. The approved dosing regimen is 150 mg BID for patients 6 years and older. Ivacaftor is not approved for CF patients with homozygous F508del mutations.

The Sponsor supports this NDA submission with 18 clinical/clinical pharmacology studies including 12 Phase 1 studies for LUM or LUM/IVA, 3 Phase 2 dose ranging studies (770-104, 809-101, 809-102), 2 Phase 3 studies (809-103, 809-104), and a safety extension study (809-105). Majority of the clinical pharmacology studies for IVA have been previously reviewed in NDA 203188 (Dr. Lokesh Jain, review dated 01/18/2012).

The efficacy of LUM/IVA 400/250 mg q12h dose was investigated in 1 Phase 2 (809-102) and 2 Phase 3 (809-103, 104) trials in CF patients. In these trials, LUM/IVA resulted in statistically significant improvements in absolute change in % predicted FEV1 compared to placebo, ranging from 2.7-3.0% for the proposed dose of LUM/IVA 400 mg/250mg q12h. Additionally, the number and annual rate of exacerbations were reduced in the LUM/IVA group compared to the placebo in all phase 3 trials. The hazard ratio (95% CI) was 0.6 (0.5, 0.8) in pooled data from phase 3 trials. The most common adverse events observed in the trials were liver enzyme elevations. Notably, the phase 3 studies were not designed to show contribution of individual components, with only LUM/IVA

combination therapy and the placebo treatments. As the LUM monotherapy has shown a dose dependent decrease in lung function (Figure 2), and IVA monotherapy was determined earlier as "not effective" for this particular mutation, no monotherapy arm was included in phase 3 studies.

Rational for 400/250 bid dose regimen selection

Figure 1 Dose Regimens in Phase 3 Studies

Dosing Regimen 1 Lumacaftor 600 mg QD Ivacaftor 250 mg Q12h	
Morning	Evening
lumacaftor/ivacaftor	ivacaftor
200/83	125
200/83	125
200/83	

Dosing Regimen 2 Lumacaftor 400 mg Q12h Ivacaftor 250 mg Q12h	
Morning	Evening
lumacaftor/ivacaftor	lumacaftor/ivacaftor
200/125	200/125
200/125	200/125

Figure 1. Dose regimens in Phase 3 studies

***-Lumacaftor*:** LUM 600 mg qd/IVA 250 mg q12h regimen was assessed in the phase 2 study 102, and was carried forward to phase 3 studies. In Study 102, all treatment groups either remained stable or demonstrated a dose dependent reduction in FEV1 during the 28-day period of lumacaftor monotherapy (Figure 2). In contrast, during the 28-day period of combination therapy, an increase in FEV_1 was observed in all active treatment cohorts, with the largest increase in the LUM 600 mg qd/IVA 250 mg q12h cohort.

LUM 400mg/IVA 250 mg q12h regimen was also studied in phase 3, given the simplicity of the dosing regimen (Figure 1) and the potentially advantageous PK profile (smaller peak to trough concentration ratio with the BID regimen) of lumacaftor.

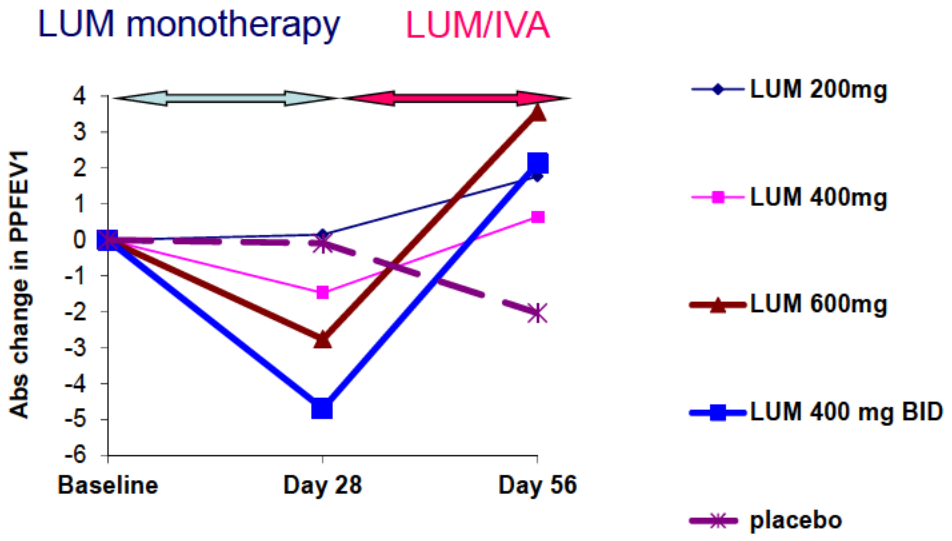


Figure 2. PPFEV1 change from baseline, study 809-102
(source: reviewer summary)

-Ivacaftor: Based on the observed reduction in ivacaftor exposure when lumacaftor was administered in combination, the dosage of ivacaftor was increased to 250 mg q12h from the approved ivacaftor dosage of 150 mg q12h when administered alone. However, the ivacaftor exposure in the LUM/IVA combination therapy is still much lower compared to that of the ivacaftor 150 mg q12h monotherapy (Figure 3). The sponsor theorized that ivacaftor potency is 7-fold higher in F508del-CFTR (EC90 at 60ng/ml) compared to G551D-CFTR (EC90 at 423 ng/ml) in the *in vitro* studies, and therefore the IVA 250 mg q12h dose was sufficient for the patients with F508del.

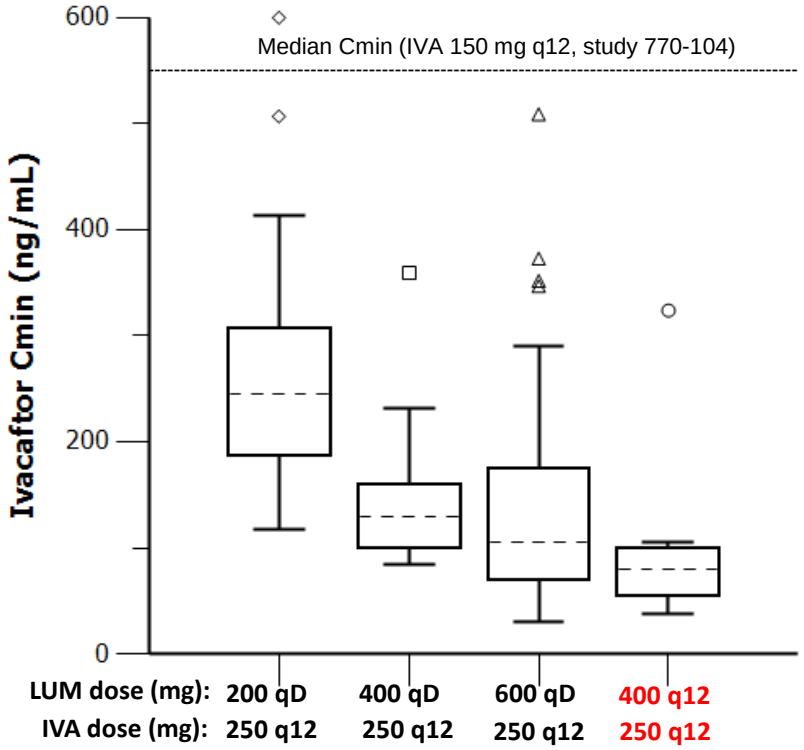


Figure 3. Lower Ivacaftor exposure with increased dose of Lumacaftor (study 102)
(source: reviewer analysis)

-Efficacy in Phase 3 trials:
Studies 103 and 104 were Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies that evaluated the efficacy and safety of LUM/IVA combination therapy for 24 weeks in subjects 12 years and older with CF who are homozygous for the F508del-CFTR mutation. These studies evaluated 2 doses of LUM in combination with IVA (Figure 1), in comparison to placebo. Study 105 was a long-term, rollover study to assess the persistence of efficacy.

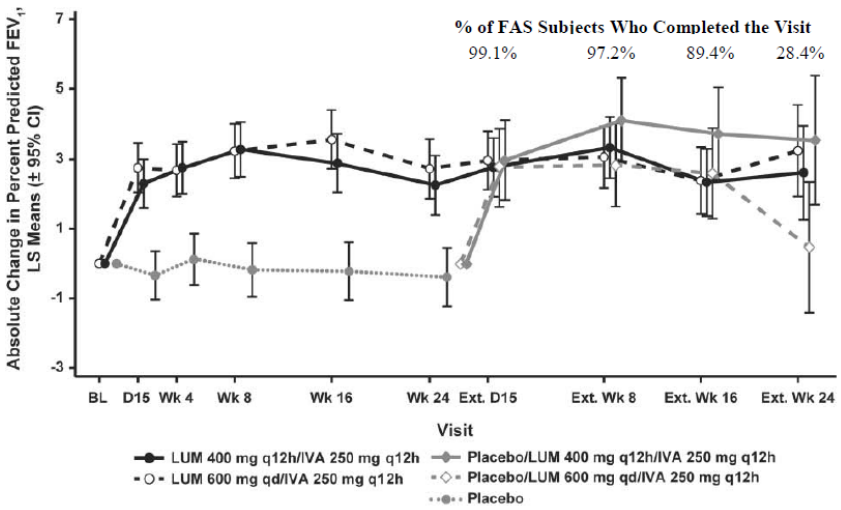


Figure 4. Absolute Change From Baseline in Percent Predicted FEV1 (first 24 weeks, pooled data of study 103 and 104; Ext time, data from extension study 105)
(Source: Figure 9 of the Summary of Efficacy)

Phase 3 studies indicated that both dosing regimens showed improvement compared to placebo in the primary endpoint (Figure 4) and other key secondary endpoints (e.g. exacerbation), and there was no clear differentiation between the 2 combination therapy regimens. Therefore, the sponsor sought approval for LUM/IVA 400/250 mg BID due to simplicity of the dosing regimen.

-Contribution of LUM in LUM/IVA:
Ivacaftor was labeled as "not effective" for F508del homologous mutation at the initial approval in 2012. This is based on study 770-104, with an effect size of 1.7% (-0.6%, 4.1%)) improvement in PPFEV1, compared to the effect size of 10-12% for the approved indication, G551D mutation in CFTR.

In LUM/IVA phase 3 studies, LUM/IVA 400/250mg BID had an effect size of 2.6-3.0% in PPFEV1, with similar exacerbation benefit as monotherapy (hazard ratio 0.6-0.7), making the contribution of LUM unclear. In this review, we have demonstrated that the ivacaftor exposure in the LUM/IVA combination (400/250 mg BID) is less than 20% of the ivacaftor exposure in study 770-104 (Figure 3). Based on exploratory E-R analysis for ivacaftor monotherapy study 770-104, Ivacaftor alone would not account for the efficacy observed in study 809-103 and 809-104 at the concentrations observed in phase 3 studies. This suggested a likely contribution of lumacaftor (See section 3 of pharmacometrics review, appendix 4.1). One possible hypothesis could be that lumacaftor reduces the EC50 for ivacaftor, as indicated by some *in vitro* data. Thus even at low exposures of ivacaftor in combination therapy, a response similar to the ivacaftor monotherapy is observed. . The hypothesis that lumacaftor reduces the ivacaftor EC50 should be viewed in context that the overall efficacy in combination therapy was similar to the efficacy that was observed in ivacaftor monotherapy study. Thus from a net effect perspective, the contribution of lumacaftor remains unclear because similar response could have been achieved with ivacaftor monotherapy; although at higher ivacaftor exposures. Based on the current ivacaftor label, the safety profile at these high exposures

is acceptable.

Pharmacokinetics

CF vs. Healthy

- The exposure (AUC) of lumacaftor is approximately 2 fold higher in healthy adult volunteers compared to exposure in patients with CF. The exposure of ivacaftor is similar between healthy adult volunteers and patients with CF.

Absorption

- LUM Systemic exposure (AUC) and peak plasma concentration (C_{max}) increased roughly dose proportional in the dose range of 50 mg to 1000 mg qd in healthy subjects, and 25 mg qd to 400 mg q12h in CF patients.
- T_{max} was reached by 4.0 hours (2.0; 9.0) in the fed state.
- When a single dose of LUM/IVA was administered with fatty foods, lumacaftor exposure is approximately 2 times higher and ivacaftor exposure is approximately 3 times higher than when taken in a fasting state.
- Upon twice daily dosing, steady-state was reached by one week with 1.9 fold accumulation for lumacaftor.
- LUM is a not substrate of P-gp transporter.

Distribution

- LUM is approximately 99% bound to plasma proteins, primarily to albumin.
- The typical apparent volumes of distribution for the central and peripheral compartments (CV) were estimated to be 23.5 L (48.7%) and 33.3 L (30.5%), respectively.

Metabolism and Transporters

- Lumacaftor is not extensively metabolized in humans with the majority of lumacaftor excreted unchanged in the feces.
- At steady state, the major metabolite in blood is M28-LUM, which is <10% compared to lumacaftor. M28-LUM is not active at clinical relevant concentrations.
- Ivacaftor is extensively metabolized in humans by CYP3A and excreted in feces as metabolites. The major metabolites are M1-IVA and M6-IVA, which are both CYP3A products. When given in combination, the metabolite to parent ratio (i.e., $AUC_{0\text{-tlast}}$ for metabolite/$AUC_{0\text{-tlast}}$ for ivacaftor) for M1 and M6 at steady-state were 3.7 and 8.1, respectively.
- Lumacaftor is a strong inducer of CYP3A. Based on *in vitro* studies, lumacaftor has the potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19; inhibition of CYP2C8 and CYP2C9 was also observed *in vitro*.
- Based on *in vitro* results, lumacaftor has the potential to both inhibit and induce P-gp.

Elimination

- Approximately 89.6% of administered dose gets excreted in feces and 8.6% is eliminated by urine. There was negligible urinary excretion of lumacaftor as unchanged parent (mean of 0.18%)

- The mean terminal half-life of lumacaftor and ivacaftor when given in combination are approximately 26 and 9 hours, respectively.

Special Population

- No dose adjustments are recommended based on weight, age, race and gender.
- No dedicated PK study was conducted in patients with renal impairment or end stage renal disease. No dose adjustments are recommended for mild and moderate renal impairment patients because of minimal elimination of lumacaftor/ivacaftor and their metabolites in urine. The safety and efficacy of lumacaftor/ivacaftor have not been established in patients with severe renal impairment. Caution is recommended when administering ORKAMBI to patients with severe renal impairment
- The ORKAMBI dose should be reduced to 2 tablets (400/250 mg) in the morning and 1 tablet(200/125) in the evening (lumacaftor 600 mg/ivacaftor 375 mg total daily dose) for patients with moderate hepatic impairment (Child-Pugh Class B). These subjects had approximately 50% higher exposures (AUC0-12h) than matched healthy subjects.
- The impact of mild hepatic impairment (Child-Pugh Class A) on pharmacokinetics of lumacaftor has not been studied, but the increase in exposure is expected to be less than 50%. Therefore, no dose adjustment is necessary for patients with mild hepatic impairment.
- Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C) due to safety concern, but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, use with caution at a maximum dose of 1 tablet in the morning and 1 tablet in the evening (lumacaftor 400 mg /ivacaftor 250 mg total daily dose), or less, in patients with severe hepatic impairment after weighing the risks and benefits of treatment.

Drug-Drug Interaction (DDI)

Drug-Drug Interactions between LUM and IVA

- Lumacaftor is a strong inducer of CYP3A. Co administration of lumacaftor with ivacaftor, a sensitive CYP3A substrate, decreased ivacaftor exposure by approximately 80%. There was no meaningful impact of IVA on the PK of LUM.

Effect of coadministered drugs on LUM/IVA exposure

- IVA is a CYP3A substrate. A minor extent of the biotransformation of LUM consisted of CYP3A pathways.
- LUM exposure is not affected by co-administration of CYP3A inhibitors (itraconazole, ciprofloxacin) or inducers (rifampin).
- Co-administration with itraconazole (strong CYP3A4 inhibitor) increased exposure to ivacaftor 4.3-fold based on AUC and 3.6-fold based on Cmax compared to administration of LUM/IVA alone. However, this increase in ivacaftor exposure does not require a dose adjustment, as ivacaftor exposure is still less than what is observed for ivacaftor monotherapy (Kalydeco).
- Co-administration with the CYP3A4 inducer rifampin, decreased exposure to ivacaftor by 57% based on AUC and 50% based on Cmax. Therefore, coadministration with rifampin or other CYP3A inducers is not recommended.

- No significant change in exposure (AUC and Cmax) of lumacaftor and ivacaftor was observed following co-administration with ciprofloxacin. Therefore, no dose adjustment is recommended.

Effect of LUM/IVA on exposure of coadministered drugs

- Lumacaftor is a strong inducer of CYP3A. *In vitro* studies suggest that LUM has the potential to induce P-gp, CYP2B6, CYP2C8, CYP2C9, and CYP2C19. *In vitro* studies also indicated that lumacaftor may inhibit CYP2C8 and 2C9.
- Dedicated DDI study with ivacaftor, and a study with itraconazole showed that LUM typically decreased the exposure to CYP3A substrate by >80%.
- No significant change in steady state trough concentrations of ciprofloxacin was observed following co-administration with LUM/IVA.
- No dedicated DDI studies were done for CYP2C substrates.
- CF patients are usually on many concomitant medicines, and many of these concomitant medicines are CYP3A and/or CYP2C substrates. Phase 3 studies suggested that the DDI impact of LUM was largely manageable based on clinical monitoring, dose adjustment and using alternative drugs. Nevertheless, having lumacaftor in the dose regimen will limit drug choice for CF patients. Table 1 shows a partial list of common concomitant drugs that were affected by LUM.

Table 1. Partial list of common concomitant medication recommendations for IVA and LUM/IVA

Concomitant drugs	IVA *	LUM/IVA
CYP3A4 substrates		
Hormonal contraceptives	No dose adjustment	Avoid concomitant use unless the benefit outweighs the risks.
Most antifungals • itraconazole • posaconazole • voriconazole	No dose adjustment	Concomitant use not recommended May use fluconazole
Antibiotics • clarithromycin • erythromycin	No dose adjustment	Consider alternatives, such as azithromycin, ciprofloxacin
Immunosuppressant • cyclosporine • tacrolimus	No dose adjustment	Concomitant use not recommended
Benzodiazepines • midazolam • triazolam	Use with caution	Concomitant use not recommended
CYP2C substrates Proton pump inhibitor • omeprazole • esomeprazole • lansoprazole	No dose adjustment	May reduce efficacy of PPI, may need higher dose of PPI

* *Based on approved KALYDECO (ivacaftor) label*

(Source: reviewer summary)

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 or BLA

Majority of the clinical pharmacology studies for IVA have been previously reviewed in NDA 203188 (Dr. Lokesh Jain, review dated 01/18/2012). The *in vitro* studies for LUM and its major metabolite M28-LUM using human biomaterials are listed Table 2. 18 clinical/clinical pharmacology studies were submitted to support this NDA (Table 3, Table 4).

Table 2: List of Relevant *In Vitro* Studies Using Human Biomaterials

Drug	ADME	Objective	Study/Report name
Lumacaftor (VX809, VRT-0826809)	Absorption	BCS Potential, P-gp Substrate, and Inhibitor Assessment of VX-809	DM-020
	Distribution	*In Vitro* Binding of VRT-0826809 to Plasma Proteins in Mouse, Rat, Dog, Monkey, and Human Plasma	D152
		In Vitro Protein Binding of [14C]-VX-809 to Mouse, Rat, Rabbit, Dog, and Human Plasma, HSA, AAG, and HGG, and Protein Binding Displacement Interactions Between VX-809 and Warfarin	DM021
	Metabolism	Metabolism in liver microsomes and hepatocytes of different species	D072
		Metabolism in human recombinant CYPs	D071
		Metabolism in liver microsomes and hepatocytes of different species	D083
	DDI potential	LUM as PXR activator-inducer potential	K027
		the Cytotoxicity of VX-809, and Induction Potential of VX-661 and VRT-0995096 (M28) on Cytochrome P450 3A4/5 in Human Hepatocyte Cultures	DM019
		Evaluation of VRT-0826809 as an Inducer of CYP3A4 Using Primary Cryopreserved Human Hepatocytes	J174
		Evaluation of VX-809 as an Inducer of CYP2C8, CYP2C9, and CYP2C19 Using Primary Cryopreserved Human Hepatocytes	K020
		LUM on mRNA levels of CYPs-inducer potential	K028
		Inhibitory Potential of VX-809 on Human Hepatic Microsomal Cytochromes P450	DM018
		LUM as OATP transporter substrate/inhibitor	K112
		Evaluation of Inhibitor Potential of VX-809 of Uptake Transporters	K111
M28-LUM (VRT-0995096)	Distribution	*In Vitro* Binding of VRT-0995096 to Plasma Proteins in Mouse, Rat, Dog, Monkey, and Human Plasma	G085
	Metabolism	Metabolism of in human recombinant CYPs	H060
	DDI potential	M28 as CYP inhibitor	G140

(Source – reviewer summary based on summary of clin pharm, Table 1)

Table 3. List of Clinical Pharmacology Studies

Study	Study Description
Studies in Healthy Subjects	
VX07-809-001	Single-dose and multiple-dose escalation study of lumacaftor
VX08-809-003	Bioavailability and food effect of a capsule formulation of lumacaftor relative to a suspension formulation of lumacaftor
VX08-809-004	Mass balance study to investigate the absorption, metabolism, and excretion of lumacaftor
VX08-809-005	DDI study of lumacaftor and ivacaftor
VX10-809-006	DDI study of lumacaftor and ivacaftor
VX12-809-007	Relative bioavailability of a High Drug Load lumacaftor formulation compared to a reference lumacaftor formulation (Part A); Relative bioavailability of lumacaftor and ivacaftor formulated as a fixed-dose combination tablet compared to lumacaftor and ivacaftor formulated as separate tablets (Part B)
VX12-809-008	Safety, tolerability, and PK following multiple ascending doses of lumacaftor (Part A); Electrocardiogram study to evaluate the effect of lumacaftor in combination with ivacaftor on the QT/QTc interval (Part B)
VX12-809-009	DDI study of the effect of ciprofloxacin, itraconazole, and rifampin on the PK of lumacaftor in combination with ivacaftor in healthy adult subjects
VX13-809-010	PK and safety of multiple doses of lumacaftor in combination with ivacaftor in subjects with moderate hepatic impairment and in matched healthy subjects
VX13-809-012	Effect of food on the relative bioavailability of 2 fixed-dose combinations of lumacaftor and ivacaftor tablet formulations
Studies in Subjects with CF[a,b]	
VX07-809-002	PK study of lumacaftor and effect of food in pancreatic-insufficient subjects
VX13-809-011 (Part A)	PK, safety, and tolerability of lumacaftor in combination with ivacaftor in subjects 6 through 11 years of age
VX08-809-101	Multiple dose study to evaluate safety, PK, and PD of lumacaftor
VX09-809-102	Multiple-dose study to evaluate the safety, tolerability, efficacy, PK, and PD of lumacaftor monotherapy, and lumacaftor and ivacaftor combination therapy

[a] Studies included subjects with CF who are homozygous (Studies 011, 101, and 102) and heterozygous (Study 102) for the *F508del-CFTR* mutation.
[b] As part of the secondary objectives, studies VX12-809-103 and VX12-809-104 also included PK evaluations in subjects with CF who are homozygous for the *F508del-CFTR* mutation.
(Source: Table 2, Summary of clin pharm)

Table 4. Overview of Clinical Development Program for LUM/IVA in homozygous F508del CF

Drug	Purpose	Study	n	Treatment	Endpoint
IVA	Safety/efficacy	770-104	140	IVA 150mg q12h Placebo	PPFEV1, exacerbation, Sweat chloride, weight, CFQR
LUM LUM/IVA	Dose ranging	809-102	312	LUM monotherapy for 4w+LUM/IVA for 4w Placebo	PPFEV1, exacerbation, Sweat chloride, BMI, CFQR
	Pivotal Efficacy and Safety	809-103 809-104	1108 (combined)	LUM 600mg qd/IVA 250mg q12h LUM 400/IVA 250mg q12h Placebo	PPFEV1, exacerbation, Sweat chloride, BMI, CFQR

(source: reviewer summary)

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

Lumacaftor (also known as VX-809) is an F508del-CFTR conformation stabilizer that acts by facilitating the cellular processing and trafficking of F508del-CFTR, thereby increasing the amount of functional CFTR protein at the cell surface. Ivacaftor (KALYDECO, also known as VX-770) is a selective potentiator of CFTR and has been approved "for the treatment of cystic fibrosis in patients age 6 years and older who have a G551D mutation in the CFTR gene" in the United States on January 31, 2012 under NDA203188. In 2013, it was approved for use in eight additional mutations (G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R). In 2014, it was approved for use in CF patients with R117H mutation. In 2015, KALEDECO granules was approved for use in pediatric patients 2-5 years of age.

LUM/IVA was studied under IND 079521 for the treatment of CF (IND opened Oct 2007). There have been several interactions between Agency and Sponsor to discuss the clinical pharmacology program of the proposed product. The key Clinical Pharmacology and Biopharmaceutics agreements were summarized in Table 5. LUM/IVA was granted orphan designation on June 30, 2012, and breakthrough designation on Dec 7, 2014. The NDA is reviewed under priority review timelines.

Table 5. Summary of Regulatory history relevant to clinical pharmacology

PNDA (Aug 2014)	• Agreed on general clinical pharm studies adequate to support NDA filing • General advice on pop PK and PK/PD analysis
Communication (June 2013)	• Agreed on the DDI plan, additional comment to sponsor: "CF patients are usually on many concomitant medicines. Address how these common concomitant medicines should be managed when used with lumacaftor/ivacaftor in the NDA submission"
EOP1/2 (Oct 2012)	• Agreed that 12-17 yr old can be included in phase 3 studies with the same dose as adults. • Agreed on the DDI plan • Agreed on the special population assessment plan, that a moderate hepatic impairment study is reasonable, and a renal impairment study is not necessary • Discussed about dose/supra-dose selection in QT study

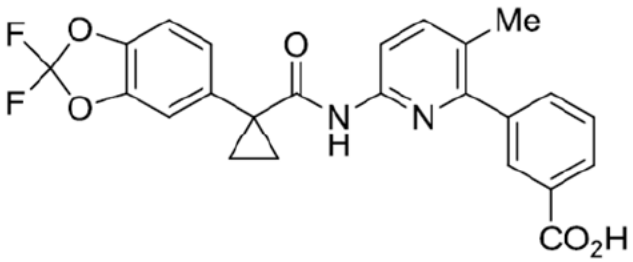
(source: reviewer summary)

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?

Lumacaftor is a small molecule drug. Its structure is shown in Figure 5 and its physicochemical properties are listed in Table 6.

Lumacaftor



Ivacaftor

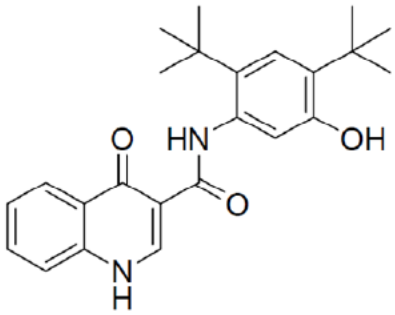


Figure 5. Molecular structure of lumacaftor and ivacaftor

Table 6: Lumacaftor physical chemical properties

Molecular Formula	$C_{24}H_{18}F_2N_2O_5$
Molecular Weight	452.41 g/mol
Physical State	Lumacaftor drug substance is a white to off-white (b) (4) solid.
Physical form	Lumacaftor drug substance manufactured by the commercial process is (b) (4)
BCS class	BCS class 2
Dissociation Constants	The pKa values of lumacaftor are (b) (4)
Solubility	practically insoluble in water (b) (4)
Partition Coefficient	The log D value of lumacaftor is (b) (4)

The drug product LUM/IVA FDC tablet (200/125 mg) contains 200 mg of lumacaftor and 125 mg of ivacaftor and has a (b) (4). It is pink film-coated tablet, printed in black ink with "2V125" on one face.

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

Lumacaftor is a CFTR protein stabilizer and ivacaftor is a CFTR potentiator. Lumacaftor is a stabilizer of F508del-CFTR that works by facilitating the cellular processing and trafficking of F508del-CFTR to increase the amount of F508del-CFTR protein at the cell surface. The channel gating activity of F508del-CFTR that has been delivered to the cell surface by LUM can be potentiated by IVA to further enhance chloride transport. The combination of a CFTR stabilizer and potentiator is a novel approach to enhance the amount and function of the defective CFTR protein in patients with CF who have the F508del-CFTR mutation.

The proposed indication is "treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene."

2.2.2.1 Based on available data/analysis, does lumacaftor contribute to the efficacy of LUM/IVA?

In vitro data suggested that lumacaftor is required to increase delivery of F508del-CFTR to cell surface, and ivacaftor can only potentiate F508del-CFTR on the cell surface. See nonclinical review by Dr. Andrew Goodwin for detailed information.

In dose ranging study 809-102, a dose response was observed for better sweat chloride improvement with increased LUM dose in LUM/IVA combination arms. However this data should be viewed with caution because as stated in the FDA briefing package, "it is not known, how and by what amount reductions in sweat chloride relate to clinical beneficial effects. However, as a generally accepted marker of the CFTR ion channel activity, a lack or low response in sweat chloride to an intervention would suggest a subsequent lack or decreased clinical benefit."

In LUM/IVA phase 3 studies, LUM/IVA 400/250mg BID had an effect size of 2.6-3.0% in PPFEV1, with similar exacerbation benefit as monotherapy (hazard ratio 0.6-0.7), making the contribution of LUM unclear. In this review, we have demonstrated that the ivacaftor exposure in the LUM/IVA combination (400/250 mg BID) is less than 20% of the ivacaftor exposure in study 770-104 (Figure 3). Based on exploratory E-R analysis for ivacaftor monotherapy study 770-104, Ivacaftor alone would not account for the efficacy observed in study 809-103 and 809-104 at the concentrations observed in phase 3 studies. This suggested a likely contribution of lumacaftor (See section 3 of pharmacometrics review, appendix 4.1). One possible hypothesis could be that lumacaftor reduces the EC50 for ivacaftor, as indicated by some *in vitro* data. Thus even at low exposures of ivacaftor in combination therapy, a response similar to the ivacaftor monotherapy is observed. . The hypothesis that lumacaftor reduces the ivacaftor EC50 should be viewed in context that the overall efficacy in combination therapy was similar to the efficacy that was observed in ivacaftor monotherapy study. Thus from a net effect perspective, the contribution of lumacaftor remains unclear because similar response could have been achieved with ivacaftor monotherapy; although at higher ivacaftor exposures. Based on the current ivacaftor label, the safety profile at these high exposures is acceptable.

2.2.3 What are the proposed dosages and routes of administration?

The proposed dose is two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours (lumacaftor 800 mg/ivacaftor 500 mg total daily dose) with fat containing food.

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

Currently there are no drugs approved to treat the underlying defect in F508del CFTR protein for cystic fibrosis (CF) patients who are homozygous for the F508del mutation in the CFTR gene. The currently approved treatments act by managing the downstream consequences of diminished CFTR function, such as controlling airway infection and inflammation, mobilizing secretions to reduce airway obstruction, and correcting nutritional deficits caused by pancreatic insufficiency. Examples of therapies used by CF

patients are listed in Table 7.

Table 7. Approved therapies for CF patients with homozygous F508del mutation

Therapy	Rationale for Use in Cystic Fibrosis	Examples
Inhaled DNase	Recombinant human deoxyribonuclease I to reduce lung mucus viscosity	dornase alfa
Chronic inhaled antibiotics	Antibiotics for the treatment of *P aeruginosa*	tobramycin, aztreonam
Pancreatic enzymes	Enzyme therapy (lipase, protease, and amylase) to aid hydrolysis of fats, starch, and protein	pancrease

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?

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?

The major endpoints are PPFEV1, exacerbation, and BMI. These endpoints are consistent with the endpoints in the previous ivacaftor submission. Sweat chloride was assessed in phase 2 studies 101 and 102, but not in phase 3 studies.

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?

Lumacaftor and its major metabolite M28-LUM; Ivacaftor and two major metabolites (M1-IVA and M6-IVA) were appropriately measured. Please refer to section 2.9 for more details.

2.4 Exposure-Response

2.4.1 Does this drug prolong QT/QTc Interval?

The effect of multiple doses of lumacaftor 600 mg once daily/ivacaftor 250 mg q12h and lumacaftor 1000 mg once daily/ivacaftor 450 mg q12h on QTc interval was evaluated in a randomized, placebo- and active controlled (400 mg moxifloxacin), parallel, thorough QT study in 168 healthy subjects. No meaningful changes in QTc interval were observed with either lumacaftor 600 mg once daily/ivacaftor 250 mg q12h and lumacaftor 1000 mg once daily/ivacaftor 450 mg q12h dose groups.

2.4.2 Based on the dose/exposure-response relationship, is the proposed dose and dosing regimen for the fixed dose combination (FDC) product of Lumacaftor/Ivacaftor (400 mg Lumcaftor/ 250 mg Ivacaftor BID) acceptable?

Yes, the proposed dose and dosing regimen in patients is acceptable, if the treatment effects (benefit/risk) are clinically acceptable. The basis for dose/dosing regimen selection and findings from phase 2 and phase 3 trials is discussed below.

Dose-Response for Efficacy:
Lumacaftor: In a phase 2 study (study 102), a range of lumacaftor doses/regimens (200 mg QD, 400 mg QD, 600 mg QD, 400 mg BID) were administered in combination with 250 mg BID of Ivacaftor. The lumacaftor 600 mg QD/ ivacaftor 250 mg BID regimen demonstrated a significant improvement in FEV1 from baseline (Table 8). The lumacaftor 400mg BID/ivacaftor 250 mg BID arm also demonstrated significant improvement in FEV1 and the response was similar to the lumacaftor 600 mg QD/ ivacaftor 250 mg BID arm. The study design does not allow for a robust assessment of dose-response of lumacaftor in combination setting because the combination therapy was preceded by lumacaftor monotherapy where a dose-dependent decline in FEV1 was observed. This resulted in various dosing groups in combination setting with different FEV1 at the start of therapy.
In the phase 3 studies, there was no clear differentiation between the two regimens (lumacaftor 600 mg QD/ ivacaftor 250 mg and lumacaftor 400 mg BID/ ivacaftor 250 mg) in terms of percent predicted FEV1 as observed from data from studies 103, 104 and 105 (Figure 6 and Figure 7). In terms of pulmonary exacerbation through week 24, there appears to be a trend for improved response in the lumacaftor 400 mg BID/ ivacaftor 250 mg arm compared to the lumacaftor 600 mg QD/ ivacaftor 250 mg arm as shown in Figure 8.
Thus from an efficacy perspective similar efficacy in terms of FEV1 and pulmonary exacerbation for the lumacaftor 400 mg BID regimen compared to lumacaftor 600 mg QD regimen, the sponsor's proposed regimen for lumacaftor (400 mg BID) in the FDC appears reasonable. This is conditional on whether the clinical team assesses the efficacy to be clinically meaningful. Additionally the 400 mg BID regimen is advantageous in terms of simplifying the dosing regimen that might increase patient compliance.

Ivacaftor: A range of doses for ivacaftor in combination therapy was not studied, thus it is unclear if the selected ivacaftor dose (250 mg BID) is optimal from an efficacy perspective. The dose, however, would be acceptable if the efficacy achieved in the phase 3 trials is deemed to be clinically meaningful.
Although the proposed dose is higher than the currently approved dose of 150 mg BID in cystic fibrosis patients with G551D mutation who are treated with ivacaftor alone, the ivacaftor exposures at the 250 mg BID dose in combination with lumacaftor is expected to be much lower compared to exposures in a monotherapy setting due to drug-drug interaction (Figure 9). Exposure-response relationship in monotherapy setting suggested a trend for increase in FEV1 with increasing steady state concentration of ivacaftor. (see Pharmacometrics review for details).

Dose-Response for Safety:
Lumacaftor: The phase 2 study is limited in terms of short duration and small sample size to draw any meaningful conclusions regarding safety at various lumacaftor dose levels. In the phase 3 study, no meaningful difference is observed in adverse events between the

treatment arms except for nasopharyngytis which was slightly higher in the lumacaftor 400 mg BID arm versus lumacaftor 600 mg QD arm (13% versus 6.2%) as shown in Table 9. No meaningful difference were observed in grade 3 or grade 4 events between the treatment arms. In general the clinical team has concluded that the safety profile of the 400 mg BID lumacaftor/250 mg BID ivacaftor arm is acceptable (for details please see Clinical Review).

With respect to ivacaftor, the exposures at the 250 mg BID dose in combination with lumacaftor is much lower compared to exposures that were achieved in monotherapy setting in previously conducted trials in cystic fibrosis patients with G551D mutation or F508del mutation (Figure 9) where the safety profile for ivacaftor was deemed acceptable (for details see Dr. Durmowicz review in DARRTs dated 01/27/2012)

Table 8: Absolute change in Percent Predicted from FEV1 in Phase 2 study (study 102)

Absolute Change in Percent Predicted FEV_1 by ANCOVA, Full Analysis Set (Cohort 2 and Cohort 3 Pooled)

Treatment[a]	Absolute Change[b] LS Mean	*P* Value	Treatment Difference (vs. Placebo)[c] Difference (95% CI)	*P* Value
Absolute change from Day 28 at Day 56				
Combination Placebo (Pooled)	-1.57	0.244	NA	NA
200 mg LUM qd + 250 mg IVA q12h	1.96	0.169	3.53 (-0.32, 7.38)	0.072
400 mg LUM qd + 250 mg IVA q12h	1.99	0.171	3.56 (-0.35, 7.47)	0.074
600 mg LUM qd + 250 mg IVA q12h	6.15	<0.001	7.72 (3.75, 11.70)	<0.001
600 mg LUM qd + 250 mg IVA q12h (Heterozygotes)	2.29	0.147	3.86 (-0.27, 7.99)	0.067
400 mg LUM q12h + 250 mg IVA q12h	6.09	0.004	7.66 (2.74, 12.59)	0.003
Absolute change from Baseline at Day 28				
Monotherapy Placebo (Pooled)	-0.03	0.985	NA	NA
200 mg LUM qd	0.21	0.889	0.24 (-3.72, 4.20)	0.906
400 mg LUM qd	-1.35	0.380	-1.32 (-5.35, 2.70)	0.515
600 mg LUM qd	-2.62	0.090	-2.60 (-6.67, 1.47)	0.209
600 mg LUM qd (Heterozygotes)	-3.82	0.020	-3.79 (-7.99, 0.41)	0.076
400 mg LUM q12h	-4.52	0.032	-4.50 (-9.46, 0.47)	0.076
Absolute change from Baseline at Day 56				
Combination Placebo (Pooled)	-2.02	0.178	NA	NA
200 mg LUM qd + 250 mg IVA q12h	1.82	0.248	3.84 (-0.42, 8.09)	0.077
400 mg LUM qd + 250 mg IVA q12h	0.64	0.688	2.66 (-1.66, 6.99)	0.225
600 mg LUM qd + 250 mg IVA q12h	3.59	0.027	5.61 (1.21, 10.01)	0.013
600 mg LUM qd + 250 mg IVA q12h (Heterozygotes)	-1.68	0.334	0.34 (-4.23, 4.91)	0.884
400 mg LUM q12h + 250 mg IVA q12h	2.16	0.344	4.18 (-1.27, 9.63)	0.131

ANCOVA: analysis of covariance; CI: confidence interval; IVA: ivacaftor; LS: least squares; LUM: lumacaftor; NA: not applicable; q12h: every 12 hours; qd: once daily; vs: versus

Baseline: Baseline was defined as the last measurement before initial dosing of study drug.

[a] Homozygous and heterozygous subjects who received placebo (monotherapy or combination) in Cohort 2 and Cohort 3 were pooled. For all other treatment groups, values for homozygous subjects are shown unless otherwise indicated.

[b] Change is estimated by the LS mean change from baseline (or Day 28), obtained from the ANCOVA model: Change = Treatment + Baseline (or Day 28) + Baseline Age.

[c] Difference between treatments for the LS mean change from baseline (or Day 28), obtained from the ANCOVA model.

Source: Synopsis of study 102 CSR

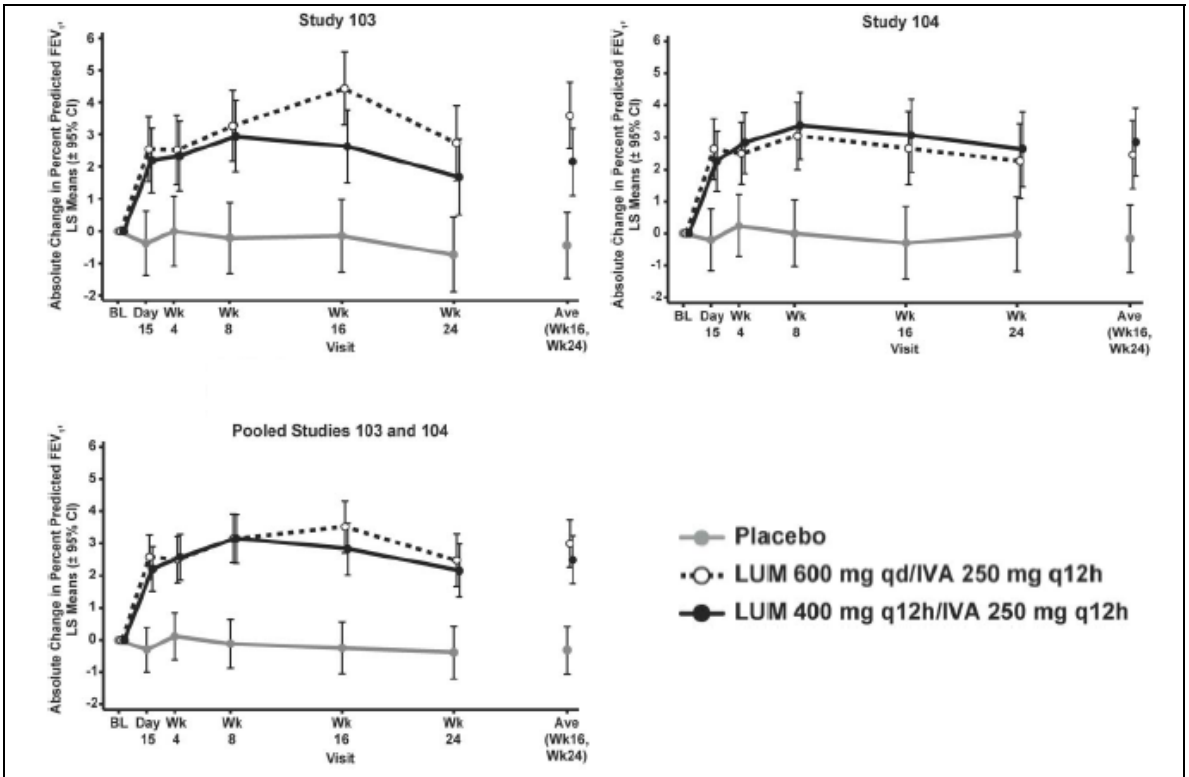


Figure 6: Absolute change in percent predicted FEV1 by visit in study 103, study 104 and pooled studies 103 and 104 (Phase 3)
Source: Figure 2 of the Summary of Efficacy

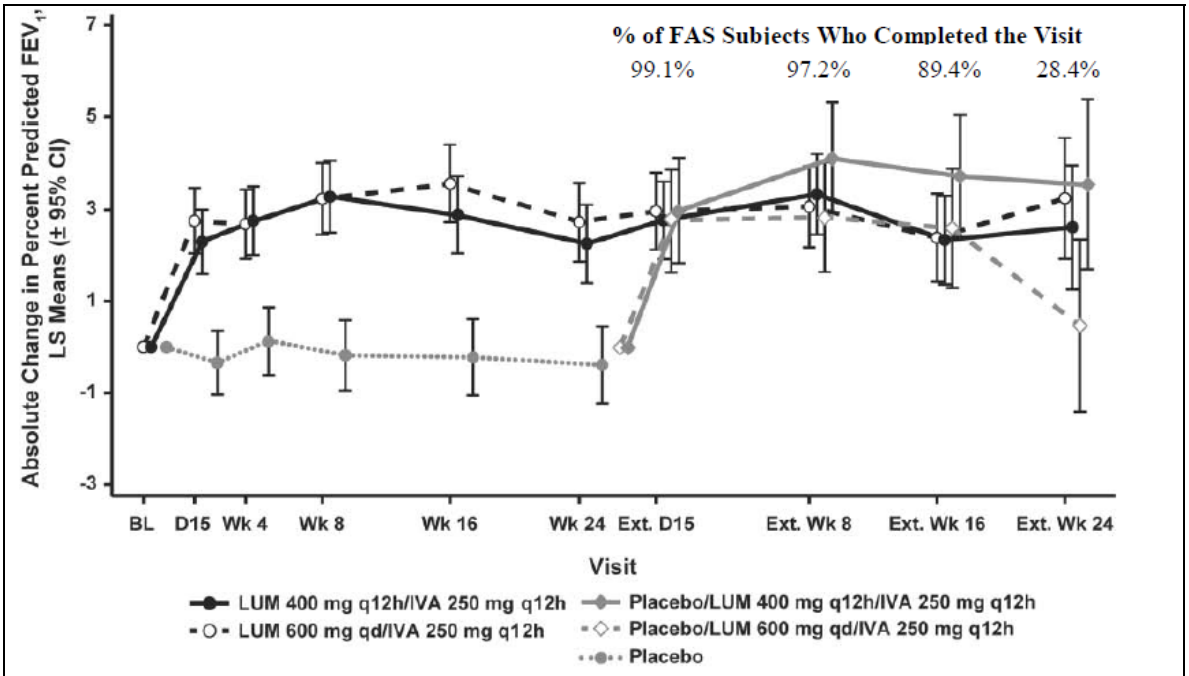


Figure 7: Absolute change in percent predicted FEV1 by visit in study 105 (Uncontrolled rollover study)
Source: Figure 9 of the Summary of Efficacy

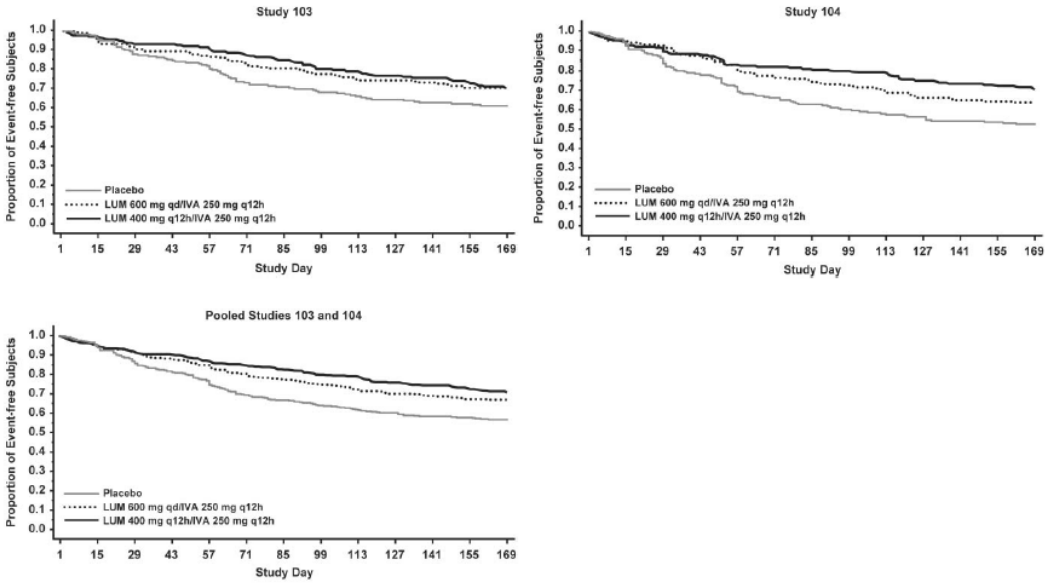


Figure 8: Pulmonary Exacerbation through Week 24.
Source: Figure 4 of the Summary of Efficacy

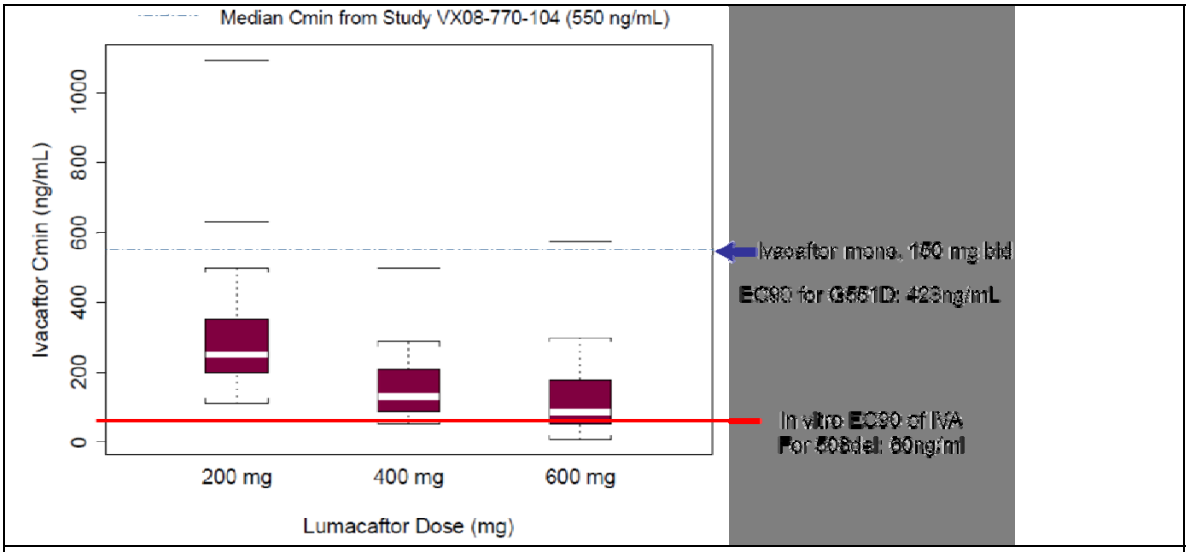


Figure 9: Ivacaftor exposures with increased lumacaftor exposures in study 102
Source: Figure 13 of Sponsor's End-of-Phase 1 briefing package

Table 9: Summary of Adverse Event by Treatment Groups in Pooled Placebo Controlled Phase 3 studies (study 103 and study 104)

Preferred Term	Placebo N = 370 n (%)	LUM/IVA LUM 600 mg qd/ IVA 250 mg q12h N = 369 n (%)	LUM/IVA LUM 400 mg q12h/ IVA 250 mg q12h N = 369 n (%)	LUM/IVA Total LUM/IVA N = 738 n (%)
Subjects with any AEs	**355 (95.9)**	**356 (96.5)**	**351 (95.1)**	**707 (95.8)**
Infective pulmonary exacerbation of cystic fibrosis	182 (49.2)	145 (39.3)	132 (35.8)	277 (37.5)
Cough	148 (40.0)	121 (32.8)	104 (28.2)	225 (30.5)
Headache	58 (15.7)	58 (15.7)	58 (15.7)	116 (15.7)
Sputum increased	70 (18.9)	55 (14.9)	54 (14.6)	109 (14.8)
Dyspnoea	29 (7.8)	55 (14.9)	48 (13.0)	103 (14.0)
Haemoptysis	50 (13.5)	52 (14.1)	50 (13.6)	102 (13.8)
Diarrhoea	31 (8.4)	36 (9.8)	45 (12.2)	81 (11.0)
Nausea	28 (7.6)	29 (7.9)	46 (12.5)	75 (10.2)
Respiration abnormal	22 (5.9)	40 (10.8)	32 (8.7)	72 (9.8)
Nasopharyngitis	40 (10.8)	23 (6.2)	48 (13.0)	71 (9.6)
Oropharyngeal pain	30 (8.1)	44 (11.9)	24 (6.5)	68 (9.2)
Pyrexia	34 (9.2)	35 (9.5)	33 (8.9)	68 (9.2)
Fatigue	29 (7.8)	30 (8.1)	34 (9.2)	64 (8.7)
Upper respiratory tract infection	20 (5.4)	24 (6.5)	37 (10.0)	61 (8.3)
Abdominal pain	32 (8.6)	26 (7.0)	33 (8.9)	59 (8.0)
Nasal congestion	44 (11.9)	33 (8.9)	24 (6.5)	57 (7.7)
Viral upper respiratory tract infection	25 (6.8)	28 (7.6)	23 (6.2)	51 (6.9)
Rhinitis	18 (4.9)	30 (8.1)	16 (4.3)	46 (6.2)
Flatulence	11 (3.0)	20 (5.4)	24 (6.5)	44 (6.0)
Blood creatine phosphokinase increased	20 (5.4)	14 (3.8)	27 (7.3)	41 (5.6)
Rash	7 (1.9)	16 (4.3)	25 (6.8)	41 (5.6)
Sinusitis	19 (5.1)	24 (6.5)	16 (4.3)	40 (5.4)
Rhinorrhoea	15 (4.1)	17 (4.6)	21 (5.7)	38 (5.1)
Vomiting	11 (3.0)	21 (5.7)	16 (4.3)	37 (5.0)
Influenza	8 (2.2)	16 (4.3)	19 (5.1)	35 (4.7)
Abdominal pain upper	18 (4.9)	22 (6.0)	12 (3.3)	34 (4.6)
Constipation	21 (5.7)	12 (3.3)	14 (3.8)	26 (3.5)
Pulmonary function test decreased	20 (5.4)	9 (2.4)	3 (0.8)	12 (1.6)

Source: Module 5.3.5.3/VX-809 ISS/Table 2.2.2.4.
AE: adverse event; IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours; qd: daily.
Note: A subject with multiple events within a preferred term category were counted only once in that category.

Source: Table 17 of Summary of Clinical Safety

2.4.3 Is the proposed dose and dosing regimen for the fixed dose combination (FDC) product of Lumacaftor/Ivacaftor (400 mg Lumcaftor/ 250 mg Ivacaftor BID) acceptable for pediatrics of ages 12 to 17 years?

Yes, the proposed dose is reasonable from a clinical pharmacology perspective as the exposures achieved in pediatrics of ages 12-17 years is similar to adults. In the phase 3 trials (study 103 and 104), pediatric patients accounted for 26% of the patients enrolled in each arm (Table 10). The observed trough concentrations achieved in the phase 3 trials in pediatrics and adults were similar (Figure 10 and Table 11). Additionally the efficacy in

pediatric were similar to adults (data not shown). There was slightly higher incidence of headaches and abdominal pain in pediatrics compared to adults while other adverse events were generally comparable between the two groups (data not shown). Please see the clinical review for the assessment of the efficacy and safety in pediatrics patients compared to adults.

Table 10: Number of Subjects by Age Category in Pooled Placebo Controlled Phase 3 studies (study 103 and study 104)

Age Groups (years)	Number (%) of subjects in each group		
	Placebo N = 371	Lumacaftor 600 mg QD/ Ivacaftor 250 mg BID N = 368	Lumacaftor 400 mg BID/ Ivacaftor 250 mg BID N=369
12 to < 18	96 (25.9%)	96 (26.1%)	98 (26.6%)
≥ 18	275 (74.1%)	272 (73.9%)	271 (73.4%)

Source: Table 12 in Summary of Clinical Efficacy

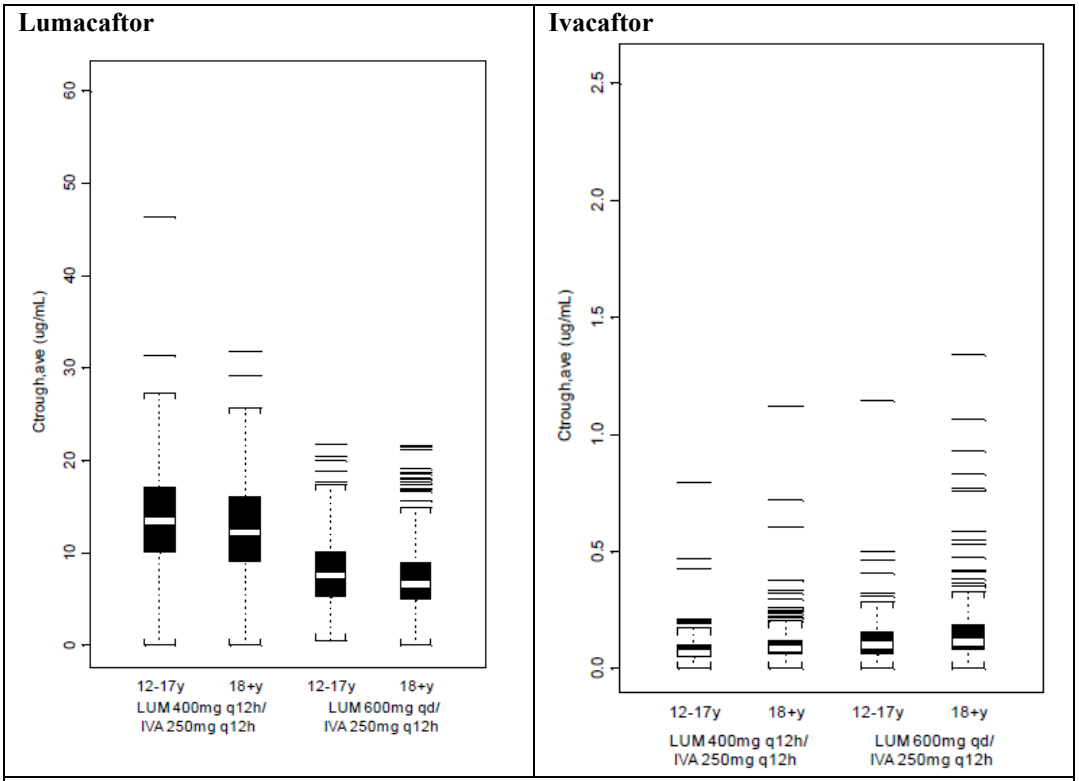


Figure 10: Lumacaftor and Ivacaftor Ctrough by Age Group
Source: Figure 9-9 and 9-10 of sponsor's pharmacokinetic study report (report # k272)

Table 11: Lumacaftor and Ivacaftor Ctrough by Age Group (study 103 and study 104)

Age Groups (years)	Median Ctrough (ug/ml)			
	Lumacaftor 600 mg QD/ Ivacaftor 250 mg BID		Lumacaftor 400 mg BID/ Ivacaftor 250 mg BID	
	LUM Ctrough (ug/ml)	IVA Ctrough (ug/ml)	LUM Ctrough (ug/ml)	IVA Ctrough (ug/ml)
12 to < 18	7.54	0.102	13.4	0.069
≥ 18	6.62	0.114	12.2	0.086
Source: Reviewer's Analysis				

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 and CF patients?

Single dose PK in healthy adults

The PK profile of lumacaftor has been investigated in healthy subjects following single oral dosing in 5 studies (Studies 001, 003, 004, 007, and 012).

PK for single dose ranging from 25 to 400 mg was characterized in study 001 following administration of a lumacaftor aqueous suspension formulation. The plasma concentration-time profiles for these dose levels are shown in Figure 11. After a single oral administration under fasting conditions in healthy male subjects, VX-809 was slowly absorbed with a median time to peak concentration in plasma of approximately 3 hours. Lumacaftor appears to follow bi-exponential disposition kinetics in healthy volunteers. The PK parameter estimates suggested a relatively low clearance of VX-809 (1.1 to 1.5 L/hr), limited distribution within the body (mean apparent volume of distribution of 37 to 54 L), and a rather long terminal half-life (23 to 28 hours) over the 25- to 400-mg dose range tested. The slopes of the terminal phase on log scale are similar across dose range of 25-400 mg, indicating linear elimination kinetics. PK parameters after single dose of lumacaftor under fast conditions are summarized in Table 12.

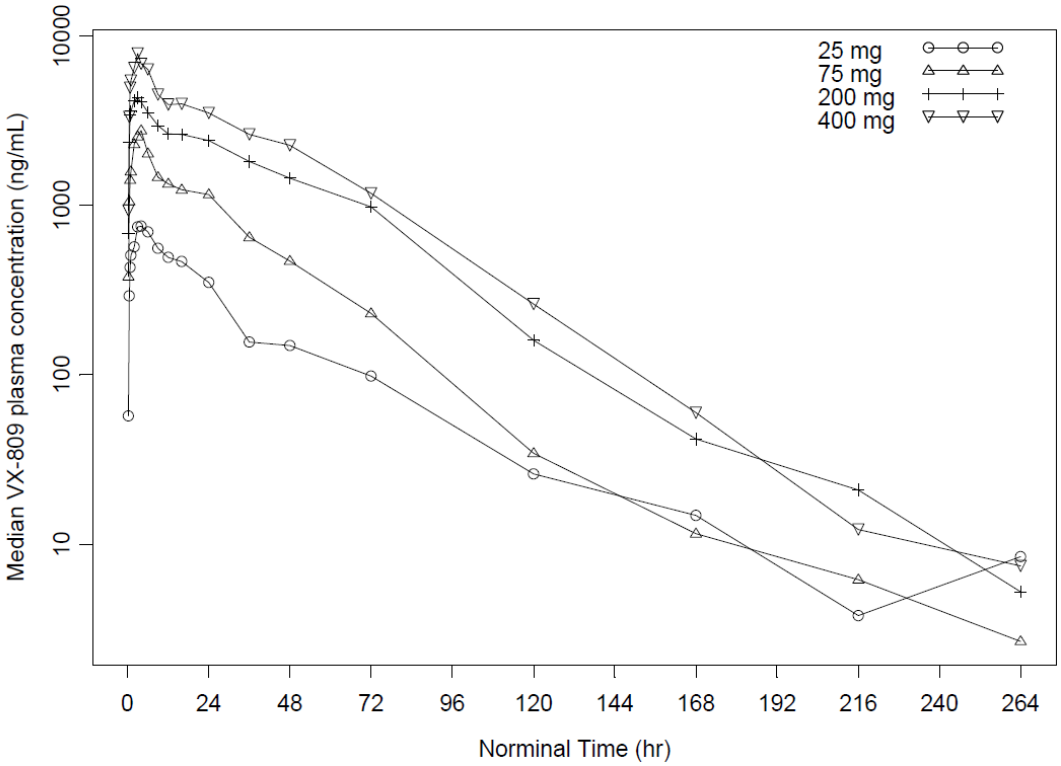


Figure 11. Median VX-809 Concentration (ng/mL) Versus Nominal Time (hours), Part A (Healthy Male Subjects)
(Source – Figure 11-2, Study 809-001 report)

Table 12. Summary of Selected LUM Pharmacokinetic Parameters following a Single dose of LUM suspension, mean (CV%)

Gender	Dose (mg)	N	Tmax* (h)	Cmax (ng/mL)	AUCinf (ng.h/mL)	T1/2 (h)
Male	25	5	4.0 (3.0, 6.1)	886.4 (23.8%)	24606 (35.5%)	28.3 (47.4%)
	75	12	4.0 (2.0, 4.1)	2942.5 (28.5%)	76199 (37.8%)	24.4 (26.8%)
	200	11	3.0 (1.0, 6.0)	4930.0 (26.4%)	185001 (34.3%)	24.7 (33.8%)
	400	11	4.0 (0.75, 4.1)	8332.7 (38.8%)	286789 (31.3%)	25.0 (34.8%)
Female	75	6	3.5 (2.0, 4.0)	3505.0 (25.5%)	85929 (15.3%)	29.5 (13.3%)
	200	5	2.0 (0.3, 6.0)	8060.0 (19.6%)	243986 (33.9%)	29.8 (11.9%)
	400	4	2.5 (2.0, 3.0)	10785 (25.1%)	376565 (18.9%)	25.5 (5.0%)

*median (range)
(Source: Table 11-1, Table 11-2, study 809-001 report)

Multiple doses PK in healthy volunteers

Selected PK parameters following administration of multiple doses in healthy volunteers

are summarized in Table 13. Across studies for doses ranging from 50 mg q24h to 1000 mg q24h, the lumacaftor exposure increases approximately proportional with the dose. The steady-state was reached by day 7 and accumulation ratio was approximately 1.9 with twice daily dosing ($AUC\tau_{\_day10}/AUC_{last\_day1}$, study 809-010). The mean terminal half-life was approximately similar after a single-dose and at steady-state, i.e., 20-26 hours.

Table 13. Selected Multiple-dose Lumacaftor PK Parameters in Healthy Subjects

				Median (min, max)	Arithmetic Mean (SD)		
Study	**Dose and Duration**	**Type of Subjects**	**N**	**t_{max} (h)**	**C_{max} (µg/mL)**	**AUC_{τ} (µg·h/mL)**	**$t_{1/2}$ (h)**
Study 005	LUM 200 mg q24h, 14 days	HS	18	4.00 (0.00, 8.00)	12.7 (4.52)	202 (94.0)	22.5 (4.6)
Study 006	LUM 200 mg qd, 14 days	HS	18	6.00 (4.00, 10.0)	17.2 (5.13)	242 (75.2)	26.4 (8.07)
	LUM 400 mg qd, 14 days	HS	17	6.00 (4.00, 10.0)	27.9 (8.90)	435 (139)	27.3 (10.2)
Study 008 (Part A)	LUM 600 mg qd, 7 days	HS	8	4.00 (3.00, 8.00)	35.6 (12.6)	497 (132)	21.0 (5.96)
	LUM 1000 mg qd, 7 days	HS	8	3.50 (2.00, 4.07)	60.4 (10.5)	798 (209)	20.8 (4.73)[a]
	LUM 1200 mg qd, 7 days	HS	8	4.00 (3.00, 6.00)	59.2 (14.2)	708 (179)	20.6 (3.34)
Study 008 (Part B)	LUM 600 mg qd/ IVA 250 mg q12h, 7 days	HS	50	4.00 (0.52, 6.00)	35.9 (9.69)	525 (157)	NR
	LUM 1000 mg qd/ IVA 450 mg q12h, 7 days	HS	36	4.00 (2.00, 4.00)	41.1 (10.9)	566 (154)	NR
Study 009 (Cohort 1)	LUM 200 mg q12h/ IVA 250 mg q12h, 14 days	HS	17	3.00 (0.00, 6.00)	23.3 (6.17)	228 (61.3)	NR
Study 009 (Cohort 2)	LUM 200 mg q12h/ IVA 250 mg q12h, 14 days	HS	18	3.02 (0.00, 6.00)	23.3 (9.87)	216 (99.5)	NR
Study 009 (Cohort 3)	LUM 200 mg q12h/ IVA 250 mg q12h, 14 days	HS	18	3.01 (2.00, 9.13)	24.1 (5.17)	230 (50.1)	NR
Study 010	LUM 200 mg q12h/ IVA 250 mg q12h, 10 days	HS	11	2.00 (0.00, 6.00)	18.0 (6.32)	153 (56.8)	25.20 (9.94)

(Source: Table 23, summary of clin pharm)

The nominal dosage of ivacaftor at 250 mg q12h in combination with lumacaftor, is increased in comparison with the dose approved for ivacaftor monotherapy (Kalydeco) of 150 mg q12h. Due to the induction of CYP3A by lumacaftor, the overall level of

ivacaftor exposure is considerably lower than the ivacaftor exposure when given in the absence of lumacaftor at a dose of 150 mg q12h (Table 19) .

Single dose PK of ivacaftor (CF subjects)

Based on non-compartmental analysis, PK for single 200 mg dose of lumacaftor administered as 50-mg capsules in fast and fed state (study 002 and 003) was similar between healthy subjects and subjects with CF (Table 14).

Table 14. Single-dose Lumacaftor PK Parameters in Healthy Subjects and Subjects With Cystic Fibrosis

Subjects	Food Status	t_{max} (h)[b]	C_{max} (µg/mL)[a]	$AUC_{0-\infty}$ (µg·h/mL)[a]	$t_{1/2}$ (h)[a]	CL/F (L/h)[a]	V_z/F (L)[a]
CF N = 7 (Study 002)	Fasted	4.00 (3.00, 6.00)	9.88 (1.08)	189 (77.1)	23.4 (11.7)	1.19 (0.380)	35.7 (12.6)
	Fed	6.10 (3.00, 9.10)	7.82 (1.97)	217 (83.7)	23.4 (11.3)	1.05 (0.400)	33.3 (17.9)
HS N = 18 (Study 003)	Fasted	4.00 (3.00, 6.00)	6.97 (2.48)	208 (79.0)	25.6 (6.4)	1.11 (0.46)	38.4 (12.6)
	Fed	6.00 (4.00, 9.10)	9.09 (2.61)	240 (84.4)	25.7 (6.7)	0.93 (0.31)	32.5 (7.4)

[a] C_{max}, $AUC_{0-\infty}$, CL/F, V_z/F, and $t_{1/2}$ data are presented as mean (standard deviation).
[b] t_{max} data are presented as median (range).
(Source: Table 22, summary of clin pharm)

Multiple doses PK in CF

Overall, the lumacaftor Cmax and AUC increased proportionally over the LUM 25 mg qd to 400 mg q12h dose range in subjects with CF. The median plasma Tmax for lumacaftor ranged from 3 to 4 hours, and the mean plasma lumacaftor terminal t1/2 ranged from 19.0 to 41.5 hours across the tested dose range. From the assessment of predose plasma concentrations of lumacaftor measured on Days 7, 14, 21, and 28, steady state was reached after 7 days of treatment. Based on AUC, the average accumulation ratio (AUC0-24h Day 28/AUC0-24h Day 1) of lumacaftor in plasma ranged from 1.7 to 2.0. While the $t_{1/2}$ and accumulation findings are consistent with the data observed in healthy subjects, the median steady-state AUCss in Studies 101 and 102 in subjects with CF were approximately 2-fold lower than that of Study 005 in healthy subjects when comparing the same dose (200 mg qd). The lower exposure of lumacaftor in CF patients was also observed in other multiple dose studies (Table 16). Table 15 provides selected multiple-dose lumacaftor PK parameters evaluated in Study 101 and 102.

The PK of M28-lumacaftor was also assessed in Studies 101 and 102. The mean AUC and Cmax of M28-lumacaftor increased less than dose proportionally over the lumacaftor dose range of LUM 25 to 800 mg total daily dose. The metabolite to parent drug ratio (M28-lumacaftor/lumacaftor) based on AUC at steady state decreased from 33% at a LUM 25 mg/day dose to 8% at a LUM 800 mg/day dose after 28 days of lumacaftor treatment. This decrease in metabolic ratio observed with increasing lumacaftor dose was related to the dose proportional increase in lumacaftor concentrations versus the less than dose proportional increase in M28-lumacaftor concentrations over the studied dose range.

Table 15. Selected Multiple-dose Lumacaftor PK Parameters in Subjects With Cystic Fibrosis

Study	Dose and Duration	Diagnosis of Subjects[a]	N	Median (min, max) t_{max} (h)	Mean (SD) C_{max} (µg/mL)	Mean (SD) AUC_{0-24h} (µg·h/mL)[b]	Mean (SD) $t_{1/2}$ (h)
Study 101	LUM 25 mg qd, 28 days	CF	17	4.00 (2.90, 12.00)	1.10 (0.443)	12.9 (4.92)	41.5 (73.6)[c]
	LUM 50 mg qd, 28 days	CF	17	3.10 (0.80, 9.00)	2.64 (0.986)	28.7 (13.0)	20.1 (8.81)
	LUM 100 mg qd, 28 days	CF	16	3.10 (1.50, 6.00)	4.62 (1.84)	54.1 (31.6)	19.0 (7.74)
	LUM 200 mg qd, 28 days	CF	18	3.00 (1.50, 6.10)	10.3 (4.58)	119 (73.8)	27.2 (18.1)
Study 102	LUM 200 mg qd monotherapy, 28 days	CF	21	3.10 (1.00, 4.10)	13.3 (3.04)	132 (34.4)	-- --
	LUM 200 mg qd/ IVA 250 mg q12h combination therapy, 28 days	CF	18	3.05 (1.00, 6.30)	11.4 (2.31)	122 (48.1)	-- --
	LUM 400 mg qd monotherapy, 28 days	CF	20	3.00 (1.00, 6.00)	22.0 (7.37)	226 (86.5)[d]	-- --
	LUM 400 mg qd/ IVA 250 mg q12h combination therapy, 28 days	CF	20	2.55 (2.00, 6.10)	21.1 (5.17)	219 (79.4)	-- --
	LUM 600 mg qd monotherapy, 28 days	CF	20	3.10 (2.00, 9.10)	32.1 (8.98)	309 (152)[d]	-- --
	LUM 600 mg qd/ IVA 250 mg q12h combination therapy, 28 days	CF	20	4.00 (1.00, 8.50)	27.7 (7.51)	290 (127)	-- --
	LUM 400 mg q12h monotherapy, 28 days	CF	11	3.00 (1.00, 6.20)	23.7 (6.19)	331 (93.4)	-- --
	LUM 400 mg q12h/ IVA 250 mg q12h combination therapy, 28 days	CF	10	3.10 (1.00, 4.00)	24.2 (6.99)	371 (135)	-- --
	LUM 400 mg q12h/ IVA 250 mg q12h combination therapy, 28 days	CF[e]	56	2.15 (0.00, 12.00)	25.0 (7.96)	396 (130)	-- --

e. Data shown is for CF subjects who are heterozygous for the *F508del-CFTR* mutation; All other CF subjects are homozygous for F508del-CFTR mutation.
(source: Table 24, summary of clin pharm)

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

The pharmacokinetic characteristics of lumacaftor were consistent between healthy volunteers and CF patients after single dose of LUM (Table 14). At steady state, dose normalized LUM exposure was 60% higher in healthy subjects than subjects with CF (0.875 vs 0.55, Table 16), and IVA exposure was similar in healthy subjects and CF subjects.

Table 16: Exposure of LUM/IVA in healthy and CF patients at steady state

Study	Subjects	Treatment	LUM AUC* (µg.h/mL)	IVA AUC* (µg.h/mL)	Normalized LUM AUC* (µg.h/mL/mg)	Normalized IVA AUC** (ng.h/mL/mg)
008	Healthy	LUM 600qd/IVA 250 mg q12h	525	3.58	0.875	14.32
103 and 104	CF	LUM/IVA 400/250 mg q12h Steady State	432	3.38	0.54	13.52
103 and 104	CF	LUM 600qd/IVA 250 mg q12h	336	4.02	0.56	16.08

N: Total subjects; SD: single dose; q12h: twice daily dose
* AUC0--∞ for SD; $AUC_{0\text{-}24h}$,ss for LUM, $AUC_{0\text{-}12h}$,ss for IVA,
(Source – Table 3, clinical overview; Table 2-4, study report 809-008)

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Based on population PK analysis the inter-individual variability on clearance of lumacaftor is 28% (CV%).

2.5.4 What are the characteristics of drug absorption?

The absolute bioavailability of lumacaftor in humans has not been determined. As lumacaftor has poor solubility, no intravenous formulation suitable for human administration is available. Lumacaftor is orally bioavailable as suspension, capsule, and tablet formulations. Ivacaftor is also orally available. *In vitro* studies established that lumacaftor and ivacaftor are not P-gp substrates.

Following multiple oral dose administrations of lumacaftor, the exposure of lumacaftor increased roughly proportionally with dose from 25 to 1000 mg qd. In subjects with CF, the lumacaftor Cmax and AUC also increases approximately proportional with the dose over the LUM 25 mg qd to 400 mg q12h dose range. The exposure of lumacaftor increased approximately 1.6- to 2.0-fold when given with fat containing food (Study 012). The median (range) time of the maximum concentration (tmax) is approximately 4.0 (2.0, 9.0) hours in the fed state.

Following multiple oral dose administration of ivacaftor in combination with lumacaftor, the exposure of ivacaftor generally increased with dose from 150 mg q12h to 250 mg q12h (Study 809-006), and from 250 mg q12h to 450 mg q12h (Study 809-008). When given in combination with lumacaftor, the exposure of ivacaftor increased approximately

2.5- to 3.4-fold when given with food containing fat (Study 012). Therefore, ivacaftor given in combination with lumacaftor should be administered with fat-containing food. The median (range) tmax is approximately 4.0 (2.0, 6.0) hours in the fed state.

2.5.5 What are the characteristics of drug distribution?

The plasma protein binding of lumacaftor and M28-lumacaftor was high: greater than 98% in all species examined. The mean protein binding values of [14C]-lumacaftor ranged from 99.97% to 100.00% in human plasma. The observation that radioactivity in plasma was higher than that observed in whole blood in human ADME Study 004, suggests lumacaftor does not partition into human red blood cells. Human serum albumin (HAS) was observed to be the major plasma component in [14C]-lumacaftor binding.

In the single- and multiple-dose escalation study (Study 001), lumacaftor had a moderate mean apparent volume of distribution (approximately 36 to 53 L) over the 25- to 400-mg dose range studied.

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

LUM is eliminated primarily by biliary/fecal excretion with minimal renal excretion. The major route of excretion of total [^{14}C]-radioactivity was via feces, demonstrated by a fecal excretion of 89.5% of dose within 480 hours. 8.6% of the total dose was recovered in urine.

Most of the radioactivity observed in feces was associated with unchanged lumacaftor and a monohydroxylated metabolite (M22-lumacaftor), accounting for an average of 51% (lumacaftor) and 17% (M22-lumacaftor) of the radioactive dose in Study 004(Table 17). These findings as well as the low levels of plasma-circulating glucuronides indicate that the majority of lumacaftor was likely eliminated unchanged from the body into the feces. In urine, the majority of the radioactivity excreted was associated with M20-lumacaftor (glucuronide metabolite), with a mean of 3.4% of the radioactive dose in Study 004. There was negligible urinary excretion of lumacaftor as unchanged parent (mean of 0.18%; range 0.10% to 0.27%), indicating that the contribution of renal clearance to the total clearance was low.

Table 17: VX-809 and Major Metabolites in Human Plasma, Urine and Feces Expressed as Percent of Total Administered Radioactivity

Metabolite Number	Metabolite Identification	Percent of Administered Dose (Mean)			
		Matrix			
		Plasma	Urine	Feces	Total
VX-809	VX-809	D	0.18	50.7	50.9
M20	Urea adduct of VX-809 glucuronide	ND	3.39	ND	3.39
M22	O-VX809-1	D	0.68	17.2	17.9
M28	Hydroxy-pyrrolidone-VX-809	D	0.07	ND	0.07
Other minor metabolites	Account for <1% in total excretion		1.41	3.8	5.21
Total	Total	NA	6.41	71.7	78.1

D: detected; ND: not detected
(source: Reviewer summary based on Table 11-4, VX08-809-004 study report Errata)

2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

After a single oral dose of 200 mg lumacaftor, most of the circulating radioactivity in plasma was associated with parent drug and M28-lumacaftor.Comparison of AUC values in plasma for parent drug versus total radioactivity suggested that approximately 62% of the radioactivity was associated with unchanged lumacaftor. M28-lumacaftor was the major metabolite in plasma, which represented 21% of the total radioactivity and a metabolite: parent AUC ratio of 35%. No other metabolite exposure exceeded a 5% metabolite ratio (Table 18). The oxidation pathway yielded a metabolite M22 that only account for 1.7% radioactivity in plasma in the human [14C]-ADME study but a major metabolite in excreta, predominantly feces (17% of dose). The major metabolite in plasma, M28-lumacaftor is also produced by oxidation pathway, with metabolite: parent AUC ratio<10% at steady state.

Ivacaftor is extensively metabolized in humans. M1-ivacaftor and M6-ivacaftor are the 2 major circulating metabolites of ivacaftor. After 150 mg q12h of the commercial tablet formulation in the fed state, the mean AUC ratio was approximately 4.9 for M1/ivacaftor and approximately 1.7 for M6/ivacaftor. When IVA is coadministered with LUM, There was a large decrease in plasma exposure of ivacaftor and M1 (approximately 80%), but no meaningful impact on the exposure of M6-ivacaftor. Therefore, the M6/IVA ratio increased significantly. When coadministered with LUM at a regimen of LUM/IVA 200/250 mg q12h in healthy subjects (study 010), the mean AUC ratio was approximately 3.7 for M1/ivacaftor and approximately 8.1 for M6/ivacaftor on day 10. When coadministered with LUM in the form of LUM/IVA 600 mg qd/250 mg q 12h in healthy volunteers (study 008), the mean AUC ratio was approximately 3.4 for M1/ivacaftor and approximately 11.3 for M6/ivacaftor on day 7.

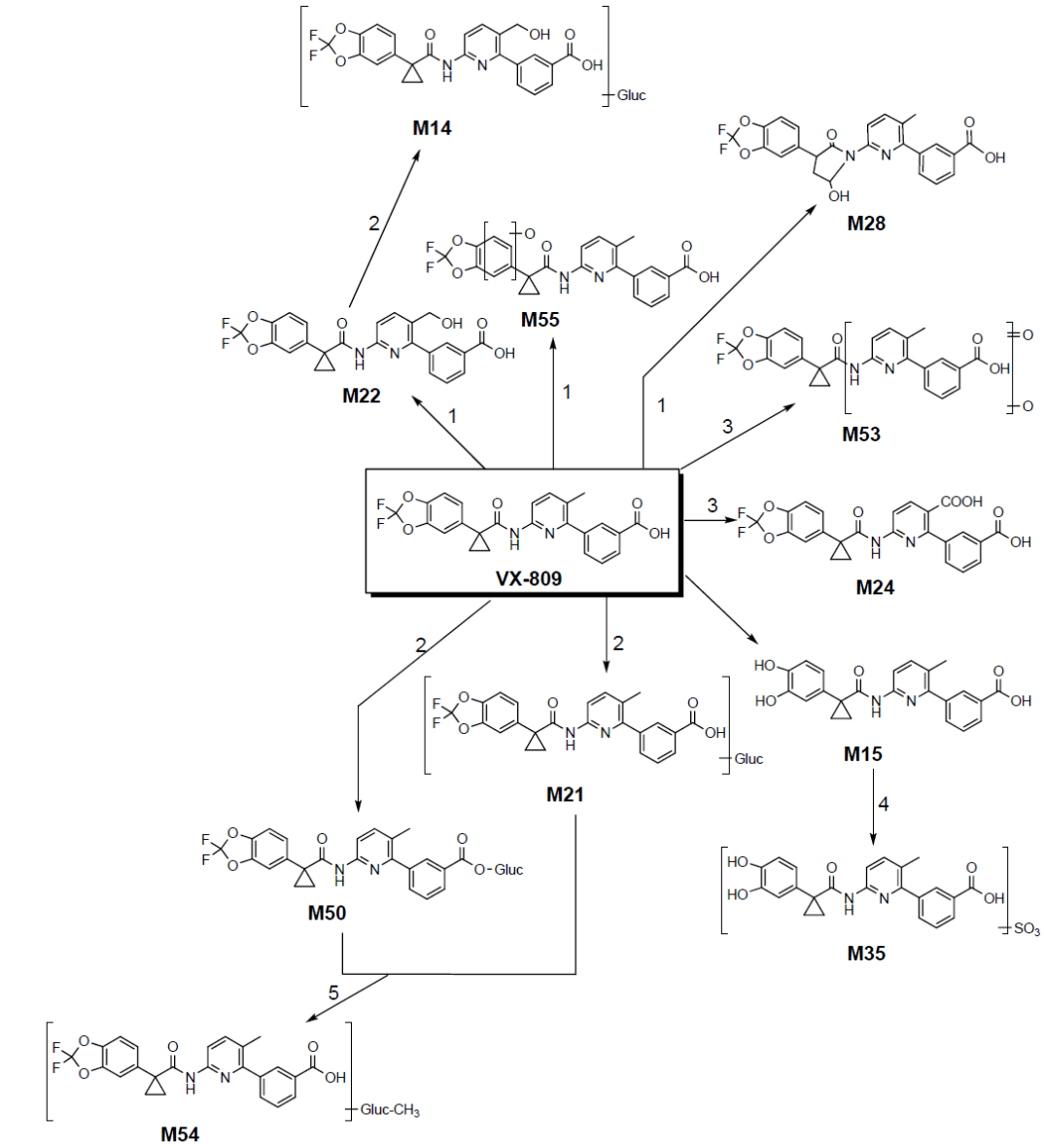
Table 18. Pharmacokinetic Parameters for Mean concentrations of Total Radioactivity, Parent Drug, and Selected Metabolites (account for >3% radioactivity in Plasma) Collected from Healthy Male Subjects Following a Single Oral Administration (200 mg) of [14C]-VX-809

Metabolite Number	Metabolite Identification	Tmax (hr)	Cmax (ng/g)[a]	t1/2,λz (hr)	$AUC_{0\text{-}264\ hr}$ Of Radioactivity (%)	$AUC_{0\text{-}264\ hr}$ Of Parent (%)
VX-809	VX-809	3	5630	27.2	61.8	100
M22	O-VX809-1	6	139	34.2	3.17	3.52
M28	Hydroxy-pyrrolidone-VX-809	72	340	186	21.4	34.6

a For total radioactivity, concentrations are ng equivalents [14C]-VX-809/g.
(source: Reviewer summary based on Table 11-3, VX08-809-004 study report Errata)

2.5.8 What are the characteristics of drug metabolism?

The proposed metabolic pathway for lumacaftor is shown in Figure 12. Lumacaftor is not extensively metabolized in human with the majority of lumacaftor excreted unchanged in the feces. *In vitro* and *in vivo* data indicate that lumacaftor is mainly metabolized via oxidation and glucuronidation. Hydroxy-lumacaftor (M22-lumacaftor, hydroxylation of methyl pyridine) was the primary metabolite observed following incubation of lumacaftor with liver microsomal preparations while lumacaftor glucuronide (M2-lumacaftor; glucuronidation) was the primary metabolite detected following incubation of lumacaftor with hepatocytes. However, these metabolites were not considered to be major metabolites as their levels were less than 10% in mass balance Study 004. Most of the circulating radioactivity in plasma was associated with the parent drug and M28-lumacaftor, which represented 21% of the total radioactivity and a metabolite: parent AUC ratio of 35% (Table 18). Most of the radioactivity observed in feces was associated with unchanged lumacaftor and a monohydroxylated metabolite (M22-lumacaftor), accounting for an average of 51% (lumacaftor) and 17% (M22-lumacaftor) of the radioactive dose (Table 17). At higher dose, the ratio of M28 to lumacaftor became lower, with metabolite: parent AUC ratio <10% at steady-state exposure of therapeutic doses.



1. Oxidation
2, Glucuronidation
3. Dioxidation
4. Sulfation
5. Methylation

Figure 12. Proposed Metabolic Pathway of VX-809 in Humans
(source: Figure 11-6, VX08-809-004 study report)

The proposed metabolic pathway for ivacaftor is shown in Figure 13. Ivacaftor is extensively metabolized in humans. *In vitro* and *in vivo* data indicate that ivacaftor is primarily metabolized by CYP3A. M1-ivacaftor and M6-ivacaftor are the 2 major metabolites of ivacaftor in humans.

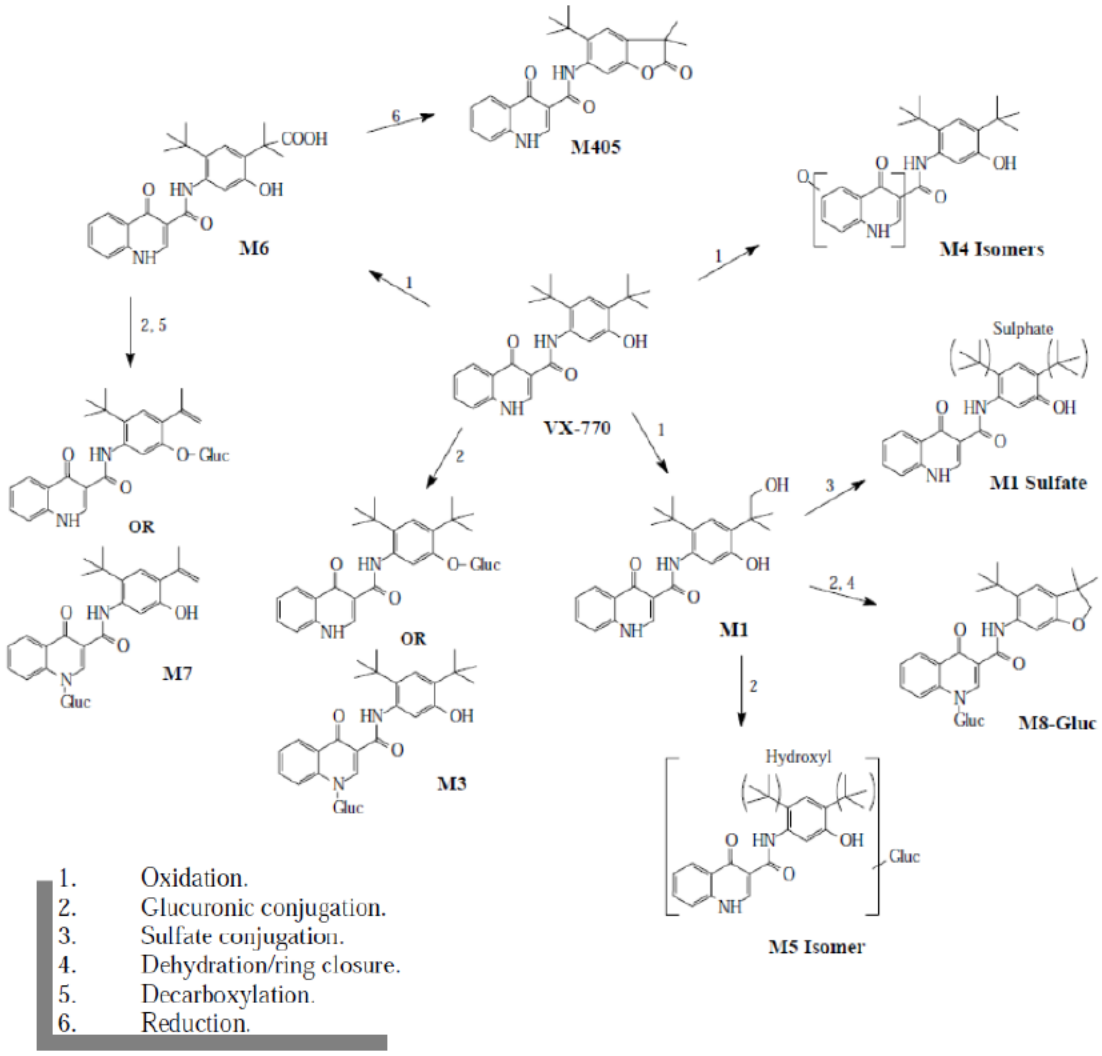


Figure 13. metabolic pathway of 14C-ivafactor (or 14C-VX-770) in healthy subjects
(Source – Figure 11, NDA203188 clin pharm review, dated 1/18/2012)

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

The amount of unchanged VX-809 found in the feces may be due to non-absorbed material from the gut, but also from drug being absorbed and released in the gut via the bile. In bile-cannulated rats dosed orally with VX-809, a large amount of parent drug (26% to 30% of the dose) was observed in the bile.

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

For doses up to 1200 mg, there were no secondary peaks observed in plasma concentration – time profiles of lumacaftor (Figure 11). There is no evidence of enterohepatic recirculation at the proposed therapeutic dose of 400 mg q12h.

2.5.11 What are the characteristics of drug excretion in urine?

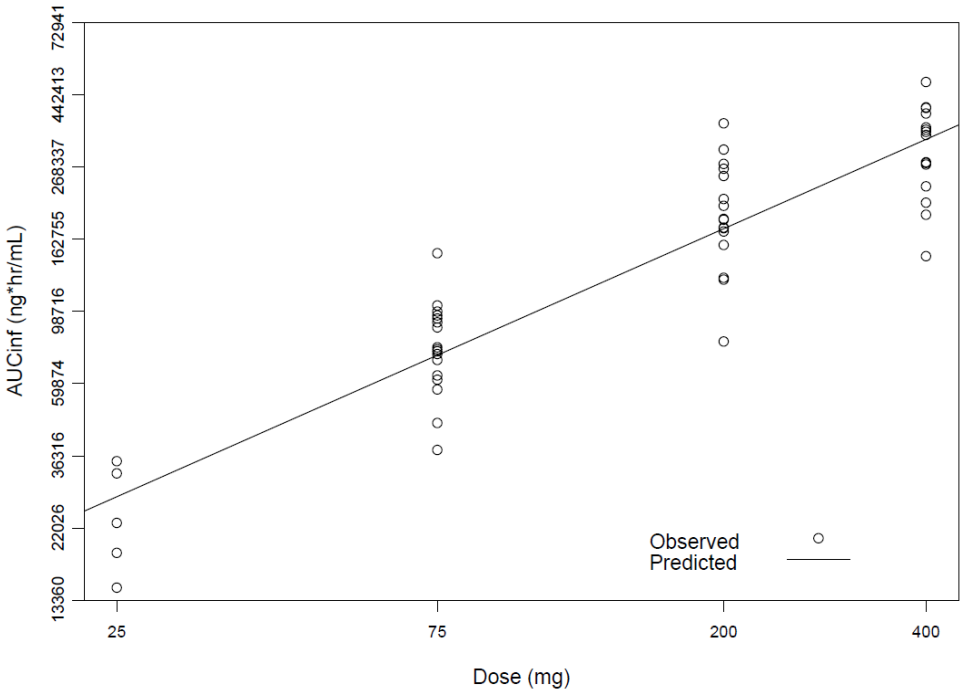
In the mass balance study 004, 8.6% of the total dose was recovered in urine. The majority of the radioactivity excreted in urine was associated with M20-lumacaftor (glucuronide metabolite), with a mean of 3.4% of the radioactive dose in Study 004. There was negligible urinary excretion of lumacaftor as unchanged parent (mean of 0.18%; range 0.10% to 0.27%). For M28-lumacaftor, the major plasma metabolite of lumacaftor in Study 004, urinary excretion was also negligible (0.01% to 0.16%).

For ivacaftor and its metabolites, elimination in the feces as metabolites was the predominant route of elimination, with minimal renal excretion of parent plus metabolites and with negligible renal excretion of parent.

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

Overall, the PK results for studies in healthy subjects suggest increases in lumacaftor Cmax and total AUC values are approximately proportional with the dose after single (LUM 25 to 600 mg) and multiple (LUM 50 to 1000 mg qd) oral administrations when lumacaftor was dosed alone (Table 12, Table 13). In subjects with CF, the lumacaftor Cmax and AUC also increases approximately proportional with the dose over the LUM 25 mg qd to 400 mg q12h dose range (study 809-101, 809-102, Table 15).

A.



B.

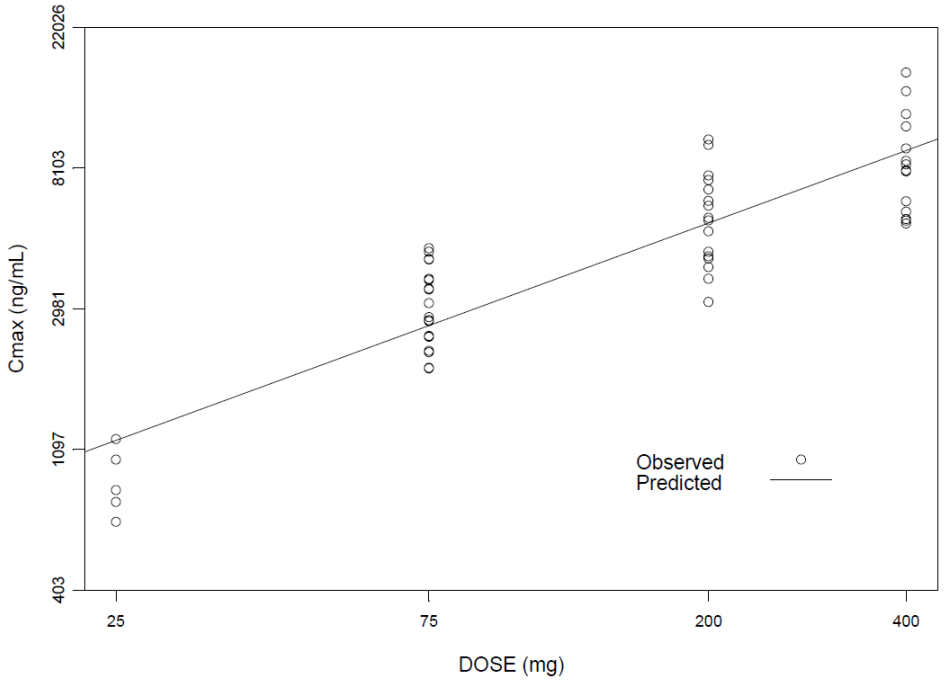


Figure 14. Assessment of dose proportionality for ivacaftor. (A) natural log (AUCinf) vs. natural log (Dose), and (B) natural log (Cmax) vs. natural log (Dose)
(Source: Figure 11-8, 11-9 study 809-001 report)

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

$AUC_{0-\infty}$ for lumacaftor and ivacaftor after single dose is compared with $AUC_{\tau,ss}$ at steady state. The linearity index, derived as $AUC_{\tau,ss}/AUC_{0-\infty}$ was 0.69 for lumacaftor (525/766, Table 19). This difference may be a combination of inter-study variability, and

increased CYP3A4 activity at steady state. PK information was collected in phase 2 and Phase 3 studies in CF patients. Trough (pre-dose) concentrations and concentrations at 3-6 hr post dose are similar over 16 week period (week 2, 4, 8, and 16), indicating no time-dependency in PK of lumacaftor after the concentration reached steady state.

The linearity index, derived as $AUC_{\tau,ss}/AUC_{0-\infty}$ was 0.22 for ivacaftor (3.58/16.4, Table 19). The lower exposure of ivacaftor at steady state is expected due to CYP3A induction of lumacaftor. PK information was collected in phase 2 and Phase 3 studies in CF patients. Trough (pre-dose) concentrations and concentrations at 3-6 hr post dose are similar over 16 week period (week 2, 4, 8, and 16), indicating no time-dependency in PK of ivacaftor after the concentration reached steady state.

Table 19: Exposure of LUM/IVA after single or multiple doses

Study	Subjects	Treatment	LUM AUC* (µg.h/mL)	IVA AUC** (µg.h/mL)
012	Healthy	LUM/IVA 600/250 mg SD	766	16.4
008	Healthy	LUM 600qd/IVA 250 mg q12h	525	3.58
012	Healthy	LUM/IVA 400/250 mg SD	565	18.7
103/104	CF	LUM 400 /IVA 250 mg q12h	198	3.38

N: Total subjects; SD: single dose; q12h: twice daily dose

* $AUC_{0-\infty}$ for SD; $AUC_{\tau,SS}$ for LUM and IVA

(Source – Table 3, clinical overview; Table 11-3, study report 809-012, Table 2-4, study report 809-008)

2.5.14 Is there evidence for a circadian rhythm of the PK?

There is no evidence for lumacaftor or ivacaftor exposure to be affected by circadian rhythm. No discernible differences in plasma exposures of ivacaftor were observed between the morning and evening doses of IVA when IVA150mg q12h is coadministered with LUM 200mg QD (dose in the morning) (study 809-005).

2.6 Intrinsic Factors

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

The sponsor's used an allometric model to fix the relationship between PK parameters and body weight. Thus it is unclear the inter-individual variability on clearance that is explained by bodyweight. Age was identified as a covariate for lumacaftor clearance. The change in exposure due to age effect is modest. The inter-individual variability on

clearance (CL/F) reduced from 29.4% to 27.9% after inclusion of age as a covariate.

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?

2.6.2.1 Severity of Disease State

Based on population PK analysis, lumacaftor bioavailability was 1.8 times higher in healthy subjects compared to patients

2.6.2.2 Pediatric Patients

See section 2.4.5

2.6.2.3 Race/Ethnicity

Based on population PK analysis, race did not affect the PK of lumacaftor.

2.6.2.6 Renal Impairment

The contribution of renal excretion after oral administration of lumacaftor both as unchanged drug (about 0.18% of dose) and as drug related radioactivity was minor (about 8.6% of dose, mostly as M20-LUM, glucuronide metabolite). Therefore, no dedicated study in renal impaired patients has been performed.

Based on population PK analysis, creatinine clearance did not affect the PK of lumacaftor and was not identified as a covariate. No data were collected for patients with baseline CrCL<50ml/min, as these patients were excluded from the study.

2.6.2.7 Hepatic Impairment

Hepatic metabolism and/or excretion are major route of elimination for lumacaftor and ivacaftor. Impact of moderate hepatic impairment on LUM/IVA PK was assessed in a nonrandomized, open-label, multiple doses Study 809-010. LUM 200 mg q12h/IVA 250 mg q12h was administered orally on Days 1 through 9 and with only a single morning dose on Day 10.

On Day 1, lumacaftor and ivacaftor exposures (both Cmax and AUC0-tlast) were similar in subjects with moderate hepatic impairment and healthy subjects. The metabolite exposures (M28-lumacaftor, M1-ivacaftor, and M6-ivacaftor) were higher in healthy subjects than in subjects with moderate hepatic impairment on Day 1.

On Day 10, Lumacaftor and ivacaftor total exposures at steady state were higher (Table 20, AUCτ by approximately 50% and Cmax by approximately 30%) in subjects with moderate hepatic impairment than in matched healthy subjects. The M28-lumacaftor exposures were lower (approximately 25%) in subjects with moderate hepatic impairment compared with healthy subjects. M1-ivacaftor and M6-ivacaftor exposures were comparable between subjects with moderate hepatic impairment and healthy subjects. The t1/2 for lumacaftor was similar in subjects with moderate hepatic impairment and healthy subjects. The t1/2 was prolonged for ivacaftor, M1-ivacaftor, and M6-ivacaftor in

subjects with moderate hepatic impairment compared with healthy subjects.

The extent of protein binding was similar in subjects with moderate hepatic impairment and healthy subjects.

Table 20. Summary of Results of LUM/IVA Pharmacokinetic Parameters in Subjects with Moderate Hepatic Impairment Compared with Healthy Subjects

Day	Analyte	Parameter	Group comparison	Mean	Ratio	90% CI of the ratio
Day 10	LUM	AUCτ (ng h/mL)	Moderate hepatic impairment/healthy	219000/153000	1.47	(1.14, 1.88)
		Cmax (ng/mL)	Moderate hepatic impairment/healthy	23000/18000	1.31	(1.04, 1.65)
	IVA	AUCτ (ng h/mL)	Moderate hepatic impairment/healthy	6700/3710	1.62	(1.12, 2.34)
		Cmax (ng/mL)	Moderate hepatic impairment/healthy	773/580	1.26	(0.91, 1.75)

(Source –Table 11-2, Table 11-3, Study 809-010 report)

Table 21. Special population PK

Special population	Effect on PK	AUC_{inf}	C_{max}	Dosing recommendation
Renal impairment	NA	NA	NA	Caution in severe and end-stage renal impairment
Mild hepatic impairment	Lumacaftor	NA	NA	No dose adjustment
	Ivacaftor	NA	NA	
Moderate hepatic impairment	↑ Lumacaftor	1.5	1.3	A dose reduction to 2 tablets in the morning and 1 tablet in the evening (LUM 600 mg/IVA 375 mg total daily dose)
	↑ Ivacaftor	1.6	1.3	
Severe hepatic impairment	Lumacaftor	NA	NA	Max dose 200/125 mg BID
	Ivacaftor	NA	NA	

↑- Increase, ↔ - no change
(Source –Reviewer summary)

2.7 Extrinsic Factors

2.7.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Yes, *in vitro* studies suggested that lumacaftor has a potential for drug interactions through induction of CYP2C and CYP3A subfamilies as well as P-gp. Lumacaftor may have a potential for inhibition of CYP2C8, CYP2C9, and CYP2C19 enzymes.

In vitro studies also indicated that ivacaftor and M1 may have a potential for drug interactions through inhibition of CYP2C8, CYP2C9, and CYP3A4 enzymes, and P-gp transporter. However, the combined effect of LUM and IVA is strong induction of

CYP3A based on dedicated DDI studies in human.

2.7.2 Is the drug a substrate of CYP enzymes?

A minor extent of the biotransformation of lumacaftor consisted of CYP pathways, predominantly CYP3A4. The percentage of parent and metabolites remaining after 1 hour incubation with recombinant CYP enzymes is shown in Table 22. In the drug interaction study 009, LUM exposure is not increased with strong CYP3A4 inhibitor itraconzaole.

Table 22. Summary of Stability Data (Percent Remaining) for VRT-826809 (LUM) and Control Compounds after 1 Hour Incubation at 37°C with Human CYP450 Isozymes

Initial VRT-826809 concentration	Mean (SD) Percent of VRT-826809 Remaining (%)				
	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
2 µM	99 (7)	103[a]	99 (3)	106 (1)	87 (3)
20 µM	102 (2)	107 (16)	128 (22)	124 (6)	92 (4)
	Mean (SD) Percent of Control Compound Remaining (%)				
Positive Control	Phenacetin	Diclofenac	Amitriptyline	Dextromethorphan	Quinidine
2 µM	45 (4)	0.2 (0.1)	4 (2)	1 (1)	13 (2)
20µM	29 (1)	1 (1)	32 (1)	3 (2)	42 (3)

n = 3
[a] n = 2
(Source – Table 8-1, Report D071)

Ivacaftor and M1-ivacaftor are substrates for CYP3A enzymes, CYP3A4 and CYP3A5, while M6-ivacaftor is metabolically stable. The percentage of parent and metabolites remaining after 30 min incubation with recombinant CYP enzymes is shown in Table 23. Only 1.8% and 6% of ivacaftor and M1 remained unmetabolized, respectively, following 30 minutes incubation with CYP3A4; and for CYP3A5 this proportion was 29% and 53%. While with other enzymes, unmetabolized ivacaftor and M1 proportion was 58 to 100%.

Table 23. Metabolism of ivacaftor, M1 and M6 by human recombinant CYPs

Analyte (1 µM)	% Remaining after 30 minutes Supersome Incubation								
	1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4	3A5
Ivacaftor	71(12)	72(6)	81(4)	85(11)	77(11)	103(12)	88(2)	1.8(0)	29(6)
M1	90(4)	65(5)	87(11)	58(6)	69(27)	71(10)	100(25)	6(4)	53(3)
M6	98(11)	103(10)	111(21)	83(9)	97(4)	88(4)	91(3)	91(5)	90(10)
Control	43(6) Phena-cetin	82(11) Bupro-pion	63 (10) Pacli-taxel	0(0) Diclo-fenac	0(0) Mepheny-toin	0.1(0) Dextro-methorphan	67(4) Chlorzo-xazone	11(1) Testo-sterone	91(7) Testo-sterone

(source: Table 20, NDA203188 clin pharm review)

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

Lumacaftor is a strong inducer of CYP3A. Lumacaftor was found to be a pregnane X receptor (PXR) activator in DPX2 cells (a cell line derived from the HepG2 human liver

carcinoma cell line) and therefore has the potential to induce CYP2C and CYP3A subfamilies as well as P-gp. *In vitro* studies to evaluate the effect of lumacaftor on mRNA levels and/or isozyme-selective CYP activities in cultured human hepatocytes also suggested lumacaftor to be a potential inducer of CYP2B6, CYP2C8/9/19, and CYP3A4/5 enzymes at 10-30 μM. M28-lumacaftor did not appear to induce CYP3A4/5 activities.

Based on *in vitro* results, lumacaftor also has the potential to both inhibit CYP2C8 and CYP2C9 at therapeutic concentrations. The net effect of LUM on CYP2C8 and 2C9 substrates is not clear. .*In vitro* studies with human liver microsomes and probe substrates for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 enzymes indicated that lumacaftor inhibited amodiaquine N-deethylase (CYP2C8) and diclofenac 4'-hydroxylase (CYP2C9) activities with apparent concentration resulting in 50% of the maximum inhibition (IC50) values of 12 μM (CYP2C8) and 32 μM (CYP2C9). The Cmax at steady-state following administration of 400 mg bid dose for 28 days in fed state was 24.2 μg/mL (~53.5 μM).

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

In *in vitro* studies, lumacaftor was shown not to be a substrate of OATP-1B1, OATP-1B3, OATP-2B1, or P-gp. *In vitro* studies also indicated that lumacaftor is an inhibitor of P-gp with an IC50 value of 14 μM.

In vitro studies determined that ivacaftor and metabolite M6 are not substrate for P-gp transporters, while metabolite M1 is a substrate for P-gp. *In vitro* and human *in vivo* data showed ivacaftor to be a weak inhibitor of P-gp.

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

No other metabolic enzyme or transported pathway is known to be important for disposition of LUM/IVA in addition to those already discussed in sections 2.7.2 and 2.7.4.

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

The effect of extrinsic factors on LUM/IVA exposure was summarized in Table 24.

Table 24. Extrinsic Factors

Co-administered drug	Effect on PK	AUC_{inf}	C_{max}	Dosing recommendation
Strong CYP3A inhibitor: itraconazole	↔ Lumacaftor	0.97	0.99	CYP3A4 inhibitor add to LUM/IVA, no dose adjustment; initiate LUM/IVA on background of strong CYP3A inhibitor, 200/125 qd x 1w.
	↑ Ivacaftor	4.30	3.64	
CYP3A inducer: Rifampin	↔ Lumacaftor	0.87	0.96	Co-administration not recommended
	↓ Ivacaftor	0.43	0.50	
Moderate CYP3A inhibitor: Ciprofloxacin	↔ Lumacaftor	0.86	0.88	No dose adjustment
	↔ Ivacaftor	1.29	1.29	

↑- Increase, ↔ - no change
(source: reviewer summary)

2.7.7 What are the drug-drug interactions?

Drug-Drug Interactions between LUM and IVA

Lumacaftor is a strong inducer of CYP3A. Co administration of lumacaftor with ivacaftor, a sensitive CYP3A substrate, decreased ivacaftor exposure by approximately 80% (Table 25). There was no meaningful impact of IVA on the PK of LUM.

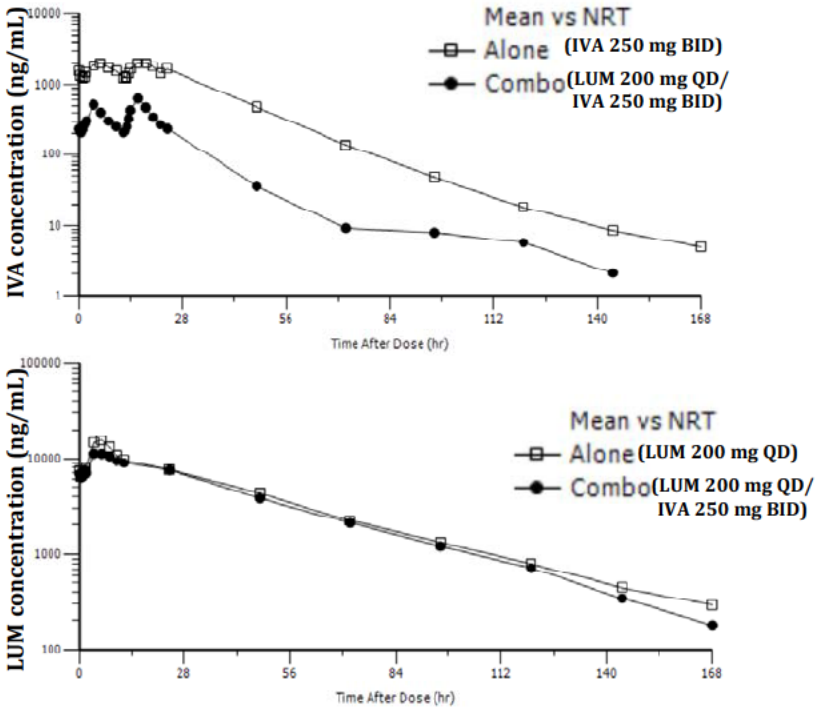


Figure 15. Mean Plasma Concentration Versus Time Profiles (Semi log Scale) on Nominal Day 14 After Administration of Ivacaftor and Lumacaftor alone or in combination
(Source: Figure 11-2 and Figure 11-12, VX10-809-006 study report)

Table 25. Summary of Steady State (Nominal Day 14) Pharmacokinetic Parameters for Lumacaftor and Ivacaftor

Analyte	Interacting Drug	N	Median (min, max) t_{max} (h)	Arithmetic Mean (SD) C_{max} (ng/mL)	AUC_{tau} (h*ng/mL)	CLss/F (L/h)	Vz/F (L)	$t_{1/2}$ (h)
Lumacaftor 200 mg qd	None	18	6.00 (4.00,10.0)	17200 (5130)	242000 (75200)	0.905 (2.72)	33.8 (13.6)	26.4 (8.07)
Lumacaftor 200 mg qd	Ivacaftor 250 mg q12h	16	4.01 (0.00, 8.00)	13200 (5600)	212000 (107000)	1.35 (1.17)	44.1 (37.1)	24.1 (7.16)
Lumacaftor 400 mg qd	None	17	6.00 (4.00, 10.0)	27900 (8900)	435000 (139000)	1.00 (0.304)	38.3 (13.7)	27.3 (10.2)
Lumacaftor 400 mg qd	Ivacaftor 150 mg q12h	13	6.00 (2.00, 11.9)	25000 (8660)	387000 (142000)	1.14 (0.343)	42.4 (17.7)	26.3 (8.95)
Ivacaftor 250 mg q12h	None	17	6.00 (0.500, 6.02)	2140 (1370)	40600 (27400)	15.7 (6.06)	207 (129)	9.13 (4.16)
Ivacaftor 250 mg q12h	Lumacaftor 200 mg qd	16	4.00 (2.00, 6.03)	544 (189)	8530 (2850)	72.9 (29.9)	705 (373)	7.20 (4.62)
Ivacaftor 150 mg q12h	None	15	6.00 (2.00, 10.0)	1330 (438)	23600 (8300)	14.1 (5.11)	187 (96.6)	9.73 (5.98)
Ivacaftor 150 mg q12h	Lumacaftor 400 mg qd	13	4.00 (1.50, 11.9)	572 (312)	6180 (2840)	65.6 (38.6)	515 (536)	4.86 (1.78)

AUC: area under concentration versus time curve; AUC_{tau}: AUC for the dosing interval. Lumacaftor tau = 24 h and Ivacaftor tau = 12 h (AM [0 - 12 h] tau is reported in table); CI: confidence interval; CLss/F: apparent clearance; C_{max}: maximum observed concentration; N: number of subjects; qd: daily; q12h: every 12 hours; t_{max}: time of maximum concentration; $t_{1/2}$: terminal phase half-life; Vz/F: apparent volume of distribution (based on the terminal phase).

(Source – Table on page 8, Study 809-006 report)

-Effect of other drugs on LUM/IVA

Effect of co-administration of itraconazole, rifampicin, and ciprofloxacin on LUM/IVA exposure (AUC) and C_{max} was evaluated (Table 24).

IVA is a CYP3A substrate. A minor extent of the biotransformation of LUM consisted of CYP pathways. LUM exposure is not affected by co-administration of CYP3A inhibitors or inducers. Co-administration with itraconazole (P-gp and CYP3A4 inhibitor) increased exposure to ivacaftor 4.3-fold based on AUC and 3.6-fold based on Cmax in a dedicated drug-drug interaction study. In a drug-drug interaction study with the CYP3A4 inducer rifampicin, exposure to ivacaftor decreased by 57% based on AUC and 50% based on Cmax upon co-administration with rifampin compared to administration of LUM/IVA alone.

Reviewer's comments

1. *Co-administration with itraconazole (P-gp and CYP3A4 inhibitor) increased exposure to ivacaftor 4.3-fold based on AUC and 3.6-fold based on Cmax in a dedicated drug-drug interaction study. However, this increase in ivacaftor exposure does not require a dose adjustment, as ivacaftor exposure is still less than what is observed for ivacaftor monotherapy (Kalydeco).*

2. *Coadministration with rifampin significantly reduced AUC and C_{max} of ivacaftor by ~57% and 50%, respectively. Rifampin is an inducer for CYP3A4. These lower exposures may result in inefficacious concentrations; therefore, coadministration with rifampicin or other CYP3A inducers is not recommended.*

3. *No significant change in exposure (AUC and Cmax) of lumacaftor and ivacaftor was observed following co-administration with ciprofloxacin. However, this may not be extrapolated to other moderate CYP3A inhibitors. According to the Kalydeco (ivacaftor) approved label,* (b) (4) *moderate CYP3A inhibitor fluconazole increased the exposure of ivacaftor by 3 fold. Nevertheless, the potential increase in ivacaftor exposure with LUM/IVA does not require any dose adjustment. As discussed above for strong CYP3A inhibitors, the ivacaftor exposure would still be less than what is observed for ivacaftor monotherapy (Kalydeco). Therefore, no further study is needed.*

-Effect of LUM/IVA on other drugs

Lumacaftor is a strong inducer of CYP3A. *In vitro* studies suggest that LUM has the potential to induce P-gp, CYP2B6, CYP2C8, CYP2C9, and CYP2C19. *In vitro* studies also indicated that lumacaftor may inhibit CYP2C8 and 2C9. Therefore, concomitant use of LUM/IVA may alter exposure of many medicines commonly used in CF patients.

In two DDI studies, co-administration with lumacaftor decrease the exposure to ivacaftor by >80%. In another study with itraconazole, co-administration with lumacaftor decreased the exposure to itraconazole by >80% when compared with historical data. Based on trough concentration, ciprofloxacin exposure was not affected by lumacaftor.

Table 26 provided dosing recommendations as a result of drug interactions with lumacaftor and/or ivacaftor with an emphasis on important and/or frequently used (used by ≥15% of subjects in the pivotal Phase 3 clinical studies) medications in the CF population and/or medicinal products with narrow therapeutic windows. These recommendations are based on either drug-drug interaction studies (indicated by an asterisk*) or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Table 26. Established and Other Potentially Significant Drug Interactions - Dose Recommendations for Use of common concomitant drugs when coadministered with ORKAMBI

Concomitant drug class: Drug name	Effect[a]	Sponsor Recommendation[b]	Rationale by sponsor	Reviewer comment
Anti-allergics: montelukast	↓	No dose adjustment for montelukast is recommended. Employ appropriate clinical monitoring, as is reasonable, when co-administered with	Label: (b) (4)	Agree

		ORKAMBI.	[redacted] (b) (4)	
Antibiotics: Clarithromycin Telithromycin erythromycin	↓	Consider an alternative to these antibiotics, such as azithromycin and ciprofloxacin.	Clarithromycin and telithromycin are substrates of CYP3A	Agree See reviewer comment 1 and 2
Antifungals: Itraconazole* Ketoconazole Posaconazole Voriconazole Fluconazole	↓ ↓	• Concomitant use of ORKAMBI is not recommended. Monitor patients closely for breakthrough fungal infections if such drugs are necessary. • [redacted] (b) (4)	• Itraconazole, ketoconazole, and voriconazole are substrates of CYP3A. Known inducers (rifabutin and phenytoin) have been shown to decrease plasma concentrations of posaconazole • [redacted] (b) (4)	• Consider an alternative antifungal, such as fluconazole. • [redacted] (b) (4)
Anti inflammatories: Ibuprofen	↓	A higher dose of ibuprofen may be required to obtain the desired clinical effect	Oxidative metabolism of ibuprofen is complex and involves multiple CYP enzymes. The exposure of ibuprofen may be decreased due to CYP induction by lumacaftor	Agree See reviewer comment 4
Benzodiazepines: midazolam, triazolam	↓	Concomitant use of ORKAMBI is not recommended.	Midazolam and triazolam are sensitive substrates of CYP3A and their exposures will be significantly decreased due to CYP3A induction by lumacaftor.	Agree
Hormonal contraceptives: ethinyl, estradiol, norethindrone, and other progestogens	↓	Do not rely on hormonal contraceptives, including oral, injectable, transdermal, and implantable as an effective method of contraception	Lumacaftor is a strong inducer of CYP3A. There are consistent data demonstrating that strong (e.g. rifampin, carbamazepine) and moderate (e.g. bosentan, efavirenz) inducers of CYP3A decrease the levels of hormonal contraceptives and thus, may render the contraceptives less effective.	Avoid concomitant use unless the benefit outweighs the risks. See reviewer comment 5.
Immunosuppres	↓	Concomitant use of	Cyclosporine, everolimus,	Agree

sants: Cyclosporine, Everolimus, Sirolimus, tacrolimus		ORKAMBI is not recommended.	sirolimus and tacrolimus are extensively metabolized by CYP3A. The exposures of these immunosuppressants will be decreased due to CYP3A induction by lumacaftor.	
Proton pump inhibitors: Esomeprazole Lansoprazole omeprazole	↓	(b) (4) may be required to obtain the desired clinical effect	• Labels: (b) (4)	Agree See reviewer comment 6
Antiarrhythmics: digoxin	↓ or ↑	Monitor the serum concentration of digoxin and titrate the digoxin dose to obtain the desired clinical effect.	Digoxin is a substrate for P-glycoprotein, at the level of intestinal absorption, renal tubular section and biliary-intestinal secretion. Therefore, drugs that induce/inhibit P-glycoprotein have the potential to alter digoxin pharmacokinetics." ORKAMBI may alter the exposure of digoxin due to induction or inhibition of P-gp.	Agree Therapeutic drug monitoring, no need for DDI study
Anticoagulants: Warfarin	↓ or ↑	Monitor INR (b) (4)	Label: (b) (4)	Agree Titrate to INR, no need for DDI study
Antidepressants: Citalopram Escitalopram sertraline	↓	A higher dose of these antidepressants may be required to obtain the desired clinical effect	• Label: (b) (4)	Agree Titrate to clinical response, no need for DDI study

			(b) (4) • Label: (b) (4)	
Corticosteroids, systemic: Methylprednisolone prednisone	↓	A higher dose of these systemic corticosteroids may be required to obtain the desired clinical effect	ORKAMBI may decrease the exposures of methylprednisolone and prednisone due to induction of CYP3A.	Agree
H2 blockers: ranitidine	↓ or ↑	Dose adjustment of ranitidine may be required to obtain the desired clinical effect	Rifampicin, a strong inducer, had been shown to reduce the exposure of ranitidine. This interaction may occur through induction of P-gp	Agree
Oral hypoglycemics: Repaglinide sulfonylurea	↓ Repaglinide ↓ or ↑ sulfonylurea	Dose adjustment may be required to obtain the desired clinical effect	• Label: (b) (4)	Agree For hypoglycemic, metformin does not require dose adjustment. Dose of other hypoglycemic could be titrated to clinical response.

a. For effect of other drugs on LUM/IVA, see **Table 24**.
b. For recommendations of LUM/IVA dose adjustment when coadministered with other drugs, see **Table 24**.

↓:ORKAMBI may decrease the exposure of the concomitant drug, which may reduce its efficacy.
↑:ORKAMBI may increase the exposure of the concomitant drug, which may cause toxicity.

(Source: reviewer summary and analysis based on Annotated table, label section 7)

Reviewer's comments

1. *LUM is a strong CYP3A inducer. As the exposure of victim drug is decreased by more than 80% with some variability, dose adjustment is hard for concomitant sensitive CYP3A substrates. Therefore, the patients need to seek alternate drugs (Table 28), or consider temporarily stopping LUM/IVA based on benefit/risk assessment. For example, concomitant use of hormonal contraceptives, most antifungals, benzodiazepines, immunosuppresants are not recommended.*

2. *No significant change in steady state trough concentrations of ciprofloxacin was observed following co-administration with LUM/IVA. While trough concentration may not be a sensitive measure to evaluate the DDI effect, the lack of PK interaction is consistent with the mechanism of elimination for ciprofloxacin. Therefore, ciprofloxacin may be administered with LUM/IVA without dose adjustment.*

3. *The induction potential of LUM for CYPs is similar to that of rifampin based on in vitro data. Dose adjustment is not necessary for a 23% decrease in exposure.*

4. *Therapeutic monitoring is available for high dose ibuprofen in CF patients.*

5. *Besides contraception, hormonal contraceptives are also used for other indications. Besides the risk of failed contraception, phase 3 studies also identified significant increased risk of menstruation AEs for hormonal contraceptives concomitantly used with LUM. Therefore, concomitant use of hormonal contraceptives is not recommended.*

6. *Omeprazole was used by ~30% patients in phase 3 studies (Table 29), with no outstanding AEs. Omeprazole was approved for a large range of doses (eg. 20-60mg qd, PRILOSEC), with relatively flat dose response (Table 27). Therefore, potential reduced exposure of omeprazole may have limited impact on clinical response, and dose adjustment based on clinical response is reasonable.*

Table 27. Omeprazole dose response

Treatment of Active Duodenal Ulcer % of Patients Healed		
	PRILOSEC	
	20 mg (n = 34)	40 mg (n = 36)
Week 2	*83	*83
Week 4	*97	*100
Week 8	100	100

*($p \leq 0.01$)

Treatment of Gastric Ulcer % of Patients Healed (All Patients Treated)		
	PRILOSEC 20 mg once daily (n = 202)	PRILOSEC 40 mg once daily (n = 214)
Week 4	47.5**	55.6**
Week 8	74.8**	82.7**,+

**($p < 0.01$) PRILOSEC 40 mg or 20 mg versus placebo

+($p < 0.05$) PRILOSEC 40 mg versus 20 mg

(Source: reviewer summary based on PRILOSEC label)

The clinical pharmacology program for strong CYP 3A4 inducers (such as efavirenz) usually includes extensive DDI studies to direct the dose adjustment of concomitant medicines. To recommend a reasonable DDI assessment plan for treatment of CF, a rare disease with expedited development timeline, we assessed whether a dedicated DDI study

is necessary for each class of common concomitant medicine used in CF patients before the phase 3 studies (Dr. Jianmeng Chen, IND079521, review dated 06/18/2013). In our analysis, we concluded that most DDIs were manageable by dose titration and alternative drugs. Table 28 showed the list of common concomitant drugs that were not affected by LUM.

Table 28. List of drugs whose exposure not affected by LUM/IVA

Concomitant drug class: Drug name	Rationale by sponsor	Reviewer comment
azithromycin, aztreonam, budesonide, (b) (4) (b) (4) ceftazidime, cetirizine, ciprofloxacin, colistimethate, colistin, dornase alfa, fluticasone, ipratropium, levofloxacin, (b) (4) pancreatin, pancrelipase, salbutamol, salmeterol, sulfamethoxazole and trimethoprim, tiotropium, and tobramycin	Not eliminated by CYP3A or CYP2C pathway; Or/and local acting	Agree

(Source: reviewer summary and analysis based on Annotated table, label section 7)

2.7.8 Does the label specify coadministration of another drug?

No, the label does not specify administration of LUM/IVA with any particular drug.

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

CF patients are usually on many concomitant medicines, and many of these concomitant medicines are CYP3A4 substrates. In the phase 3 studies, the sponsor allowed the use of CYP3A4 substrates, and the general instruction was "*Each investigator should evaluate the benefit/risk ratio of using such drugs with lumacaftor during this study. Investigators should discuss any concerns regarding the use of CYP3A substrates during this study with the Vertex medical monitor or designee*". The safety database and concomitant medication information suggested that the DDI impact of LUM was largely manageable in phase 3 trials with clinical monitoring, dose adjustment and using alternative drugs. Nevertheless, having lumacaftor in the dose regimen will limit drug choice for CF patients.

Table 29 provides the most common (at least 15% incidence) concomitant medications in any treatment group by preferred term in the pooled placebo-controlled Phase 3 studies. Overall, the most commonly reported concomitant medications (at least 30% incidence) were indicated for management of CF complications: dornase alfa (76.4%), pancreatin (70.8%), salbutamol (70.8%), sodium chloride (67.6%), azithromycin (63.1%), tobramycin (53.4%), ciprofloxacin (33.7%), and Seretide (32.1%).

The use of these concomitant medications was generally similar between the total LUM/IVA and placebo groups. The percentage of subjects who received sodium chloride, tobramycin, ciprofloxacin, Bactrim, vitamin D, and ceftazidime was lower (at least 5% difference) in the total LUM/IVA group compared with the placebo group. The small differences are unlikely to be of any clinical significance or have any impact on the overall safety data. Subjects were receiving multiple medications typical for CF concurrently with LUM/IVA; thus, the safety experience with respect to the effect of

concomitant medications is likely representative of that expected in clinical use. Overall, there was no clinically meaningful difference in concomitant medication use that suggested an underlying trend or safety concern requiring specific treatment.

Table 29. Concomitant Medications in At Least 15% of Subjects in Any Treatment Group by Preferred Term: Pooled Placebo-Controlled Phase 3 Studies, Safety Set

		LUM/IVA		
Preferred Term	**Placebo N = 370 n (%)**	**LUM 600 mg qd/ IVA 250 mg q12h N = 369**	**LUM 400 mg q12h/ IVA 250 mg q12h N = 369**	**Total LUM/IVA N = 738**
Subjects with any concomitant medication	370 (100.0)	369 (100.0)	369 (100.0)	738 (100.0)
Dornase alfa	284 (76.8)	290 (78.6)	273 (74.0)	563 (76.3)
Pancreatin	253 (68.4)	261 (70.7)	270 (73.2)	531 (72.0)
Salbutamol	265 (71.6)	267 (72.4)	252 (68.3)	519 (70.3)
Sodium chloride	264 (71.4)	238 (64.5)	247 (66.9)	485 (65.7)
Azithromycin	241 (65.1)	242 (65.6)	216 (58.5)	458 (62.1)
Tobramycin	225 (60.8)	192 (52.0)	175 (47.4)	367 (49.7)
Ciprofloxacin	140 (37.8)	120 (32.5)	113 (30.6)	233 (31.6)
Seretide	130 (35.1)	110 (29.8)	116 (31.4)	226 (30.6)
Omeprazole	93 (25.1)	117 (31.7)	104 (28.2)	221 (29.9)
Colecalciferol	85 (23.0)	104 (28.2)	112 (30.4)	216 (29.3)
Aztreonam lysine	115 (31.1)	99 (26.8)	97 (26.3)	196 (26.6)
Paracetamol	91 (24.6)	98 (26.6)	91 (24.7)	189 (25.6)
Pancrelipase	110 (29.7)	101 (27.4)	87 (23.6)	188 (25.5)
Aquadeks	100 (27.0)	100 (27.1)	84 (22.8)	184 (24.9)
Ibuprofen	88 (23.8)	81 (22.0)	96 (26.0)	177 (24.0)
Influenza vaccine	101 (27.3)	85 (23.0)	85 (23.0)	170 (23.0)
Bactrim	105 (28.4)	101 (27.4)	63 (17.1)	164 (22.2)
Vitamin D NOS	105 (28.4)	80 (21.7)	82 (22.2)	162 (22.0)
Vitamins NOS w/zinc	87 (23.5)	79 (21.4)	83 (22.5)	162 (22.0)
Ursodeoxycholic acid	75 (20.3)	72 (19.5)	85 (23.0)	157 (21.3)
Vitamins NOS	59 (15.9)	76 (20.6)	64 (17.3)	140 (19.0)
Fluticasone propionate	72 (19.5)	63 (17.1)	72 (19.5)	135 (18.3)
Tocopherol	59 (15.9)	62 (16.8)	63 (17.1)	125 (16.9)
Colistimethate sodium	72 (19.5)	53 (14.4)	65 (17.6)	118 (16.0)
Montelukast sodium	50 (13.5)	66 (17.9)	47 (12.7)	113 (15.3)
Prednisone	60 (16.2)	38 (10.3)	47 (12.7)	85 (11.5)
Ceftazidime	67 (18.1)	34 (9.2)	37 (10.0)	71 (9.6)

Source: Module 5.3.5.3/VX-809 ISS/Table 2.1.6.4.
IVA: ivacaftor; LUM: lumacaftor; NOS: not otherwise specified; q12h: every 12 hours; qd: daily; WHO-DDE: World Health Organization – Drug Dictionary Enhanced.
(source: Table 14, summary clin safety)

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

In CF subjects, there is a decline in FEV1 after LUM monotherapy (Figure 2, study 809-102). In healthy subjects, there is a decline in FEV1 within 4 hours of treatment and last to 21/24 day as last tested, with LUM/IVA dosed every 12 hour. Treatment with long-acting bronchodilators (indacaterol and tiotropium) largely prevented the decline observed in FEV1 following dosing with LUM/IVA, and treatment with short-acting

bronchodilators (albuterol and ipratropium) led to a reversal of the decline in healthy subjects.

It is not clear whether the bronchodilators have similar protective effects against the FEV1 declining effect of LUM in CF patients. In study 809-102, LUM monotherapy reduced FEV1 (pre-bronchodilator assessment) in a dose dependent manner despite the concomitant use of bronchodilators in most CF patients.

In phase 3 protocols, there is no specific instruction on concomitant use of bronchodilators to prevent the FEV1 declining effect of LUM, and the bronchodilator use is similar between placebo group and treatment (LUM/IVA) groups.

2.8 General Biopharmaceutics

The formulations used in different *in vivo* clinical studies are listed in Table 30, Table 31, and Table 32.

Table 30. Formulations of Lumacaftor Used in Clinical Studies

Formulation Description (Abbreviated)	Formulation Description	Clinical Study Number[a]		
		Phase 1	Phase 2	Phase 3
Suspension	25-, 50-, 75-, 100-, 200-, or 400 mg oral suspension (b) (4) (b) (4)	001, 003		
Suspension	200 mg oral suspension prepared from (b) (4) [^{14}C] labeled and unlabeled lumacaftor in (b) (4)	004		
Capsule	25- or 50 mg capsule prepared from (b) (4)	002, 003, 005, 006	101	
Phase 2 film-coated tablet	200 mg film-coated tablet prepared by (b) (4)	007, 009, 010	102	
(b) (4) film-coated tablet	200 mg film-coated tablet prepared by (b) (4) (b) (4)	007, 008		

[a] Study numbers are abbreviated to the last 3 digits

(source: Table 2, section 2.3.P.2, pharmaceutical development)

Table 31. Formulations of Ivacaftor Used in Clinical Studies

Formulation Description (Abbreviated)	Formulation Description	Clinical Study Number (Abbreviated)[a]		
		Phase 1	Phase 2	Phase 3
(b) (4) (b) (4) tablet	50 mg tablet with (b) (4) ivacaftor/HPMCAS/SLS (b) (4)	005		
Film-coated tablet	100- and/or 150 mg film-coated (b) (4) ivacaftor/HPMCAS/SLS (b) (4)	006, 007, 008, 009, 010	102	
Film-coated tablet (intended commercial tablet)[b]	125 mg film-coated (b) (4) (b) (4) ivacaftor/HPMCAS/SLS (b) (4)	011		103, 104, 105

HPMCAS: hypromellose acetate succinate; (b) (4) SLS, sodium lauryl sulfate.

[a] Study numbers are abbreviated to the last 3 digits

[b] Clinical studies used a 125 mg tablet with a blue film coat (b) (4) (b) (4)

(source: Table 3, section 2.3.P.2, pharmaceutical development)

Table 32. Formulations of Lumacaftor/Ivacaftor Used in Clinical Studies

Formulation Description (Abbreviated)	Formulation Description	Clinical Study Number (Abbreviated)[a]		
		Phase 1	Phase 2	Phase 3
200/125 mg film-coated FDC tablet (b) (4)	200 mg lumacaftor/125 mg ivacaftor[c] film-coated FDC tablet prepared by a (b) (4) process	007, 011, 012	102	103, 104, 105
200/83 mg film-coated FDC tablet (b) (4)	200 mg lumacaftor/83 mg ivacaftor[c] film-coated FDC tablet prepared by a (b) (4) process	012		103, 104, 105

FDC: lumacaftor/ivacaftor fixed dose combination; (b) (4) (b) (4)

[a] Study numbers are abbreviated to the last 3 digits (b) (4)

[c] Ivacaftor is provided as an (b) (4) (b) (4) in the formulation.

(source: Table 4, section 2.3.P.2, pharmaceutical development)

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?

Lumacaftor is considered to be a BCS Class 2 (low solubility/high permeability) compound. The solubility of the lumacaftor (b) (4) drug substance in water (b) (4) is 0.018 mg/mL, which is classified as practically insoluble. Although (b) (4) solubility was observed, the lumacaftor

drug substance is practically insoluble in water [redacted] (b) (4)

Lumacaftor exhibited high permeability in 2 studies conducted using the Caco-2 cell line, which is a widely accepted *in vitro* model to predict intestinal drug permeability in humans. At 75 µM, the apparent permeability coefficient (Papp) of lumacaftor was high (27.1×10^{-6} cm/s) in the apical-to-basolateral direction. This value was higher than that of minoxidil (5.5×10^{-6} cm/s), a high permeability reference compound.

Ivacaftor could not be classified definitively by the BCS. It has low solubility, suggesting that it is either a BCS Class 2 (low solubility/high permeability) or Class 4 (low solubility/ low permeability) drug. However, its low solubility and non-specific binding to culture materials precluded an acceptable determination of its permeability using the Caco-2 cell system.

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

The FDC tablets (200/125 mg) used in the phase 3 trials and the final commercial formulation are the same. Therefore, no bridging BA/BE studies were necessary.

Initial clinical studies were conducted with lumacaftor only and included a lumacaftor suspension formulation used in early Phase 1 clinical studies and a lumacaftor capsule formulation used in subsequent Phase 1 and early Phase 2 studies. Clinical development then moved to combination therapy and ivacaftor was added to the regimen. Early Phase 1/2 clinical studies used individual lumacaftor and ivacaftor tablets. A bioavailability study (Study 007) was completed that supported the use of fixed dose combination (FDC) tablets in Phase 3 clinical studies. The Phase 3 pivotal studies included 2 dosing regimens and used both the LUM/IVA FDC tablet, 200/125 mg and the lumacaftor/ivacaftor FDC tablet, 200/83 mg. Additionally, in the Phase 3 regimen that utilized the LUM/IVA FDC tablet, 200/83 mg, an individual ivacaftor, 125 mg tablet was also dosed. Please refer to review by Office of New Drug Quality Assessment (ONDQA) for further details regarding formulation changes.

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

For early development formulations, Lumacaftor suspension and capsule formulation bioavailability (Study 001, 002, 003) increased modestly when administered after a high-fat breakfast (Table 33). Coadministration with food significantly affected the exposures of lumacaftor and ivacaftor for the clinical formulations used during clinical program (Study 012, Table 33).

When a single dose of LUM/IVA was administered with fatty foods, lumacaftor exposure is approximately 2 times higher and ivacaftor exposure is approximately 3 times higher than when taken in a fasting state (Table 33). Phase 2 (# 809-102 and 770-104) and Pivotal Phase 3 studies (# 103 and 104) were conducted with lumacaftor and ivacaftor

following diet appropriate for CF patients, and the label also recommends taking LUM/IVA with fat-containing food.

Table 33. Effect of food on bioavailability of different LUM, and LUM/IVA formulations tested during clinical development program

Analyte	Study	N	Subjects	Test	Reference	Geometric mean ratio (90%CI)	
						AUCinf	Cmax
LUM	809-001	7/7	healthy	200 mg suspension, food	200 mg suspension, fast	1.32 (1.13, 1.55)	1.47 (1.23, 1.75)
	809-002	7/7	CF	4X50-mg capsules, food	4X50-mg capsules, fast	1.12 (0.98, 1.28)	0.77 (0.61, 1.29)
	809-003	18/18	healthy	4X50-mg capsules, food	4X50-mg capsules, fast	1.17 (1.09, 1.25)	1.33 (1.17, 1.51)
	809-012	14/14	healthy	**FDC* LUM/IVA 2X200/125 mg, food**	**FDC* LUM/IVA 2X200/125 mg, fast**	**1.64 (1.42, 1.88)**	**2.22 (1.93, 2.57)**
		14/14	healthy	FDC LUM/IVA 3X200/83 mg, food	FDC LUM/IVA 3X200/83 mg, fast	1.95 (1.70, 2.24)	2.82 (2.45, 3.26)
IVA	809-012	14/14	healthy	**FDC* LUM/IVA 2X200/125 mg, food**	**FDC* LUM/IVA 2X200/125 mg, fast**	**2.53 (2.22, 2.88)**	**3.7 (3.00,4.56)**
		14/14	healthy	FDC LUM/IVA 3X200/83 mg, food	FDC LUM/IVA 3X200/83 mg, fast	3.39 (3.01, 3.83)	5.18 (4.15, 6.48)

*Intended final formulation

(Source – Reviewer summary, based on study reports 809-001, 002, 003, 012)

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

Two FDC strengths have been tested in the phase 3 trials: 200/125 mg and 200/83 mg of LUM and IVA. 200/125 mg strength is the to be marketed formulation. The normalized exposure comparison was similar between the two strengths based on inter-individual comparison (Table 34). Please refer to review by Office of New Drug Quality Assessment (ONDQA) for further details regarding formulation changes.

Table 34. Summary of Results of LUM/IVA Pharmacokinetic Parameters in healthy Subjects administered a single dose of LUM/IVA with food

Analyte	FDC strength (mg)	Dose (mg)	N	AUC_{inf} (ng.h/mL)	Normalized AUC_{inf} /dose (ng.h/mL/mg)	Cmax (ng/mL)	Normalized Cmax (ng/mL/mg)
LUM	200/125	400/250	14	565000	1412.5	22400	56
	200/83	600/250	14	766000	1276.7	36000	60
IVA	200/125	400/250	14	18700	74.8	1490	6.0
	200/83	600/250	14	16400	65.6	1540	6.2

(Source – Table 11-1, 11-2, 11-3, 11-4, Study VX809-012 report)

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?

Lumacaftor and its major human metabolite, M28-lumacaftor; Ivacaftor, and its metabolites M1 and M6, were measured in plasma and urine samples using the LC-MS/MS bioanalytical methods.

Analytical method for LUM and M28-LUM in plasma: report # E100

An analytical method was developed and validated for the determination of lumacaftor and M28-lumacaftor in K3 EDTA or K2 EDTA human plasma (Module 5.3.1.4/Report

(b) (4)

[redacted]

Analytical method for LUM and M28-LUM in plasma: report # E053

An analytical method was developed and validated for the determination of ivacaftor, M1-ivacaftor, and M6-ivacaftor in K3 EDTA or K2 EDTA human plasma (Report E053).

(b) (4)

[redacted]

Table 35: Analytical Method Validation Reports for Lumacaftor and M28-Lumacaftor

Report Number Date of Report	Analyte/Matrix Linear Range of Quantitation	Purpose	Laboratory
E100 VX-809-DMPK-VAL-001 14APR2009	Lumacaftor and M28-Lumacaftor[a]/Human Plasma 2.00 to 2000 ng/mL	First validation	Vertex
6438-860 15MAY2009	Lumacaftor/Human Plasma[b] 2.00 to 2000 ng/mL	CRO initial validation	(b) (4)
6438-846 15MAY2009	Lumacaftor/Human Urine 2.00 to 2000 ng/mL	Matrix change	
I079 8252560 20MAR2012	Lumacaftor and M28-Lumacaftor/Human Plasma[b] 2.00 to 2000 ng/mL	Added M28-lumacaftor	
J107 8283376 23AUG2013	Lumacaftor and M28-Lumacaftor/Human Plasma[b] 100 to 100000 ng/mL (lumacaftor); 10.0 to 10000 ng/mL (M28-lumacaftor)	Extended range	
J108 8284755 23AUG2013	Lumacaftor and M28-Lumacaftor/Human Plasma[b] 2.00 to 2000 ng/mL	Repeated validation to include additional potential interference /matrix effects (comedication, hemolysis, hyperlipidemia, etc.)	
J025 7589.022813 13DEC2013	Lumacaftor and M28-Lumacaftor/Human Plasma[b] 2.00 to 2000 ng/mL	Repeated validation at (b) (4) CRO	
J185 7695.031513 26FEB2014	Lumacaftor and M28-Lumacaftor/Human Plasma[b] 50.00 to 50000 ng/mL (lumacaftor); 5.00 to 5000 ng/mL (M28-lumacaftor)	Repeated validation with extended validation range	
K164 8397.053014 04JUN2014	Lumacaftor and M28-Lumacaftor/Human Plasma[c] 50.0 to 50000 ng/mL and 2.00 to 2000 ng/mL (lumacaftor); 5.00 to 5000 ng/mL and 2.00 to 2000 ng/mL (M28-lumacaftor)	Cross validation between 2 validation ranges	

CRO: contract research organization; M28-lumacaftor: VRT-0995096, hydroxypyrrolidone VX-809, metabolite of VX-809; NA: not applicable.

Note: Study 001 also quantitated lumacaftor in urine. The validated method (E142: VX-809-DMPK-VAL-008) was disqualified; however, results from Study 004 indicate that the renal clearance of lumacaftor is negligible (Section 3.7.1).

[a] M28-lumacaftor was first quantified by a validated method in Study 005 (Report E100 Addendum 3).

[b] Validation also included sample collection stability in whole blood (Section 2.4 and Section 3.7.3.1).

[c] Report K164 was a cross validation of bioanalytical methods with the specified range of quantitation.

(Source – Table 6, Section 2.7.1, Summary of Biopharmaceutic Studies)

Table 36: Analytical Method Validation Reports for Ivacaftor, M1-Ivacaftor, and M6-Ivacaftor

Report Number Date of Report	Analyte/Matrix Linear Range of Quantitation	Purpose	Laboratory
E053 VX-770-DMPK-VAL-033 20MAY2009	Ivacaftor, M1-, and M6-Ivacaftor/Human Plasma[a] 2.00 to 2000 ng/mL	Full validation	Vertex
J109 8284343 23AUG2013	Ivacaftor, M1-, and M6-Ivacaftor/Human Plasma[a] 2.00 to 2000 ng/mL (ivacaftor and M1-ivacaftor); 10.0 to 10000 ng/mL (M6-ivacaftor)	CRO initial validation	(b) (4)
J026 7587.022812 29JAN2014	Ivacaftor, M1-, and M6-Ivacaftor/Human Plasma[a] 2.00 to 2000 ng/mL (ivacaftor and M6-ivacaftor); 1.82 to 1820 ng/mL (M1-ivacaftor)	CRO initial validation	
K164 8397.053014 04JUN2014	Ivacaftor, M1-, and M6-Ivacaftor/Human Plasma[b] 2.00 to 2000 ng/mL (ivacaftor and M6-ivacaftor); 1.82 to 1820 ng/mL and 2.00 to 2000 ng/mL (M1-ivacaftor)	Cross validation	

CRO: contract research organization; M1-ivacaftor: VRT-837018, hydroxymethyl-VX-770, metabolite of VX-770; M6-ivacaftor: VRT-842917, carboxy-VX-770, VX-770 acid, metabolite of VX-770.

[a] Validation also included sample collection stability in whole blood (Section 2.4 and Section 3.7.3.1).

[b] Report K164 was a cross validation of bioanalytical methods with the specified range of quantitation.

(Source – Table 7, Section 2.7.1, Summary of Biopharmaceutic Studies)

2.9.2 Which metabolites have been selected for analysis and why?

Metabolite M28 for lumacaftor; M1 and M6 for ivacaftor were selected for analysis because these were the predominant metabolites formed in humans (see section 2.5.8).

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

For all analytes, total (bound + unbound) concentrations were measured.

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

Analytical methods used to measure LUM and M28-LUM in different studies are listed in Table 35. Analytical methods used to measure IVA, M1-IVA and M6-IVA in different studies are listed in Table 36. Brief description of methods for analysis of LUM and M28-LUM; IVA, M1, and M6 in plasma is provided in section 2.9.1. The remaining methods were similar to the original methods, validated in CRO or different sites.

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?

LUM

The standard curve range or linear range of quantification for different methods used for analysis is shown in Table 35. Calibration curves were generated for peak area ratios using a weighted (1/ concentration^2) linear least-squares regression curve fitting method.

IVA

The standard curve range or linear range of quantification for different methods used for analysis is shown in Table 36. Calibration curves were generated for peak area ratios using a weighted (1/ concentration^2) linear least-squares regression curve fitting method.

2.9.5.1 What are the lower and upper limits of quantitation?

LUM and M28-LUM

As listed in Table 35, the lower limit of quantification (LLOQ) and upper limit of quantitation (ULOQ) were 2.00 ng/mL (most validation reports) and 100000 ng/mL (J107), respectively for lumacaftor.

IVA

As listed in Table 36, the lower limit of quantification (LLOQ) and upper limit of quantitation (ULOQ) were 2.00 ng/mL and 2000 ng/mL (most validation reports) , respectively for IVA.

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

All methods for LUM and IVA met the acceptance criteria summarized below:

- Standards should have back-calculated concentration within ±15.0% of nominal except at the LLOQ where ±20.0% of the nominal is acceptable.
- At least seventy-five percent (75%) of the standards should meet minimum accuracy requirements for the method.
- Within-run and between-run precision and accuracy: The overall bias must be within ±15.0% of the nominal value and the %CV must be ≤15.0%

Selectivity for LUM

Six low QCs spiked with standards of Rifampin, Ciprofloxacin, Itraconazole, IVA, M1-IVA and M6-IVA were analyzed to determine any effect on the determination of LUM in human plasma (J025). These samples met the acceptance criteria (±15% Bias and ≤15% CV) for LUM, demonstrating the method was selective for LUM in the intended concentration range. Selectivity was also assessed with analysis of LLOQ samples from six different lots of blank plasma. These samples met the acceptance criteria (±15% Bias and ≤15% CV), and no relevant interference between the analytes or the internal standards was observed.

Selectivity for IVA

Six low QCs spiked with standards of Rifampin, Ciprofloxacin, Itraconazole, LUM, and M28-LUM were analyzed to determine any effect on the determination of IVA in human plasma (J026). These samples met the acceptance criteria (±15% Bias and ≤15% CV) for IVA, demonstrating the method was selective for IVA in the intended concentration range. Selectivity was also assessed with analysis of LLOQ samples from six different lots of blank plasma. These samples met the acceptance criteria (±15% Bias and ≤15% CV), and no relevant interference between the analytes or the internal standards was observed.

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

The stability characteristics of lumacaftor and M28-lumacaftor in human plasma and urine are summarized in Table 37. The sample collection stability of lumacaftor and M28-lumacaftor in human whole blood was also confirmed at room temperature and under wet ice conditions for 2 hours and it was demonstrated that the presence of hemolyzed red blood cells (Report 8252560) or IVA/M1-IVA/M6-IVA (Report J025)in the human plasma did not affect the quantification of lumacaftor and M28-lumacaftor.

The lumacaftor and M28-lumacaftor stock solution stability in DMSO was established for 137 days at -80°C (Report J025).

Table 37. Stability Characteristics of Lumacaftor and M28-Lumacaftor in Human Plasma and Urine

	Demonstrated Stability of Lumacaftor and M28-Lumacaftor		
	Human Plasma		Human Urine
Conditions	**Lumacaftor**	**M28-Lumacaftor**	**Lumacaftor**
Bench-top stability (room temperature)	26 hours	26 hours	24 hours
Freeze-thaw stability (-10°C to -30°C and -60°C to -80°C)	6 cycles	6 cycles	5 cycles
Autosampler stability (2 to 8°C)	167 hours	167 hours	86 hours[a]
Long-term frozen stability (-10°C to -30°C and -60°C to -80°C)	368 days	368 days	182 days

Sources: Module 5.3.1.4/Report E100 Amendment 1 and Module 5.3.1.4/Report J108 for human plasma and Module 5.3.1.4/Report 6438-846 for human urine.
NA: not available.
[a] Value based on reinjection reproducibility when refrigerated.
(Source: Table 12, Summary of biopharm)

The stability characteristics of ivacaftor, M1-ivacaftor, and M6-ivacaftor in human plasma are summarized in Table 38 (Report E053 and J109). The sample collection stability of ivacaftor, M1-ivacaftor, and M6-ivacaftor in human whole blood was also confirmed at room temperature and under wet ice conditions for 2 hours and it was demonstrated that the presence of hemolyzed red blood cells or LUM/M28-LUM (Report J026) in the human plasma did not affect the quantification of ivacaftor, M1-ivacaftor, and M6-ivacaftor.

Table 38. Stability Characteristics of Ivacaftor, M1-Ivacaftor, and M6-Ivacaftor in Human Plasma

	Demonstrated Stability of Ivacaftor and Metabolites in Plasma		
	Human Plasma		
Conditions	**Ivacaftor**	**M1-Ivacaftor**	**M6-Ivacaftor**
Bench-top stability (room temperature)	27 hours	27 hours	27 hours
Freeze-thaw stability (-60°C or below)	6 cycles	6 cycles	6 cycles
Autosampler stability (4°C)	118 hours	118 hours	118 hours
Long-term frozen stability (-60°C or below)	633 days	633 days	633 days

(Source: Table 13, Summary of biopharm)

3. Detailed Labeling Recommendations

At the time of finalizing this review, labeling discussions within the review team are ongoing and information request from sponsor requested by the review team is pending. However, the revised labeling language based on the preliminary review is as below. Based on the clinical pharmacology review, most revisions are related to drug-drug interactions. In addition, the following information request was sent to the to the sponsor on 5/19/15:

"**a.** Update your clinical pharmacology section based on the draft guidance "Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products—Considerations, Content and Format."
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf)

b. You stated that "The exposure (AUC) of lumacaftor is approximately 2 fold higher in healthy adult volunteers compared to exposure in patients with CF." Provide the source study/data to support the claim in the label (not just general "see summary of clinical pharmacology").

c. Under distribution, you stated the (b) (4) for lumacaftor and ivacaftor. (b) (4) eplace this statement with Vd_ss in CF subjects."

DRUG INTERACTIONS

(b) (4)

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4. Appendix

4.1. Appendix – Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

Application Number	NDA 206038
Submission Date	
Compound	Lumacaftor/Ivacaftor Fixed Dose Combination (FDC)
Dosing regimen (route of administration)	400 mg Lumacaftor/250 mg Ivacaftor BID (oral administration)
Dose strengths	Tablets: Lumacaftor 200 mg/ Ivacaftor 125 mg
Indication	Treatment of cystic fibrosis in patients age 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.
Clinical Division	DPARP
Primary PM Reviewer	Anshu Marathe, Ph.D., Luning Zhuang, Ph.D.
Secondary PM Reviewer	Yaning Wang, Ph.D.

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

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

1.1.1.1 Based on the dose/exposure-response relationship, is the proposed dose and dosing regimen for the fixed dose combination (FDC) product of Lumacaftor/Ivacaftor (400 mg Lumcaftor/ 250 mg Ivacaftor BID) acceptable?

Yes, the proposed dose and dosing regimen in patients is acceptable, if the treatment effects (benefit/risk) are clinically acceptable. The basis for dose/dosing regimen selection and findings from phase 2 and phase 3 trials is discussed below.

Dose-Response for Efficacy:

Lumacaftor: In a phase 2 study (study 102), a range of lumacaftor doses/regimens (200 mg QD, 400 mg QD, 600 mg QD, 400 mg BID) were administered in combination with 250 mg BID of Ivacaftor. The lumacaftor 600 mg QD/ ivacaftor 250 mg BID regimen demonstrated a significant improvement in FEV1 from baseline (**Table 39**). The lumacaftor 400mg BID/ivacaftor 250 mg BID arm also demonstrated significant improvement in FEV1 and the response was similar to the lumacaftor 600 mg QD/ ivacaftor 250 mg BID arm. The study design does not allow for a robust assessment of dose-response of lumacaftor in combination setting because the combination therapy was preceded by lumacaftor monotherapy where a dose-dependent decline in FEV1 was observed. This resulted in various dosing groups in combination setting with different FEV1 at the start of therapy.

In the phase 3 studies, there was no clear differentiation between the two regimens (lumacaftor 600 mg QD/ ivacaftor 250 mg and lumacaftor 400 mg BID/ ivacaftor 250 mg) in terms of percent predicted FEV1 as observed from data from studies 103, 104 and 105 (**Figure 16** and **Figure 17**). In terms of pulmonary exacerbation through week 24, there appears to be a trend for improved response in the lumacaftor 400 mg BID/ ivacaftor 250 mg arm compared to the lumacaftor 600 mg QD/ ivacaftor 250 mg arm as shown in **Figure 18**.

Thus from an efficacy perspective similar efficacy in terms of FEV1 and pulmonary exacerbation for the lumacaftor 400 mg BID regimen compared to lumacaftor 600 mg QD regimen, the sponsors's proposed regimen for lumacaftor (400 mg BID) in the FDC appears reasonable. This is conditional on whether the clinical team assesses the efficacy to be clinically meaningful. Additionally the 400 mg BID regimen is advantageous in terms of simplifying the dosing regimen that might increase patient compliance.

Ivacaftor: A range of doses for ivacaftor in combination therapy was not studied, thus it is unclear if the selected ivacaftor dose (250 mg BID) is optimal from an efficacy perspective. The dose, however, would be acceptable if the efficacy achieved in the phase 3 trials is deemed to be clinically meaningful.

Although the proposed dose is higher than the currently approved dose of 150 mg BID in cystic fibrosis patients with G551D mutation who are treated with ivacaftor alone, the

ivacaftor exposures at the 250 mg BID dose in combination with lumacaftor is expected to be much lower compared to exposures in a monotherapy setting due to drug-drug interaction (**Figure 19**). Exposure-response relationship in monotherapy setting suggested a trend for increase in FEV1 with increasing steady state concentration of ivacaftor (see section 3.1).

Dose-Response for Safety:
Lumacaftor: The phase 2 study is limited in terms of short duration and small sample size to draw any meaningful conclusions regarding safety at various lumacaftor dose levels. In the phase 3 study, no meaningful difference is observed in adverse events between the treatment arms except for nasopharyngytis which was slightly higher in the lumacaftor 400 mg BID arm versus lumacaftor 600 mg QD arm (13% versus 6.2%) as shown in **Table 40**. No meaningful difference were observed in grade 3 or grade 4 events between the treatment arms. In general the clinical team has concluded that the safety profile of the 400 mg BID lumacaftor/250 mg BID ivacaftor arm is acceptable (for details please see Clinical Review).
With respect to ivacaftor, the exposures at the 250 mg BID dose in combination with lumacaftor is much lower compared to exposures that were achieved in monotherapy setting in previously conducted trials in cystic fibrosis patients with G551D mutation or F508del mutation (**Figure 19**) where the safety profile for ivacaftor was deemed acceptable(for details see Dr. Durmowicz review in DARRTs dated 01/27/2012)

Table 39: Absolute change in Percent Predicted from FEV1 in Phase 2 study (study 102)

Absolute Change in Percent Predicted FEV_1 by ANCOVA, Full Analysis Set (Cohort 2 and Cohort 3 Pooled)

Treatment[a]	Absolute Change[b] LS Mean	*P* Value	Treatment Difference (vs. Placebo)[c] Difference (95% CI)	*P* Value
Absolute change from Day 28 at Day 56				
Combination Placebo (Pooled)	-1.57	0.244	NA	NA
200 mg LUM qd + 250 mg IVA q12h	1.96	0.169	3.53 (-0.32, 7.38)	0.072
400 mg LUM qd + 250 mg IVA q12h	1.99	0.171	3.56 (-0.35, 7.47)	0.074
600 mg LUM qd + 250 mg IVA q12h	6.15	<0.001	7.72 (3.75, 11.70)	<0.001
600 mg LUM qd + 250 mg IVA q12h (Heterozygotes)	2.29	0.147	3.86 (-0.27, 7.99)	0.067
400 mg LUM q12h + 250 mg IVA q12h	6.09	0.004	7.66 (2.74, 12.59)	0.003
Absolute change from Baseline at Day 28				
Monotherapy Placebo (Pooled)	-0.03	0.985	NA	NA
200 mg LUM qd	0.21	0.889	0.24 (-3.72, 4.20)	0.906
400 mg LUM qd	-1.35	0.380	-1.32 (-5.35, 2.70)	0.515
600 mg LUM qd	-2.62	0.090	-2.60 (-6.67, 1.47)	0.209
600 mg LUM qd (Heterozygotes)	-3.82	0.020	-3.79 (-7.99, 0.41)	0.076
400 mg LUM q12h	-4.52	0.032	-4.50 (-9.46, 0.47)	0.076
Absolute change from Baseline at Day 56				
Combination Placebo (Pooled)	-2.02	0.178	NA	NA
200 mg LUM qd + 250 mg IVA q12h	1.82	0.248	3.84 (-0.42, 8.09)	0.077
400 mg LUM qd + 250 mg IVA q12h	0.64	0.688	2.66 (-1.66, 6.99)	0.225
600 mg LUM qd + 250 mg IVA q12h	3.59	0.027	5.61 (1.21, 10.01)	0.013
600 mg LUM qd + 250 mg IVA q12h (Heterozygotes)	-1.68	0.334	0.34 (-4.23, 4.91)	0.884
400 mg LUM q12h + 250 mg IVA q12h	2.16	0.344	4.18 (-1.27, 9.63)	0.131

ANCOVA: analysis of covariance; CI: confidence interval; IVA: ivacaftor; LS: least squares; LUM: lumacaftor; NA: not applicable; q12h: every 12 hours; qd: once daily; vs: versus

Baseline: Baseline was defined as the last measurement before initial dosing of study drug.

[a] Homozygous and heterozygous subjects who received placebo (monotherapy or combination) in Cohort 2 and Cohort 3 were pooled. For all other treatment groups, values for homozygous subjects are shown unless otherwise indicated.

[b] Change is estimated by the LS mean change from baseline (or Day 28), obtained from the ANCOVA model: Change = Treatment + Baseline (or Day 28) + Baseline Age.

[c] Difference between treatments for the LS mean change from baseline (or Day 28), obtained from the ANCOVA model.

Source: Table in synopsis of sponsor's CSR for study 102

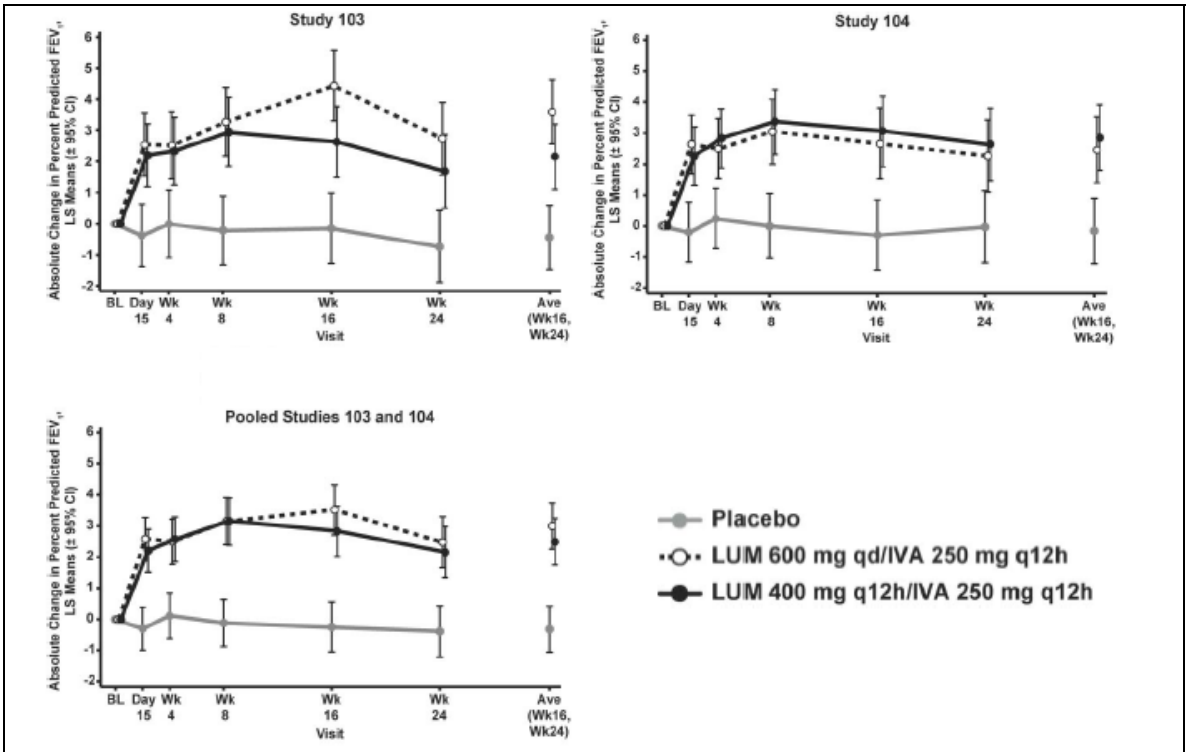


Figure 16: Absolute change in percent predicted FEV1 by visit in study 103, study 104 and pooled studies 103 and 104 (Phase 3)
Source: Figure 2 of the Summary of Efficacy

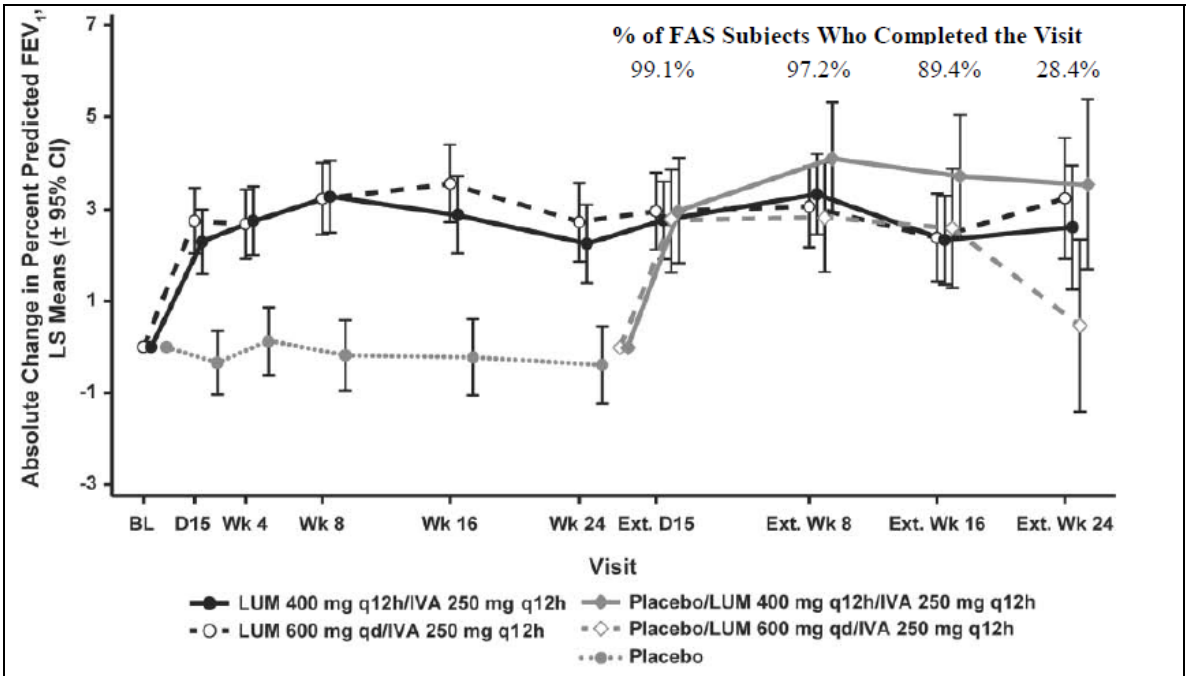


Figure 17: Absolute change in percent predicted FEV1 by visit in study 105 (Uncontrolled rollover study)
Source: Figure 9 of the Summary of Efficacy

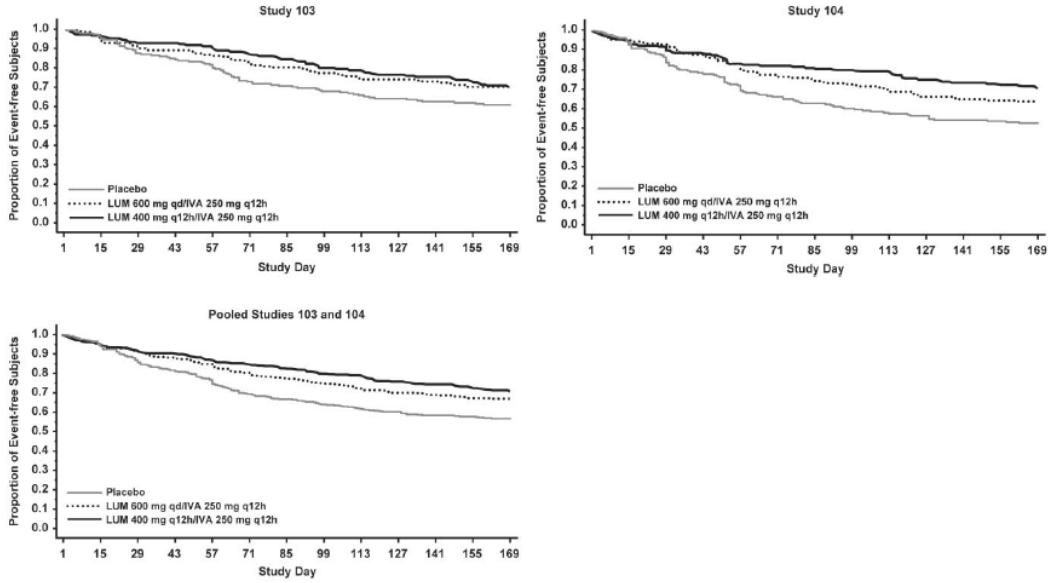


Figure 18: Pulmonary Exacerbation through Week 24.
Source: Figure 4 of the Summary of Efficacy

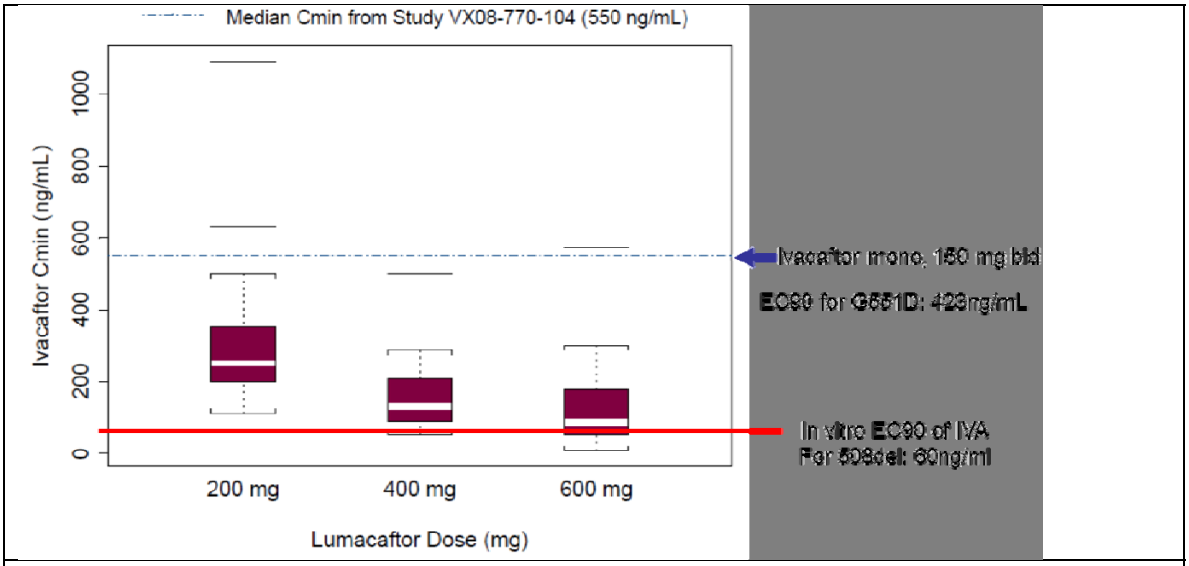


Figure 19: Ivacaftor exposures with increased lumacaftor exposures in study 102
Source: Figure 13 of Sponsor's End-of-Phase 1 briefing package

Table 40: Summary of Adverse Event by Treatment Groups in Pooled Placebo Controlled Phase 3 studies (study 103 and study 104)

Preferred Term	Placebo N = 370 n (%)	LUM/IVA LUM 600 mg qd/ IVA 250 mg q12h N = 369 n (%)	LUM/IVA LUM 400 mg q12h/ IVA 250 mg q12h N = 369 n (%)	LUM/IVA Total LUM/IVA N = 738 n (%)
Subjects with any AEs	**355 (95.9)**	**356 (96.5)**	**351 (95.1)**	**707 (95.8)**
Infective pulmonary exacerbation of cystic fibrosis	182 (49.2)	145 (39.3)	132 (35.8)	277 (37.5)
Cough	148 (40.0)	121 (32.8)	104 (28.2)	225 (30.5)
Headache	58 (15.7)	58 (15.7)	58 (15.7)	116 (15.7)
Sputum increased	70 (18.9)	55 (14.9)	54 (14.6)	109 (14.8)
Dyspnoea	29 (7.8)	55 (14.9)	48 (13.0)	103 (14.0)
Haemoptysis	50 (13.5)	52 (14.1)	50 (13.6)	102 (13.8)
Diarrhoea	31 (8.4)	36 (9.8)	45 (12.2)	81 (11.0)
Nausea	28 (7.6)	29 (7.9)	46 (12.5)	75 (10.2)
Respiration abnormal	22 (5.9)	40 (10.8)	32 (8.7)	72 (9.8)
Nasopharyngitis	40 (10.8)	23 (6.2)	48 (13.0)	71 (9.6)
Oropharyngeal pain	30 (8.1)	44 (11.9)	24 (6.5)	68 (9.2)
Pyrexia	34 (9.2)	35 (9.5)	33 (8.9)	68 (9.2)
Fatigue	29 (7.8)	30 (8.1)	34 (9.2)	64 (8.7)
Upper respiratory tract infection	20 (5.4)	24 (6.5)	37 (10.0)	61 (8.3)
Abdominal pain	32 (8.6)	26 (7.0)	33 (8.9)	59 (8.0)
Nasal congestion	44 (11.9)	33 (8.9)	24 (6.5)	57 (7.7)
Viral upper respiratory tract infection	25 (6.8)	28 (7.6)	23 (6.2)	51 (6.9)
Rhinitis	18 (4.9)	30 (8.1)	16 (4.3)	46 (6.2)
Flatulence	11 (3.0)	20 (5.4)	24 (6.5)	44 (6.0)
Blood creatine phosphokinase increased	20 (5.4)	14 (3.8)	27 (7.3)	41 (5.6)
Rash	7 (1.9)	16 (4.3)	25 (6.8)	41 (5.6)
Sinusitis	19 (5.1)	24 (6.5)	16 (4.3)	40 (5.4)
Rhinorrhoea	15 (4.1)	17 (4.6)	21 (5.7)	38 (5.1)
Vomiting	11 (3.0)	21 (5.7)	16 (4.3)	37 (5.0)
Influenza	8 (2.2)	16 (4.3)	19 (5.1)	35 (4.7)
Abdominal pain upper	18 (4.9)	22 (6.0)	12 (3.3)	34 (4.6)
Constipation	21 (5.7)	12 (3.3)	14 (3.8)	26 (3.5)
Pulmonary function test decreased	20 (5.4)	9 (2.4)	3 (0.8)	12 (1.6)

Source: Module 5.3.5.3/VX-809 ISS/Table 2.2.2.4.
AE: adverse event; IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours; qd: daily.
Note: A subject with multiple events within a preferred term category were counted only once in that category.

Source: Table 17 of Summary of Clinical Safety

1.1.1.2 Is the proposed dose and dosing regimen for the fixed dose combination (FDC) product of Lumacaftor/Ivacaftor (400 mg Lumcaftor/ 250 mg Ivacaftor BID) acceptable for pediatrics of ages 12 to 17 years?

Yes, the proposed dose is reasonable from a clinical pharmacology perspective as the exposures achieved in pediatrics of ages 12-17 years is similar to adults. In the phase 3 trials (study 103 and 104), pediatric patients accounted for 26% of the patients enrolled in each arm (**Table 41**). The observed trough concentrations achieved in the phase 3 trials in

pediatrics and adults were similar (**Figure 20** and **Table 42**). Additionally the efficacy in pediatric were similar to adults (data not shown). There was slightly higher incidence of headaches and abdominal pain in pediatrics compared to adults while other adverse events were generally comparable between the two groups (data not shown). Please see the clinical review for the assessment of the efficacy and safety in pediatrics patients compared to adults.

Table 41: Number of Subjects by Age Category in Pooled Placebo Controlled Phase 3 studies (study 103 and study 104)

Age Groups (years)	Number (%) of subjects in each group		
	Placebo N = 371	Lumacaftor 600 mg QD/ Ivacaftor 250 mg BID N = 368	Lumacaftor 400 mg BID/ Ivacaftor 250 mg BID N=369
12 to < 18	96 (25.9%)	96 (26.1%)	98 (26.6%)
≥ 18	275 (74.1%)	272 (73.9%)	271 (73.4%)
Source: Table 12 in Summary of Clinical Efficacy			

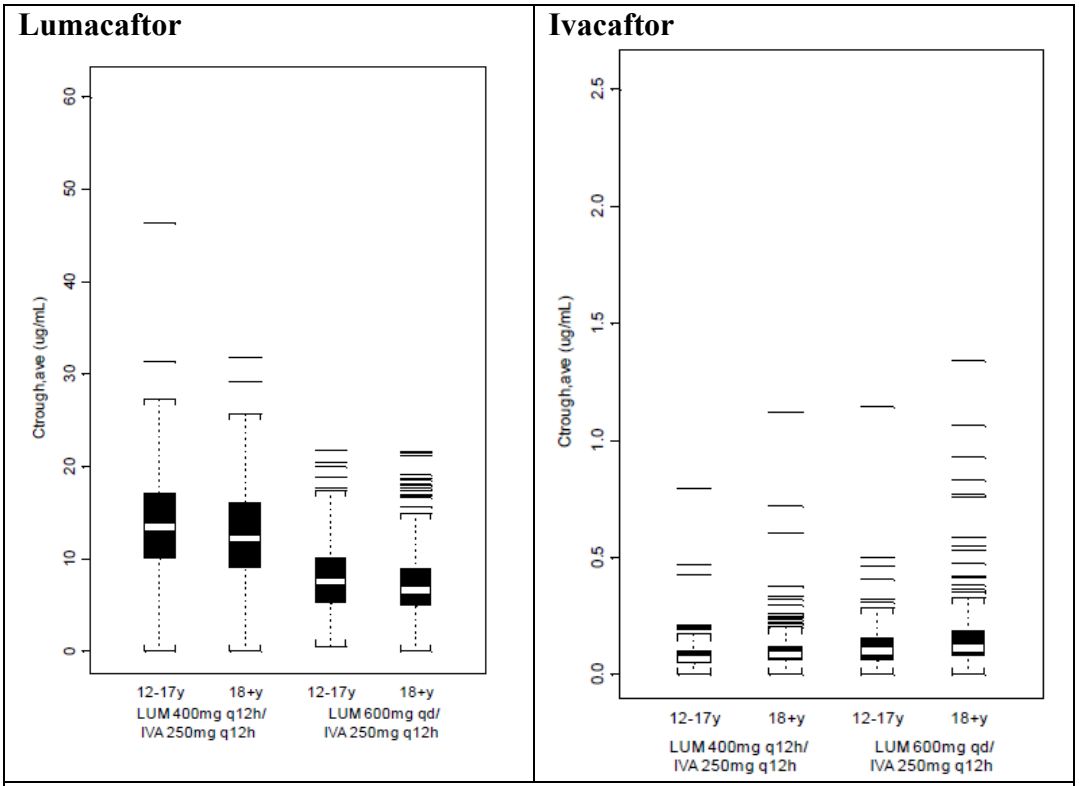


Figure 20: Lumacaftor and Ivacaftor Ctrough by Age Group
Source: Figure 9-9 and 9-10 of sponsor's pharmacokinetic study report (report # k272)

Table 42: Lumacaftor and Ivacaftor Ctrough by Age Group (study 103 and study 104)

Age Groups (years)	Median Ctrough (ug/ml)			
	Lumacaftor 600 mg QD/ Ivacaftor 250 mg BID		Lumacaftor 400 mg BID/ Ivacaftor 250 mg BID	
	LUM Ctrough (ug/ml)	IVA Ctrough (ug/ml)	LUM Ctrough (ug/ml)	IVA Ctrough (ug/ml)
12 to < 18	7.54	0.102	13.4	0.069
≥ 18	6.62	0.114	12.2	0.086
Source: Reviewer's Analysis				

1.2 Recommendations

Division of Pharmacometrics has reviewed NDA 206038 and finds the NDA acceptable provided an agreement regarding the label language can be reached between the sponsor and the Agency.

1.3 Label Statements

The following are the labeling recommendations relevant to clinical pharmacology for NDA 206038. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

12.3 Pharmacokinetics

The exposure (AUC) of lumacaftor is approximately 2-fold higher in healthy adult volunteers compared to exposure in patients with CF. The exposure of ivacaftor is similar between healthy adult volunteers and patients with CF.

Distribution

Lumacaftor is approximately 99% bound to plasma proteins, primarily to albumin. After oral administration of (b) (4) mg every (b) (4) in a fed state, (b) (4)

Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin. (b) (4)

Elimination

(b) (4)

The (b) (4) half-life is approximately 26 hours. The typical

apparent clearance, CL/F (CV), of lumacaftor was estimated to be 2.38 L/hr (29.4%) for patients with CF.

(b) (4)

Special populations

(b) (4)

Reviewer's Comments:

- *The reviewer agrees to the pop PK based estimates of volume of distribution and clearance estimates in the label*
- *The labeling statements regarding gender effects are acceptable.*
- *It is unclear if sponsor's statement regarding 2-fold higher exposure is healthy subjects compared to CF patients is based on population PK analysis. See comments to be conveyed to sponsor below.*

Comment to the sponsor:

- *It is unclear if the statement regarding 2-fold higher exposure is healthy subjects compared to CF patients in the label is based on population PK analysis. Please provide the source or justification for this statement. Additionally your POP PK analysis suggested a 1.8 times higher bioavailability in healthy subjects compared to CF patients. Please provide additional information (e.g. cross trial comparisons from NCA analysis, physiological/pharmacological justification) for this finding to support your POP PK analysis and to rule out the possibility that this is contributed due to inter-study variability and study design difference.*

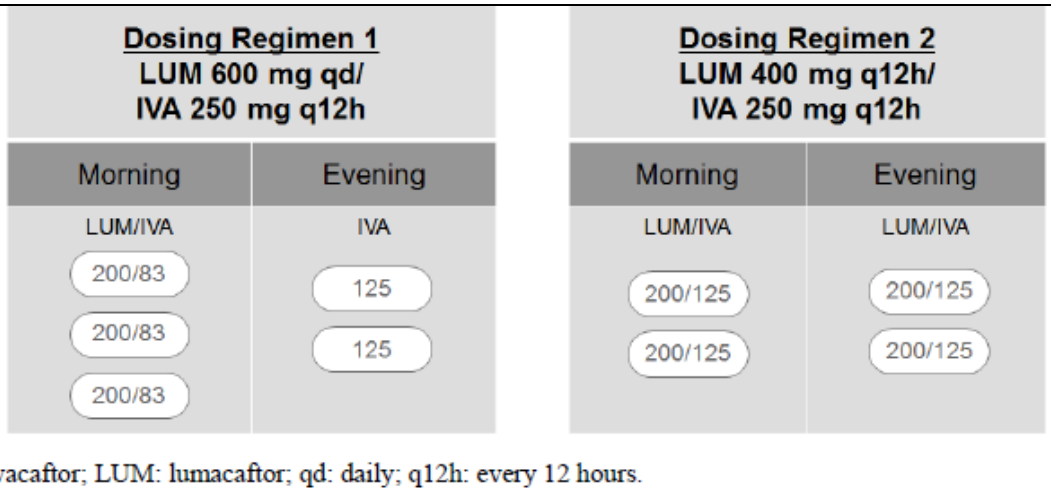
2 RESULTS OF SPONSOR'S ANALYSIS

2.1 Sponsor's Dose Selection Rationale for Phase 3 studies

Phase 2 studies demonstrated proof of concept that pharmacologic modulation of CFTR function through treatment with lumacaftor in combination with ivacaftor can result in clinical benefit in subjects who are homozygous for the F508del-CFTR mutation and hence lumacaftor in combination with ivacaftor dosing regimens were used throughout pivotal Phase 3 clinical studies. Results from Study 102 were used to select doses to be used in subsequent Phase 3 studies (Study 103, Study 104, and Study 105).

Two dosing regimens (Figure 21) were studied in Phase 3 clinical studies in order to determine the optimal clinical dose combination of lumacaftor and ivacaftor. The Phase 3

FDC regimens used both a LUM 200-mg/IVA 83-mg FDC tablet given in combination with an IVA 125-mg tablet and a LUM 200-mg/IVA 125-mg FDC tablet.



IVA: ivacaftor; LUM: lumacaftor; qd: daily; q12h: every 12 hours.

Figure 21: Schematic of dosing regimens used in sponsor's phase 3 trial.
Source: Figure 2 of summary of clinical pharmacology

2.1.1 Rationale for 600 mg QD and 400 mg BID dosage for Lumacaftor in Phase 3

Lumacaftor 600 mg QD: In study 102, a range of lumacaftor doses were administered in both monotherapy setting and in combination with ivacaftor. Table 43 shows the various treatment groups in relevant cohorts (cohort 2 and cohort 3) for dose selection from study 102. In the monotherapy setting from day 1 through day 28, 200 mg QD, 400 mg QD, 600 mg QD and 400 mg BID doses of lumacaftor were administered. Following that from day 29 through day 56, the ivacaftor 250 mg BID was administered in combination to the corresponding lumacaftor dose from the monotherapy setting. In the monotherapy setting, all treatment groups demonstrated except for 200 mg QD arm, a reduction in FEV1 was observed from baseline during the 28-day period of lumacaftor administration (**Table 39**). In fact a trend for further decrease in FEV1 was observed with increasing doses. In contrast, during the 28-day period of combination therapy, an increase in FEV1 was observed in the active treatment cohorts, while a decrease in FEV1 was observed in the placebo group as shown by the absolute change in FEV1 from day 28 at day 56. The Lumacaftor 600 mg QD + Ivacaftor 250 mg BID regimen demonstrated a significant improvement in FEV1. In subjects who received Lumacaftor 200 and 400 mg QD in combination with Ivacaftor 250 mg BID, a smaller increase in FEV1 was observed during the period of combination therapy compared to Lumacaftor 600 mg QD + Ivacaftor 250 mg BID regimen. Thus the Lumacaftor 600 mg QD + Ivacaftor 250 mg BID regimen was selected for Phase 3.

Lumacaftor 400 mg BID: Nonclinical studies of lumacaftor in airway epithelial cells derived from patients with CF and other model cell systems demonstrated a sigmoidal exposure-response relationship and suggest that a sufficiently high level of lumacaftor must be maintained throughout the dosing interval to maintain CFTR correction. To explore the potential for an advantageous PK profile and additional efficacy beyond the LUM 600 mg qd regimen, a LUM 400 mg q12h/ IVA 250 mg q12h regimen was added

to the Phase 2 study (Cohort 3 of Study 102). The LUM 400 mg q12h/IVA 250 mg q12h regimen allows for an approximately 2-fold increase in the expected trough concentration relative to the LUM 600 mg qd regimen and reduced peak-to-trough ratio while incurring only a modest increase in the total daily dose and exposure of lumacaftor. The regimen of LUM 400 mg q12h/IVA 250 mg q12h was shown to be safe and efficacious in Cohort 3 of Study 102. Although the LUM 400 mg q12h regimen was not differentiated from the LUM 600 mg qd regimen in the Phase 2 study, both doses were studied in Phase 3 given the simplicity of the dosing regimen and the potentially advantageous PK profile of the former.

Table 43: Treatments included in Cohort 2 and Cohort 3 of Study 102

Cohort 2			
Groups	**Population**	**Monotherapy - Day 1 through Day 28**	**Combination Therapy - Day 29 through Day 56**
Group 1 (N=20)	Homozygous	Lumacaftor 200 mg QD	Lumacaftor 200 mg QD + Ivacaftor 250 mg BID
Group 2 (N=20)	Homozygous	Lumacaftor 400 mg QD	Lumacaftor 400 mg QD + Ivacaftor 250 mg BID
Group 3 (N=20)	Homozygous	Lumacaftor 600 mg QD	Lumacaftor 600 mg QD + Ivacaftor 250 mg BID
Group 4 (N=20)	Heterozygous	Lumacaftor 600 mg QD	Lumacaftor 600 mg QD + Ivacaftor 250 mg BID
Group 5 (N=20)	Homozygous or Heterozygous	Placebo	Placebo
Cohort 3			
Groups	**Population**	**Monotherapy - Day 1 through Day 28**	**Combination Therapy - Day 29 through Day 56**
Group 1 (N=10)	Homozygous	Lumacaftor 400 mg BID	Lumacaftor 400 mg BID + Ivacaftor 250 mg BID
Group 2 (N=3)	Homozygous	Placebo	Placebo

Source: Sponsor's synopsis of CSR for study 102

2.2 Population PK Analysis

Primary objective of sponsor's population PK analysis were:

1. Characterize the PK of lumacaftor in subjects with CF.
2. Characterize the PK of ivacaftor in subjects with CF when co-administered with lumacaftor.
3. Estimate the effects of individual-specific covariate factors (e.g., demographics, disease status) that are predictive of the unexplained random variability in lumacaftor and ivacaftor PK

2.2.1 Methods

The population PK analysis of lumacaftor and ivacaftor were based on phase 1 studies (VX08-809-005, VX10-809-006, VX13-809-011), phase 2a study (VX09-809-101), phase 2 study (VX09-809-102) and phase 3 studies (VX13-809-103, VX13-809-104). A brief description of the studies is provided in Appendix (section 4).

Population PK modeling was performed in two steps. First, PK models were fit to Phase 1/2 data sets. After obtaining satisfactory model fits for Phase 1/2, individual exposures for Phase 3 were either by Bayesian analysis with informative priors derived from the Phase 1/2 analysis, or by fixing population parameters and estimating random effects to obtain individual parameters.

2.2.2 Results

Lumacaftor Phase 1/2 Population PK:

- A two-compartment model with zero-order delivery to the absorption compartment and subsequent first-order absorption and an absorption lag time was chosen as the lumacaftor base structural model. The parameters of the final model are shown in Table 44.
- An allometric model was used to fix the relationship between PK parameters and body weight. Body weight was an important predictor of variability in lumacfator CL/F. Based on the model, lumacaftor CL/F was 39% and 131% of the reference value of 2.38 L/h for the typical 20 kg and 100 kg subject, respectively, when compared to the reference subject (70 kg).
- Lumacaftor CL/F decreased with increasing age, with a point estimate of -0.265 for the effect estimate. For the typical 12 year old, this translates to an 11% greater CL/F when compared to the reference 18 year old. For the typical 50 year old subject, this translates to a CL/F value that is 24% lower than the reference 18 year old.
- Lumacaftor bioavailability was 1.81 times higher in healthy subjects and D1 was increased by a factor of 1.34, while ka and ALAG were decreased by factors of 0.663 and 0.514, respectively.

Lumacaftor Phase 3 Population PK:

- A Bayesian population PK model with informative priors based on the Phase 1/2 analysis was constructed to fit to the sparse Phase 3 lumacaftor data. The parameters of the final model are shown in Table 45

Ivacaftor Phase 1/2 Population PK:

- A two-compartment model with zero-order delivery to the absorption compartment and subsequent first-order absorption was chosen as the ivacaftor base structural model.
- Lumacaftor is a CYP3A inducer and the effect on ivacaftor CL/F was accounted for by an induction model, where the activity of the enzyme governing clearance (A7) was modeled. Clearance of ivacaftor was assumed to be proportional to the enzyme's activity (A7 term in CL/F).

$$\frac{dA_7}{dt} = K_{enz} \cdot (1 + SLOPE_{enz} \cdot C_p) - K_{enz} \cdot A_7$$

- where enzyme production rate (KENZ) is the enzyme production rate, the degree of change in induction with change in exposure of lumacaftor (SLOPEENZ) is the linear slope of the lumacaftor effect on enzyme induction, and Cp is the predicted lumacaftor concentration.
- An allometric model was used to fix the relationship between PK parameters and body weight. Body weight was an important predictor of variability in ivacaftor CL/F. Ivacaftor CL/F was 39% and 131% of the reference value of 25.1 L/h for the typical 20 kg and 100 kg subject, respectively, when compared to the reference subject (70 kg).
- Ivacaftor bioavailability was 1.53 times higher in healthy subjects. The reason for this is not known, since prior analyses have indicated that bioavailability in CF subjects is equivalent when comparing healthy subjects to CF subjects. Studies 011 and 102 are the only two studies contributing ivacaftor data. Since the study population of 011 was small, it is likely that Study 102 is affecting the overall estimate. It is possible that the bioavailability difference can be attributed to inter-study variability.

Ivacaftor Phase 3 Population PK:

- A Bayesian population PK model with informative priors based on the Phase 1/2 analysis was constructed to fit to the sparse Phase 3 ivacaftor data. The parameters of the final model are shown in Table 45

Reviewer's comments:

- *The sponsor's lumacaftor population PK model characterizes the data for phase 1/2 studies and phase 3 studies reasonably well as observed from sponsor's* goodness of fit plots (Figure 22and Figure 23).
- *The sponsor's ivacaftor population PK model characterizes the data for phase 1/2 reasonably well as observed from sponsor's goodness of fit plots (Figure 24). However the model does not adequately characterize the data for Phase 3 studies as bias is observed in the goodness of fit plots (Figure 25).*

- *The sponsor's analysis shows that ivacaftor bioavailability was 1.53 times higher in healthy subjects compared to patients. This is not consistent with the currently approved label for ivacaftor which states that the PK of ivacaftor is similar in CF patients and healthy subjects. As stated by the sponsor, it is likely that the bioavailability difference can be attributed to inter-study variability.*
- *The sponsor's analysis shows that lumacaftor bioavailability was 1.8 times higher in healthy subjects compared to patients. The mechanism for this observed difference is unclear. See section 1.3 for comment to sponsor in this regard.*
- *Since the sponsor's used an allometric model to fix the relationship between PK parameters and body weight, it is unclear the inter-individual variability on clearance that is explained by bodyweight.*
- *Although age is identified as a covariate for lumacaftor clearance, the changes in exposure due to age effect is modest and does not require a dose adjustment.*

Table 44: Parameter estimates of the final population PK model for lumacaftor for phase 1 and 2 studies

Description	Model	Estimate	%RSE	Variability
apparent oral clearance	$CL/F \sim \theta_1 \cdot (WT/70)^{0.75} \cdot (AGE/18)^{\theta 13} \cdot e^{\eta_1}$	2.38 L/h	0.675	
central volume of distribution	$V_c/F \sim \theta_2 \cdot (WT/70)^{1.0} \cdot e^{\eta_2}$	23.5 L	0.103	
peripheral volume of distribution	$V_p/F \sim \theta_3 \cdot (WT/70)^{1.0} \cdot e^{\eta_3}$	33.3 L	0.289	
intercompartmental clearance	$Q/F \sim \theta_4 \cdot (WT/70)^{0.75} \cdot e^{\eta_4}$	3.65 L/h	4.42	
zero-order absorption rate constant	$D1 \sim \theta_5 \cdot \theta_{10}^{HEALTHY} \cdot e^{\eta_5}$	0.701 h	9.38	
first-order absorption rate constant	$K_a \sim \theta_6 \cdot \theta_{11}^{HEALTHY} \cdot e^{\eta_6}$	0.314 h^{-1}	4.85	
lag time	$ALAG \sim \theta_7 \cdot \theta_{12}^{HEALTHY} \cdot e^{\eta_7}$	0.455 h	3.53	
disease status on bioavailability	$HEALTHY - F1 \sim \theta_9$	1.81	0.564	
disease status on D1	$HEALTHY - D1 \sim \theta_{10}$	1.34	0.145	
disease status on Ka	$HEALTHY - Ka \sim \theta_{11}$	0.633	0.119	
disease status on ALAG	$HEALTHY - ALAG \sim \theta_{12}$	0.514	3.70	
age effect on CL/F	$AGE - CL/F \sim \theta_{13}$	-0.265	7.38	
interindividual variability of CL/F	$IIV_{CL/F} \sim \Omega_{1.1}$	0.0829	8.56	%CV = 29.4
interindividual CL-Vc covariance	$cov_{CL,Vc} \sim \Omega_{2.1}$	0.0163	85.1	CORR = 0.123
interindividual variability of Vc/F	$IIV_{Vc/F} \sim \Omega_{2.2}$	0.213	18.5	%CV = 48.7
interindividual CL-Vp covariance	$cov_{CL,Vp} \sim \Omega_{3.1}$	0.0280	27.2	CORR = 0.326
interindividual Vc-Vp covariance	$cov_{Vc,Vp} \sim \Omega_{3.2}$	0.0761	24.6	CORR = 0.554
interindividual variability of Vp/F	$IIV_{Vp/F} \sim \Omega_{3.3}$	0.0889	11.9	%CV = 30.5
interindividual CL-Q covariance	$cov_{CL,Q} \sim \Omega_{4.1}$	0.00867	161	CORR = 0.0881
interindividual Vc-Q covariance	$cov_{Vc,Q} \sim \Omega_{4.2}$	0.0236	143	CORR = 0.150
interindividual Vp-Q covariance	$cov_{Vp,Q} \sim \Omega_{4.3}$	0.0214	73.9	CORR = 0.210
interindividual variability of Q/F	$IIV_{Q/F} \sim \Omega_{4.4}$	0.117	35.9	%CV = 35.2
interindividual CL-D1 covariance	$cov_{CL,D1} \sim \Omega_{5.1}$	-0.00365	312	CORR = -0.0433
interindividual Vc-D1 covariance	$cov_{Vc,D1} \sim \Omega_{5.2}$	-0.00196	1250	CORR = -0.0145
interindividual Vp-D1 covariance	$cov_{Vp,D1} \sim \Omega_{5.3}$	0.0253	53.6	CORR = 0.289
interindividual Q-D1 covariance	$cov_{Q,D1} \sim \Omega_{5.4}$	0.00293	985	CORR = 0.0293
interindividual variability of D1	$IIV_{D1} \sim \Omega_{5.5}$	0.0860	33.5	%CV = 30.0
interindividual CL-Ka covariance	$cov_{CL,Ka} \sim \Omega_{6.1}$	0.0132	171	CORR = 0.0916
interindividual Vc-Ka covariance	$cov_{Vc,Ka} \sim \Omega_{6.2}$	-0.0107	389	CORR = -0.0466
interindividual Vp-Ka covariance	$cov_{Vp,Ka} \sim \Omega_{6.3}$	-0.0153	190	CORR = -0.103
interindividual Q-Ka covariance	$cov_{Q,Ka} \sim \Omega_{6.4}$	0.00134	3530	CORR = 0.00787
interindividual D1-Ka covariance	$cov_{D1,Ka} \sim \Omega_{6.5}$	-0.000432	10100	CORR = -0.00295
interindividual variability of Ka	$IIV_{Ka} \sim \Omega_{6.6}$	0.249	56.2	%CV = 53.2
interindividual CL-ALAG covariance	$cov_{CL,ALAG} \sim \Omega_{7.1}$	0.0117	133	CORR = 0.0727
interindividual Vc-ALAG covariance	$cov_{Vc,ALAG} \sim \Omega_{7.2}$	0.0642	62.9	CORR = 0.248
interindividual Vp-ALAG covariance	$cov_{Vp,ALAG} \sim \Omega_{7.3}$	0.0240	75.8	CORR = 0.144
interindividual Q-ALAG covariance	$cov_{Q,ALAG} \sim \Omega_{7.4}$	0.00923	362	CORR = 0.0483
interindividual D1-ALAG covariance	$cov_{D1,ALAG} \sim \Omega_{7.5}$	0.0335	111	CORR = 0.204
interindividual KA-ALAG covariance	$cov_{Ka,ALAG} \sim \Omega_{7.6}$	-0.00886	752	CORR = -0.0317
interindividual variability of ALAG	$IIV_{ALAG} \sim \Omega_{7.7}$	0.314	22.5	%CV = 60.7
interoccasion variability in bioavailability	$IOV_{F1} \sim \Omega_{8.8}$	0.139	4.26	%CV = 38.6
interoccasion variability in first-order absorption	$IOV_{Ka} \sim \Omega_{16.16}$	1.09	15.6	%CV = 141
interoccasion variability in lag time	$IOV_{ALAG} \sim \Omega_{20.20}$	0.280	13.1	%CV = 56.8
interoccasion variability in zero-order absoprtion	$IOV_{D1} \sim \Omega_{24.24}$	NA	NA	%CV = NA
proportional error	$err_{prop} \sim \Sigma_{1.1}$	0.0483	0.865	%CV = 22.0
additive error	$err_{add} \sim \Sigma_{2.2}$	240	1.69	SD = 15.5

Source: Table 5 from population PK and ER report (report # k050).

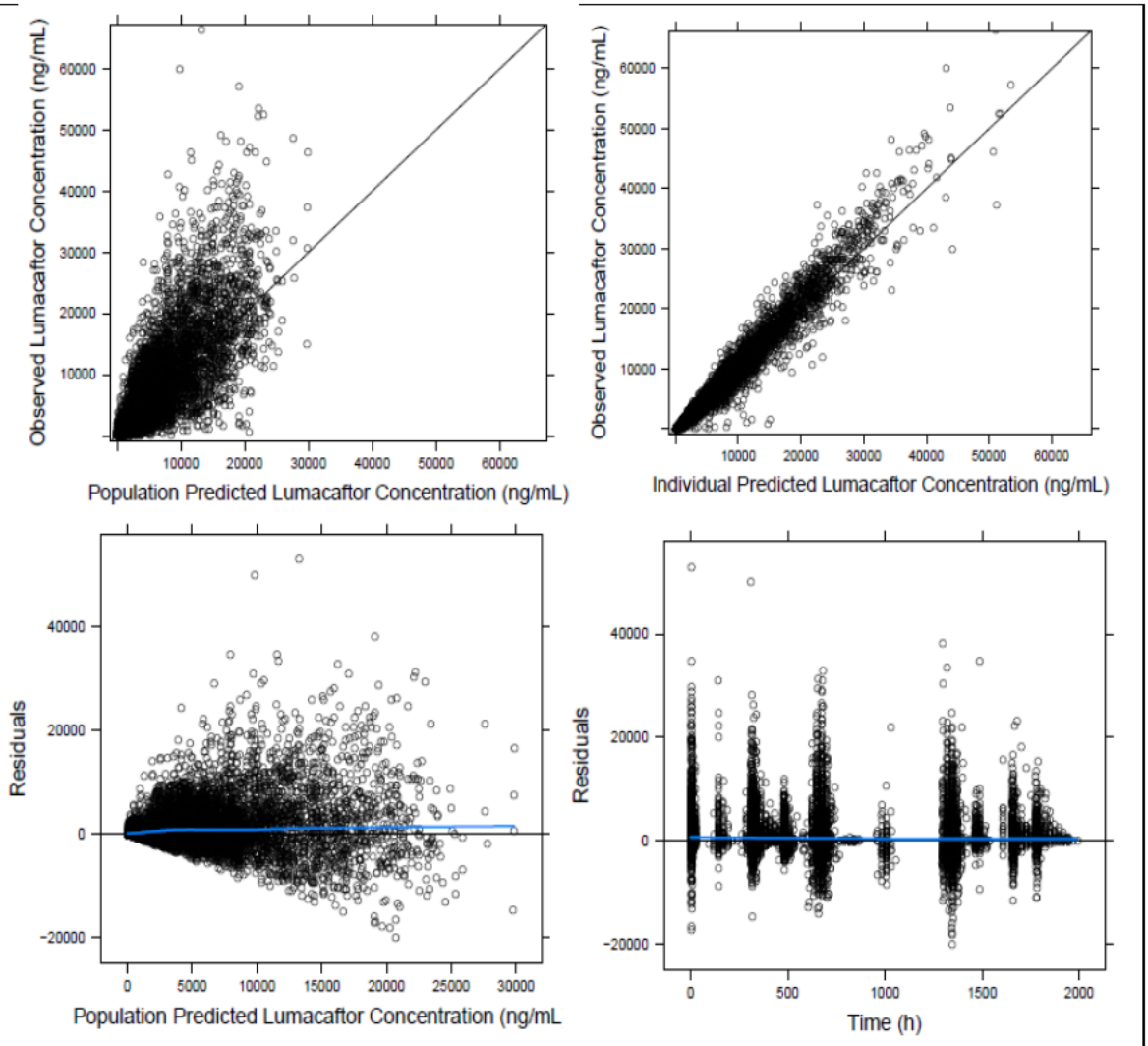


Figure 22: Goodness of fit plots for final model for Phase 1/2 of lumacaftor. Source: Figure 12, 13, 14 and 16 from population PK and ER report (report # k050).

Table 45: Parameter estimates of the final population PK model for lumacaftor for phase 3 studies

Description	Model	Estimate	95% CI	Variability
apparent oral clearance	$CL/F \sim \theta_1 \cdot (WT/70)^{0.75} \cdot (AGE/18)^{\theta 13} \cdot e^{\eta_1}$	2.31 L/h	(2.29,2.33)	
central volume of distribution	$V_c/F \sim \theta_2 \cdot (WT/70)^{1.0} \cdot e^{\eta_2}$	23.4 L	(23.3,23.6)	
peripheral volume of distribution	$V_p/F \sim \theta_3 \cdot (WT/70)^{1.0} \cdot e^{\eta_3}$	32.6 L	(32.1,33.4)	
intercompartmental clearance	$Q/F \sim \theta_4 \cdot (WT/70)^{0.75} \cdot e^{\eta_4}$	2.39 L/h	(2.19,2.59)	
zero-order absorption rate constant	$D1 \sim \theta_5 \cdot \theta_{10}^{HEALTHY} \cdot e^{\eta_5}$	0.440 h	(0.419,0.465)	
first-order absorption rate constant	$K_a \sim \theta_6 \cdot \theta_{11}^{HEALTHY} \cdot e^{\eta_6}$	0.711 $h^{-}1$	(0.652,0.768)	
lag time	$ALAG \sim \theta_7 \cdot \theta_{12}^{HEALTHY} \cdot e^{\eta_7}$	0.679 h	(0.651,0.705)	
age effect on CL/F	$AGE - CL/F \sim \theta_8$	-0.166	(-0.199,-0.134)	
interindividual variability of CL/F	$IIV_{CL/F} \sim \Omega_{1.1}$	0.0749	(0.0670,0.0834)	%CV = 27.9
interindividual CL-Vc covariance	$cov_{CL,Vc} \sim \Omega_{2.1}$	0.0327	(0.0220,0.0439)	CORR = 0.257
interindividual variability of Vc/F	$IIV_{Vc/F} \sim \Omega_{2.2}$	0.216	(0.189,0.247)	%CV = 49.1
interindividual CL-Vp covariance	$cov_{CL,Vp} \sim \Omega_{3.1}$	0.0339	(0.0254,0.0433)	CORR = 0.398
interindividual Vc-Vp covariance	$cov_{Vc,Vp} \sim \Omega_{3.2}$	0.0848	(0.0690,0.103)	CORR = 0.586
interindividual variability of Vp/F	$IIV_{Vp/F} \sim \Omega_{3.3}$	0.0969	(0.0826,0.114)	%CV = 31.9
interindividual CL-Q covariance	$cov_{CL,Q} \sim \Omega_{4.1}$	0.0125	(0.00317,0.0220)	CORR = 0.135
interindividual Vc-Q covariance	$cov_{Vc,Q} \sim \Omega_{4.2}$	0.0281	(0.0124,0.0442)	CORR = 0.179
interindividual Vp-Q covariance	$cov_{Vp,Q} \sim \Omega_{4.3}$	0.0235	(0.0120,0.0356)	CORR = 0.223
interindividual variability of Q/F	$IIV_{Q/F} \sim \Omega_{4.4}$	0.114	(0.0984,0.132)	%CV = 34.7
interindividual CL-D1 covariance	$cov_{CL,D1} \sim \Omega_{5.1}$	-0.00188	(-0.0104,0.00658)	CORR = -0.0233
interindividual Vc-D1 covariance	$cov_{Vc,D1} \sim \Omega_{5.2}$	-0.000717	(-0.0156,0.0143)	CORR = -0.00537
interindividual Vp-D1 covariance	$cov_{Vp,D1} \sim \Omega_{5.3}$	0.0271	(0.0163,0.0387)	CORR = 0.295
interindividual Q-D1 covariance	$cov_{Q,D1} \sim \Omega_{5.4}$	0.00374	(-0.00683,0.0147)	CORR = 0.0375
interindividual variability of D1	$IIV_{D1} \sim \Omega_{5.5}$	0.0869	(0.0742,0.102)	%CV = 30.1
interindividual CL-Ka covariance	$cov_{CL,Ka} \sim \Omega_{6.1}$	0.00313	(-0.00965,0.0159)	CORR = 0.0233
interindividual Vc-Ka covariance	$cov_{Vc,Ka} \sim \Omega_{6.2}$	-0.0333	(-0.0574,-0.00979)	CORR = -0.145
interindividual Vp-Ka covariance	$cov_{Vp,Ka} \sim \Omega_{6.3}$	-0.0259	(-0.0435,-0.00968)	CORR = -0.168
interindividual Q-Ka covariance	$cov_{Q,Ka} \sim \Omega_{6.4}$	-0.00611	(-0.0237,0.0111)	CORR = -0.0364
interindividual D1-Ka covariance	$cov_{D1,Ka} \sim \Omega_{6.5}$	0.000444	(-0.0159,0.0162)	CORR = 0.00308
interindividual variability of Ka	$IIV_{Ka} \sim \Omega_{6.6}$	0.245	(0.211,0.285)	%CV = 52.7
interindividual CL-ALAG covariance	$cov_{CL,ALAG} \sim \Omega_{7.1}$	0.0178	(0.00270,0.0333)	CORR = 0.117
interindividual Vc-ALAG covariance	$cov_{Vc,ALAG} \sim \Omega_{7.2}$	0.0722	(0.0444,0.102)	CORR = 0.280
interindividual Vp-ALAG covariance	$cov_{Vp,ALAG} \sim \Omega_{7.3}$	0.0299	(0.0111,0.0493)	CORR = 0.173
interindividual Q-ALAG covariance	$cov_{Q,ALAG} \sim \Omega_{7.4}$	0.0188	(-0.000509,0.0393)	CORR = 0.100
interindividual D1-ALAG covariance	$cov_{D1,ALAG} \sim \Omega_{7.5}$	0.0305	(0.0131,0.0489)	CORR = 0.187
interindividual KA-ALAG covariance	$cov_{Ka,ALAG} \sim \Omega_{7.6}$	-0.0132	(-0.0435,0.0155)	CORR = -0.0479
interindividual variability of ALAG	$IIV_{ALAG} \sim \Omega_{7.7}$	0.307	(0.263,0.357)	%CV = 59.9
interoccasion variability in bioavailability	$IOV_{F1} \sim \Omega_{8.8}$	0.131	(0.127,0.136)	%CV = 37.4
interoccasion variability in first-order absorption	$IOV_{Ka} \sim \Omega_{16.16}$	0.906	(0.829,0.989)	%CV = 121
interoccasion variability in lag time	$IOV_{ALAG} \sim \Omega_{20.20}$	0.296	(0.829,0.989)	%CV = 58.7
proportional error	$err_{prop} \sim \Sigma_{1.1}$	0.000738	(8.92e-07,0.00319)	%CV = 2.72
additive error	$err_{add} \sim \Sigma_{2.2}$	1.47e+07	(1.34e+07,1.60e+07)	SD = 3830

Source: Table 8 from population PK and ER report (report # k050).

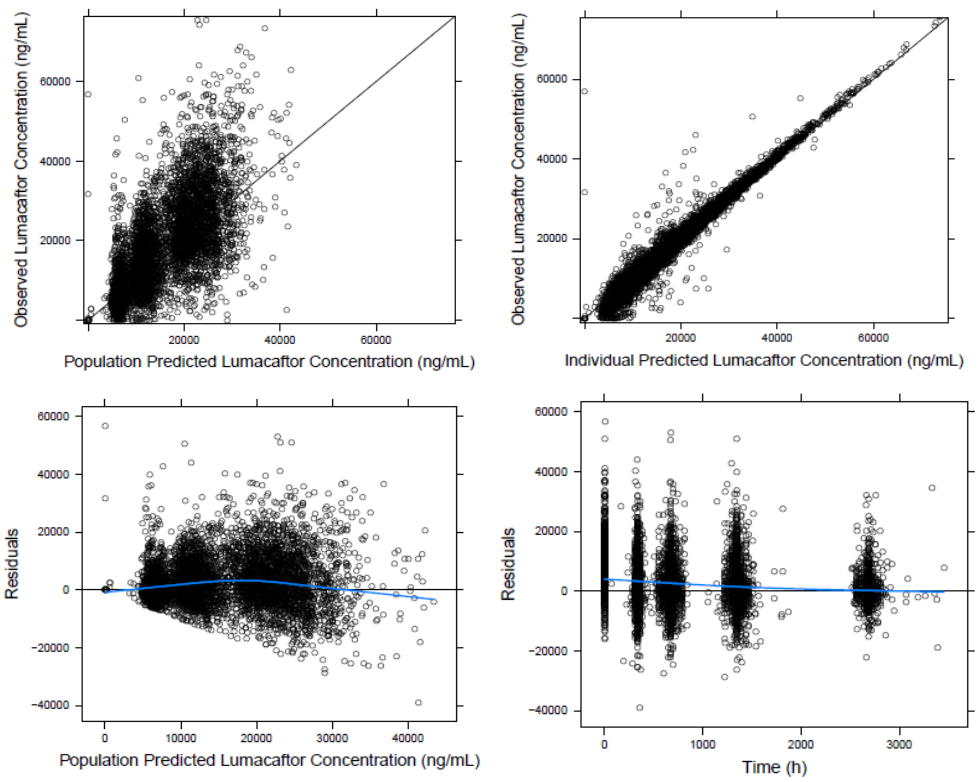


Figure 23: Goodness of fit plots for final model for Phase 3 of lumacaftor. Source: Figure 99, 100, 101 and 103 from population PK and ER report (report # k050).

Table 46: Parameter estimates of the final population PK model for ivacaftor for phase 1 and 2 studies

Description	Model	Estimate	%RSE	Variability
apparent oral clearance	$CL/F \sim \theta_1 \cdot (WT/70)^{0.75} \cdot e^{\eta_1}$	25.1 L/h	4.15	
central volume of distribution	$V_c/F \sim \theta_2 \cdot (WT/70)^{1.0} \cdot e^{\eta_2}$	95.0 L	4.46	
peripheral volume of distribution	$V_p/F \sim \theta_3 \cdot (WT/70)^{1.0} \cdot e^{\eta_3}$	201 L	5.46	
intercompartmental clearance	$Q/F \sim \theta_4 \cdot (WT/70)^{0.75}$	23.9 L/h	10.5	
zero-order absorption rate constant	$D1 \sim \theta_5 \cdot e^{\eta_4}$	2.18 h	5.63	
first-order absorption rate constant	$K_a \sim \theta_6$	0.255 h^{-1}	3.49	
first-order rate of enzyme production	$K_{enz} \sim \theta_7$	0.0418 h^{-1}	8.41	
slope of linear function for induction	$SLOPE_{enz} \sim \theta_8$	0.224 mL/ng	3.50	
effect of healthy subject status on bioavailability	$HEALTHY_F \sim \theta_9$	1.53	5.87	
interindividual variability of CL/F	$IIV_{CL/F} \sim \Omega_{1.1}$	0.152	11.8	%CV = 40.5
interindividual CL-Vc covariance	$cov_{CL,Vc} \sim \Omega_{2.1}$	0.135	18.4	CORR = 0.683
interindividual variability of Vc/F	$IIV_{Vc/F} \sim \Omega_{2.2}$	0.255	19.7	%CV = 53.9
interindividual CL-Vp covariance	$cov_{CL,Vp} \sim \Omega_{3.1}$	0.0350	41.6	CORR = 0.343
interindividual Vc-Vp covariance	$cov_{Vc,Vp} \sim \Omega_{3.2}$	0.0498	39.4	CORR = 0.377
interindividual variability of Vp/F	$IIV_{Vp/F} \sim \Omega_{3.3}$	0.0684	22.2	%CV = 26.6
interindividual variability of D1	$IIV_{D1} \sim \Omega_{4.4}$	0.0750	45.7	%CV = 27.9
interoccasion variability in bioavailability	$IOV_{F1} \sim \Omega_{6.6}$	0.187	5.57	%CV = 45.3
interoccasion variability in zero-order absorption	$IOV_{D1} \sim \Omega_{18.18}$	0.378	7.65	%CV = 67.8
proportional error	$err_{prop} \sim \Sigma_{1.1}$	0.0676	1.45	%CV = 26.0
additive error	$err_{add} \sim \Sigma_{2.2}$	34.5	6.25	SD = 5.87

Source: Table 7 from population PK and ER report (report # k050).

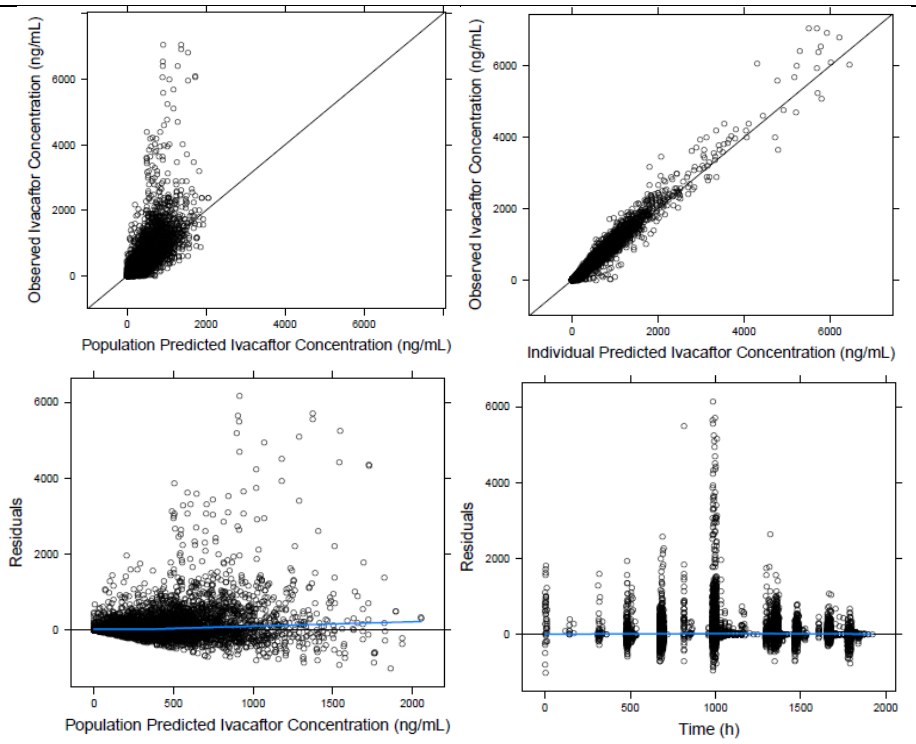


Figure 24: Goodness of fit plots for final model of ivacaftor. Source: Figure 62, 63, 64 and 66 from population PK and ER report (report # k050).

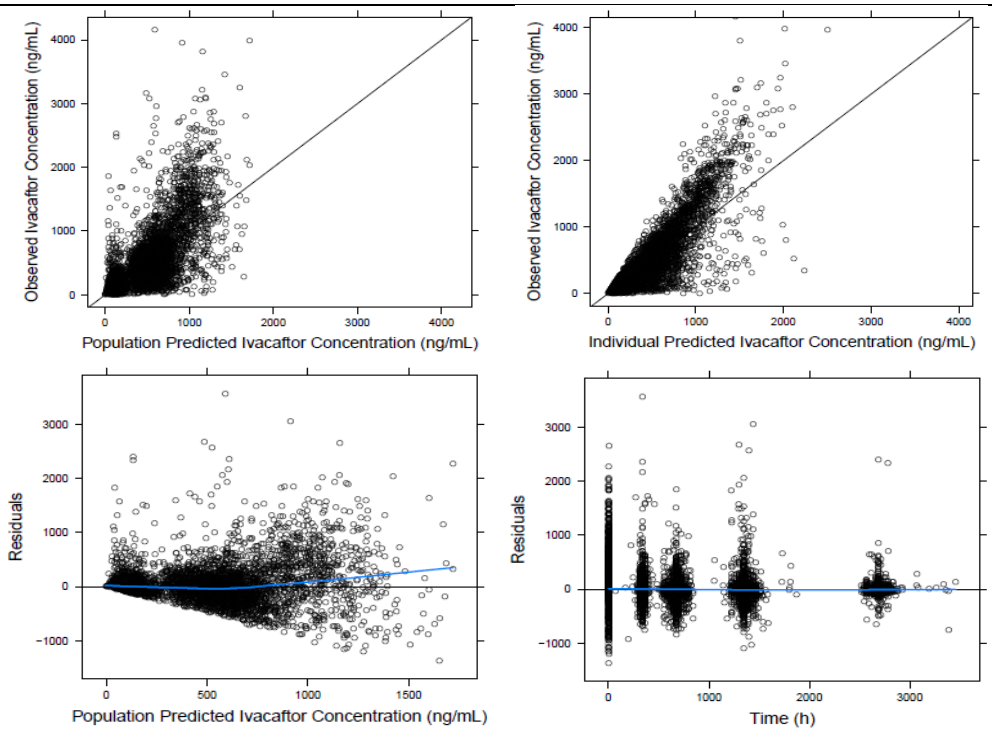


Figure 25: Goodness of fit plots for final model of ivacaftor. Source: Figure 125, 126, 127 and 129 from population PK and ER report (report # k050).

2.3 Exposure Response Analysis for Sweat Chloride (PD)

The objective of sponsor's analysis are:

1. Characterize the relationship between sweat chloride response and lumacaftor exposure in CF subjects treated with lumacaftor alone or with a combination of lumacaftor and ivacaftor;
2. Characterize the additional effect on sweat chloride response of ivacaftor when used in combination with lumacaftor;
3. Predict the average sweat chloride response to LUM 400 mg q12h/IVA 250 mg q12hand LUM 600 mg qd/IVA 250 mg q12h in Phase 3 studies VX12-809-103 and VX12-809-104, using average observed trough concentrations of lumacaftor from individual subjects.

2.3.1 Methods

The data for this pooled population PKPD analysis was obtained from two Phase 2 studies, VX08-809-101 and VX09-809-102 in which adult CF subjects were treated with lumacaftor alone or with lumacaftor in combination with ivacaftor, for periods varying between 3 and 8 weeks. Only data from CF subjects homozygous for the F508del-CFTR mutation were used.

The pooled analysis dataset used for the final structural and covariate model consisted of 837 sweat chloride concentration measurements from 189 subjects treated with lumacaftor or a combination of lumacaftor and ivacaftor.

Observed trough concentrations of lumacaftor (Ctrough) were used as the measure of exposure of lumacaftor because one of the objectives was to predict sweat chloride responses in the Phase 3 studies VX12-809-103 and VX12-809-104 using average observed Ctrough of lumacaftor. The other reason for focusing on observed lumacaftor trough concentrations was that predicted trough concentrations or AUC from a population PK model of lumacaftor resulted in model fits that were significantly worse.

2.3.2 Results

The final structural model for describing sweat chloride response consisted of an Emax model, parameterized by Emax and EC50, and an additional term, Ebase, which is the model-estimated sweat chloride baseline for each subject. The effect of the presence of ivacaftor on sweat chloride response was statistically significant and was described best by a multiplicative term (E770m) applied to Emax. The structural model is described by the equation below.

$$E = Ebase + E770m \times \frac{Emax \times C809}{EC50 + C809}$$

The parameters of the final model are shown in Table 47. The model fitting and scatter plot of observed sweat chloride responses versus lumacaftor concentrations with and without ivacaftor are shown in Figure 26.

Reviewer's comments:

- *Sponsor's population PD model for sweat chloride characterizes the data reasonably well as observed by the diagnostic plots (Figure 26).*
- *The model shows a greater reduction in sweat chloride with increasing lumacaftor concentrations and a slight increase in effect with the addition of ivacaftor. This is in general consistent with the overall findings from the study. A dose-dependent reduction in sweat chloride was observed during lumacaftor monotherapy with increasing lumacaftor dose in study 102 (Table 48). Also the addition of ivacaftor to lumacaftor monotherapy, caused a slightly further decline in sweat chloride.*
- *The results of the exposure-response analysis for sweat chloride should be viewed with caution because as stated in the FDA briefing package ,"it is not known, how and by what amount reductions in sweat chloride relate to clinical beneficial effects. However, as a generally accepted marker of the CFTR ion channel activity, a lack or low response in sweat chloride to an intervention would suggest a subsequent lack or decreased clinical benefit." This is also demonstrated in study 102. While lumacaftor monotherapy resulted in reduction in sweat chloride. This did not translate in terms on FEVI change where a dose dependent worsening of FEV1 was observed with lumacaftor monotherapy. Additionally from published literature (Durmowicz et al. 2013; CHEST, volume 143), it is known that decrease in sweat chloride is not correlated with improvement in FEV1. For the reasons mentioned above, an independent exposure-response analysis for sweat chloride was not conducted by the reviewer.*
- *The sponsor's final model included only pre-dose sweat chloride measurements. It should be noted that based on FDA briefing package the post-dose sweat chloride measurements did not show the additional effect of ivacaftor as was observed in pre-dose measurements.*

Table 47: Parameter estimates of the structural population PK-PD model for sweat chloride

Parameter	Units	Estimate	%RSE	Bootstrap 95% CI	IIV
Ebase	mmol/L	100.3	0.8	[99.0, 101.5]	9.1 (CV%)
E_{max}	mmol/L	-13.7	22.1	[-19.0, -8.4]	45.6 (CV%)
EC_{50}	µg/mL	4.5	34.8	[1.4, 7.5]	
E770m	-	1.42	9.9	[1.19, 1.65]	
Inter-individual variability					
ω^2 *Ebase*		0.00835	8.2	[.0061, .0106]	
ω^2 E_{max}		0.208	21.4	[.055, .362]	
Residual variance					
σ^2		37.2	3.7	[32.5, 41.9]	
Additive error SD					
	mmol/L	6.1			

Model: 8110. %RSE = relative standard error=|Standard Error/Estimate| *100 for *Ebase*, E_{max}, EC_{50} and *E770m*. RSE for ω^2 and σ^2 are reported on the approximate standard deviation scale (SE/variance estimate)/2. CI = Confidence Interval. IIV = Inter-Individual Variability. CV=Coefficient of Variation.

Source: Table 8-5 of sponsor's population PD report (report # k261)

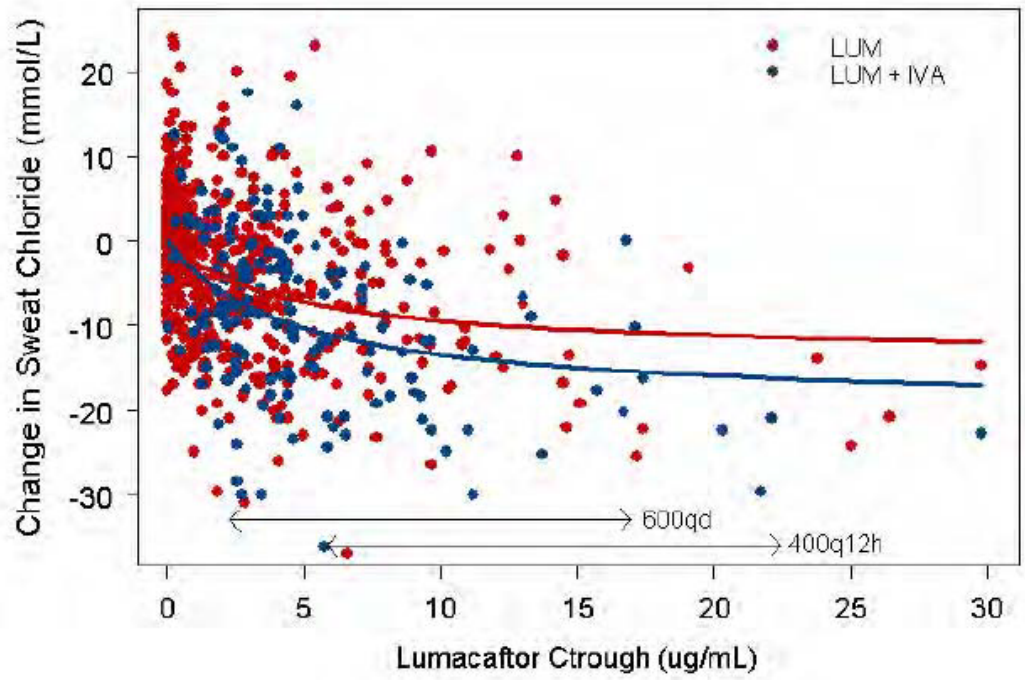
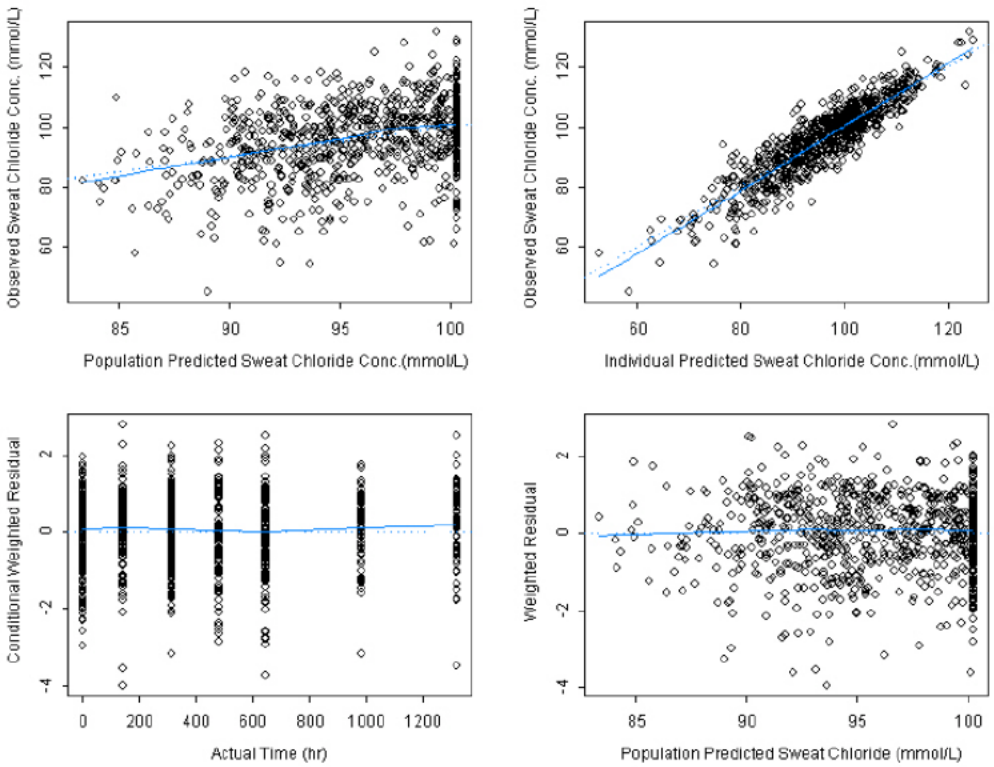


Figure 26: Change in sweat chloride versus lumacaftor concentration in phase 2 studies. Circles represent observed data and lines represent the population mean predictions.
Source: Figure 4 of summary of clinical pharmacology



Observed versus population predicted sweat chloride concentration (*top left*) and individual predicted sweat chloride concentration (*top right*) with smoothers (solid lines) and lines of identity (dashed lines) through the data. Conditional weighted residuals versus time (*bottom left*) and weighted residuals versus population predicted sweat chloride concentration (*bottom right*), with smoothers (solid line) and horizontals at y = 0 (dashed line). Model: 8110.

Figure 27: Goodness of fit plots for the structural model for population PD model of sweat chloride. Source: Figure 8-6 of sponsor's population PD report (report # k261)

Table 48: Change in sweat chloride (mmol/L) during Lumacaftor Monotherapy and Lumacaftor and Ivacaftor Combination therapy in Study 102

	Placebo (combined)	LUM 200mg qd	LUM 400mg qd	LUM 600mg qd	LUM 400mg q12h
Δ in sweat chloride (mmol/L) vs. placebo					
# of patients	26	21	19	20	10
Baseline to day 28 (lumacaftor alone) (95% CI)	--	-4.9 (-9.5, -0.28)	-8.3 (-13.0, -3.6	-6.1 (-11.0, -1.4)	-8.2 (-14.1, -2.3)
Days 28-56 (+ 250 mg ivacaftor) (95% CI)	--	-1.0 (-7.2, 5.3)	-2.5 (-8.9, 4.0)	-4.3 (-10.7, 2.1	-3.9 (-12.2, 4.4)
Baseline to day 56 (lumacaftor+ivacaftor) (95% CI)	--	-5.0 (-10.5, 0.48)	-9.8 (-15.3, -4.2)	-9.5 (-15.1, -3.9)	-11.0 (-18.3, -3.7)

Source: Table 2 of FDA Briefing document and Table 15 of summary of clinical pharmacology

2.4 Exposure Response Analysis for FEV1

The primary objective of the analysis was to describe the PK–pharmacodynamic (PD) relationship for the combination of lumacaftor and ivacaftor using percent predicted FEV1 (ppFEV1).

2.4.1 Methods

Following the development of the lumacaftor population PK model, individual predicted AUC0-24h, derived from the individual predicted CL/F obtained from the population PK analysis was implemented to describe the exposure response relationship for percent predicted FEV1. The analysis was carried out using absolute change from baseline ppFEV1. The effects of gender and age on linear slope of lumacaftor effect (SLOPE809) were also estimated.

$$\Delta ppFEV1(t)_{ij} = SLOPE_{809,i} \cdot AUC_{0-24}/1000 + \varepsilon_{ij}$$

$$SLOPE_{809,i} = SLOPE_{809} \cdot \theta_5^{FEMALE} \cdot e^{\eta_1} \qquad For\ AGE < 24$$

$$SLOPE_{809,i} = SLOPE_{809} \cdot (AGE/24)^{\theta_3} \cdot \theta_4^{FEMALE} \cdot e^{\eta_1} \qquad For\ AGE >= 24$$

The age effect was only estimated for subjects who were 24 years of age and older, since younger subjects displayed little age effect. The cutoff of 24 years was determined by a sensitivity analysis. The cutoff age was systematically changed over the range of 20-25 years and the model with the lowest objective function was chosen.
Initial modeling efforts were focused on describing the effects of ivacaftor on the lumacaftor exposure–response relationships. However, these attempts were unsuccessful resulting in problems with model fits (unsuccessful termination, unrealistic parameter estimates). This is likely due to the identifiability issues when trying to characterize the lumacaftor–ivacaftor interaction and the limited dose ranges studied in Phase 3. Therefore, a simplified approach was implemented where only lumacaftor exposures were used for PK–PD modeling.

2.4.2 Results

The models demonstrated a robust lumacaftor drug effect with a positive slope for the exposure-dependent effect; however, the trend for the exposure-dependence is mild and does not distinguish between the two regimens studied in Phase 3. The parameter estimates from the model are shown in Table 49.

Table 49: Parameter estimate from the exposure-response model for FEVI

Parameter Description	Parameter	Estimate	%RSE	95% CI	Variability
Slope of lumacaftor effect	SLOPE	0.00942 % /µg/mL	13.1	(0.00702, 0.0117)	
Age effect on slope	AGE_{SLOPE}	-3.17	25.4	(-5.35, -1.76)	
Female effect on slope	$FEMALE_{SLOPE}$	0.898	17.7	(0.625, 1.30)	
Interindividual variability of SLOPE	IIV_{SLOPE}	0.000225	9.46	(0.000181, 0.000270)	SD = 0.0150
Additive error	err_{add}	17.2	5.84	(15.3, 19.4)	

Source: Module 5.3.3.5/Report K050.
CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IIV = inter-individual variability; PD: pharmacodynamic; RSE: relative standard error.

Source: Table 27 of sponsor's clinical pharmacology summary

Reviewer's comments:

Sponsor's exposure response analysis for FEV1 does not account for the effect of ivacaftor on ppFEV1 and thus the results from this analysis cannot be interpreted meaningfully. It is known from reviewer's analysis of data from ivacaftor monotherapy study (VX08-770-104) that there is an increase in ppFEV1 with increasing ivacaftor concentrations. Additionally, sponsor's model would be unable to explain the dose-dependent decrease in FEV1 observed in lumacaftor monotherapy in phase 2.

3 RESULTS OF REVIEWER'S ANALYSIS- CONTRIBUTION OF INDIVIDIUAL COMPONENTS

3.1 Exposure Response Analysis for Ivacaftor Monotherapy

The objective of the exposure-response analysis was to characterize the relationship between ivacaftor exposure and ppFEV1 in monotherapy and combination therapy. An exploratory analysis was conducted to investigate the likely contribution of ivacaftor and lumacaftor in combination therapy.

3.1.1 Data/Methods

Data from the ivacaftor monotherapy study (VX08-770-104) and combination therapy (VX-809-103 and VX-809-104) was used for the analysis. The absolute change from baseline in ppFEV1 at week 16 was utilized for the analysis. For the monotherapy, the dataset included all patients (N=104 in treatment arm; N= 26 in placebo arm) who had efficacy measurement at week 16. For the combination therapy, the dataset included 341patients in 600 mg QD LUM/250 mg BID IVA arm and 342 patients in 400 mg BID LUM/250 mg BID IVA arm who had efficacy measurement at week 16 and observed ivacaftor steady state trough concentrations. All patients (N= 355) in the placebo arm who had efficacy measurement at week 16 were included. Four patients in the 600 mg QD LUM/250 mg BID IVA arm and two patients in the 400 mg BID LUM/250 mg BID IVA arm who had week 16 efficacy measurements could not be included as they did not have ivacaftor trough measurements.

Graphical exploration of the data was conducted by plotting the absolute change from baseline in ppFEV1 at week 16 versus steady state ivacaftor trough concentrations. The

data in the treatment arm were grouped by exposure quartiles. Additionally a linear and Emax models were explored to quantitatively describe the relationship of steady state ivacaftor trough concentrations and absolute change from baseline in ppFEV1 at week 16.

3.1.2 Results

The absolute change from baseline in ppFEV1 at week 16 versus steady state ivacaftor trough concentrations in ivacaftor monotherapy study (VX08-770-104) and lumacaftor /ivacaftor combination therapy studies (VX-809-103 and VX-809-104) are shown in Figure 28. The patients in the treatment arm were grouped based on their exposure quartile. For the monotherapy, a trend for increase in ppFEV1 is observed with increasing exposure quartile up to the third quartile. For the combination therapy, no trend was observed in the treatment arms and it appears that the response is likely in the plateau part of the exposure-response relationship. The ivacaftor exposure achieve in Phase 3 combination studies is significantly lower (~90 ng/ml for the LUM 400 mg BID/IVA 250 mg BID arm) than the exposures achieved in ivacaftor monotherapy study (~550 ng/ml). Low ivacaftor exposure would not account for the observed ppFEV1 in combination therapy; thereby suggesting lumacaftor might be contributing indirectly. Figure 28 shows that the exposure-response curve for combination therapy is shifted to the left compared to ivacaftor monotherapy. One possible hypothesis could be that lumacaftor reduces the EC_{50} for ivacaftor. This is also in agreement with *in vitro* findings.

To further explore the hypothesis that lumacaftor reduces ivacaftor EC_{50}, Emax model were investigated to quantitatively describe the relationship of steady state ivacaftor trough concentrations and ppFEVI. For the combination therapy, data from the placebo and 400 mg BID LUM/250 mg BID arm was used. The Emax model was limited by the uncertainty in parameter estimation. The standard errors associated with ivacaftor EC_{50} were large (Figure 29). Although numerically a reduction in EC_{50} was observed in combination therapy compared to monotherapy, given the large standard errors associated; it cannot be concluded from the model that lumacaftor reduced the EC_{50} of ivacaftor. Since the parameters of the Emax model could not be identified reliably, a linear structural model was also investigated. The multivariate regression analysis identified ivacaftor trough concentration as covariate for both monotherapy and combination therapy. However the slope in the combination therapy was driven by the placebo data (Figure 29).

The hypothesis that lumacaftor reduces the ivacaftor EC_{50} should be viewed in context that the overall efficacy in combination therapy was similar to the efficacy that was observed in monotherapy study. As stated in FDA's briefing book, the absolute change in ppFEV1 at week 16 in monotherapy (study 770-104) was 2.2 and in the LUM 400 mg BID/IVA 250 mg BID arm of the combination therapy studies (study 809-103 and study 809-104) was 2.6 and 2.8. Thus from a net effect perspective, the contribution of lumacaftor remains unclear because similar response could have been achieved with ivacaftor monotherapy; although at higher ivacaftor exposures. Based on the current ivacaftor label, the safety profile at these high exposures is acceptable.

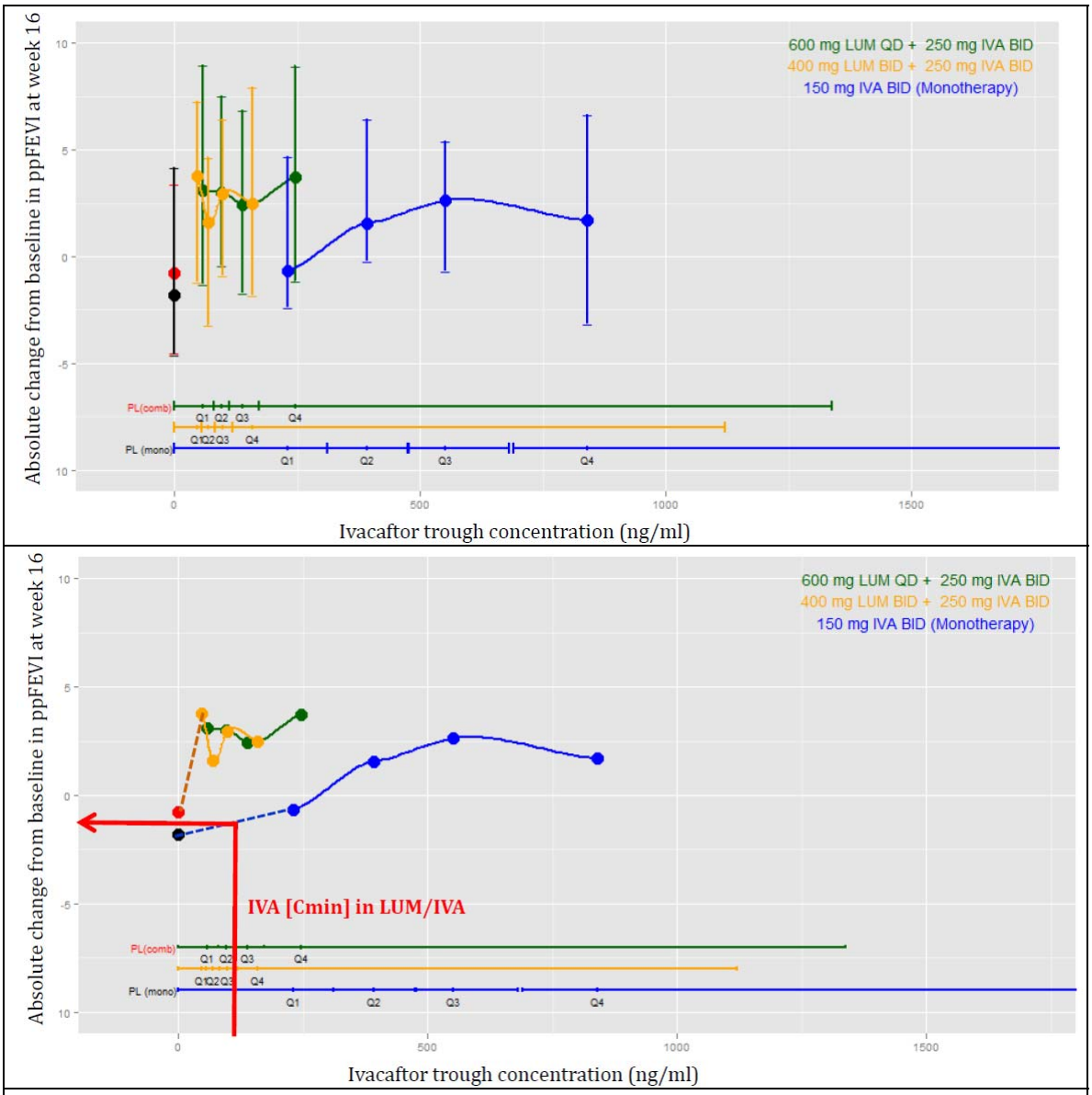


Figure 28: Absolute change from baseline in ppFEV1 at week 16 versus observed steady state ivacaftor trough concentrations in ivacaftor monotherapy (VX-770-104) and lumacaftor/ivacaftor combination therapy (VX-809-103 and VX-809-104). The symbols and vertical bars represent the median and interquartile range. The data in the treatment arm is grouped by ivacaftor exposure quartile. The horizontal bars show the range of ivacaftor exposures achieved in each quartile in the treatment arms. The data from the placebo arm in monotherapy and combination therapy are shown as black and red circles. The red arrow shows the ivacaftor exposures achieved in LUM/IVA combination studies and the likely response due to ivacaftor as such low exposures.

Ivacaftor monotherapy (VX-770-104)

Linear Model

Parameter	Estimate	SE	P-value
Intercept	3.85	4.12	0.352
Slope of IVA effect	0.0044	0.002	0.02
Age effect	-0.052	0.08	0.52
Baseline ppFEV1 effect	-0.038	0.035	0.282

Emax Model

Parameter	Estimate	SE	P-value
Emax	4.70	4.41	0.289
EC50	350	656	0.595
E0	-0.426	1.33	0.749

Lumacaftor/Ivacaftor combination therapy (VX-809-103 and VX-809-104)

Linear Model

Parameter	Estimate	SE	P-value
Intercept	10.2	1.673	<0.001
Slope of IVA effect	.0098	0.003	0.002
Age effect	-0.13	0.029	<0.001
Baseline ppFEV1 effect	-0.104	0.021	<0.001

Emax Model

Parameter	Estimate	SE	P-value
Emax	3.59	0.982	0.0003
EC50	10.5	21.1	0.618
E0	-0.420	0.382	0.273

Figure 29: Parameter estimates from the linear and Emax models in ivacaftor monotherapy (VX-770-104) and 400 mg BID lumacaftor/ 250 mg BID ivacaftor arm of the combination therapy (VX-809-103 and VX-809-104).

4 APPENDIX

Table 50: Description of studies used in Population PK Analysis

Study Number	Description	Planned Sample Size
VX08-809-005	A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Drug-Drug Interaction Study of VX-809 and VX-770 in Healthy Subjects	24
VX10-809-006	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation, Drug-Drug Interaction Study of VX-809 and VX 770 in Healthy Subjects	72
VX13-809-011	A Phase 1, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Lumacaftor in Combination With Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation	12
VX09-809-101	A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study of VX-809 to Evaluate Safety, Pharmacokinetics, and Pharmacodynamics of VX-	

	809 in Cystic Fibrosis Subjects Homozygous for the F508del- CFTR GeneMutation	
VX09-809-102	A Phase 2, Multicenter, Double-Blind, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of Lumacaftor Monotherapy, and Lumacaftor and Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTRMutation	293
VX13-809-103	A Phase 3, Randomized, Double Blind, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del CFTR Mutation	501
VX13-809-104	A Phase 3, Randomized, Double Blind, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Lumacaftor in CombinationWith Ivacaftor in Subjects Aged 12 Years and OlderWith Cystic Fibrosis, Homozygous for the F508del CFTRMutation	501

4.2. Appendix – Individual Study Review

INDIVIDUAL STUDY REVIEW

Note –

In this review, early development names VX809 and VRT-826809 are also used to refer to Lumacaftor (LUM), and VX770 is also used to refer to Ivacaftor (IVA). Majority of the clinical pharmacology studies for IVA have been previously reviewed in NDA 203188 (Dr. Lokesh Jain, review dated 01/18/2012).

ADME In-Vitro STUDIES

Absorption and Transporters

LUM

Report # DM-020

Title: BCS Potential, P-gp Substrate, and Inhibitor Assessment of VX-809

Objective:

- To assess the Biopharmaceutics Classification System (BCS) potential of VX-809.
- To assess if VX-809 is a P-gp substrate in Caco-2 cell monolayers.
- To determine the IC50 value of VX-809 towards digoxin transport in Caco-2 cells.

Method:

Permeability assessment according to BCS guidance

Permeability of VX809 was tested in AP-to-BL unidirectional permeability assays using Caco-2 cell monolayers. The VX809 concentration was 20µM (0.5% of the concentration of 400 mg LUM dissolved in 250mL) due to limited aqueous solubility. The internal control compounds, minoxidil and atenolol, were included in the unidirectional permeability experiment.

P-gp substrate assessment

The P-gp substrate assessment was performed with the bidirectional permeability. The potential for human P-glycoprotein (P-gp) to transport VX809 was investigated using Caco-2 test.

P-gp inhibitor assessment

The bi-directional transport of digoxin was measured in the absence and presence of a series of concentration of VX-809, cyclosporine A (CsA), and ketoconazole in Caco-2 cells. The purpose of this assay was to determine the effect of VX-809 on digoxin efflux transport.

Results:

Solubility

The measured solubility of VX-809 was approximately 2 and 100 µM at acidic and neutral conditions, respectively. (Table 51)

Table 51. Solubility of VX-809 in different buffers

Test	Matrix (pH)	Nominal Concentration (µM)	Measured Concentration of VX-809 (µM)			
			Replicate 1	Replicate 2	Replicate 3	Average ± SD
1	HBSSg (7.4)	2210	106	107	102	105 ± 2.65
2	USP Buffer (1.0)		2.23	2.45	2.86	2.51 ± 0.32
	USP Buffer (7.5)		124	133	205	154 ± 44

(source: Table 11, study report DM020)

Permeability

In the unidirectional permeability assay (AP-to-BL), Papp values of VX-809 from all three replicates ranged from 14.6 to 30.0 × 10^{-6} cm/s (Table 52). The results that the Papp values of VX-809 were higher than those of minoxidil indicate that VX-809 has high permeability. The Papp value of atenolol of each replicate was less than 1 × 10^{-6} cm/s, indicating that the integrity of cell monolayer remained intact during the assay period.

Table 52. Permeability and Recovery of VX-809 and Control Compounds (Unidirectional)

Compound Identification	Parameters	Replicate 1	Replicate 2	Replicate 3	Average ± SD
VX-809[1]	P_{app} (× 10^{-6} cm/s)	16.0	30.0	14.6	20.2 ± 8.6
	Recovery (%)	62.9	73.9	72.8	69.9 ± 6.0
Atenolol[1]	P_{app} (× 10^{-6} cm/s)	0.249	0.342	0.233	0.275 ± 0.06
Minoxidil[1]	P_{app} (× 10^{-6} cm/s)	4.66	7.30	4.49	5.48 ± 1.6

[1] The P_{app} values were calculated using both time points.

(source: Table 17, study report DM020)

P-gp substrate

The efflux ratios of VX-809 were 0.883, 1.55, and 0.765 at 1, 10, and 75 µM, respectively. Because the efflux ratio values were less than 2, VX-809 is not a P-gp substrate at the tested concentrations. For reference, the efflux ratio for positive control digoxin is 20.4.

P-gp inhibitor

In the absence of test or control compound, the efflux ratio of digoxin was 18.2 . The presence of 5 µM CsA or 20 µM ketoconazole decreased its efflux ratio to 1.24 and 0.943, respectively. VX-809 showed a typical inhibitory effect on digoxin transport in Caco-2 cells (Figure 30), with [I]1/IC50>0.1 (53.5/13.9).

Nominal VX-809 Concentration (µM)	Corrected Efflux Ratio
0.001	17.2
0.1	11.3
0.5	12.7
1	15.3
2[1]	19.9
10	7.65
25	6.04
75	1.20
IC_{50} (µM)	13.9
Goodness of fit (R^2)	0.8717

[1]For the purpose of the fit, the efflux ratio of digoxin in this group was not included in the IC_{50} calculation.

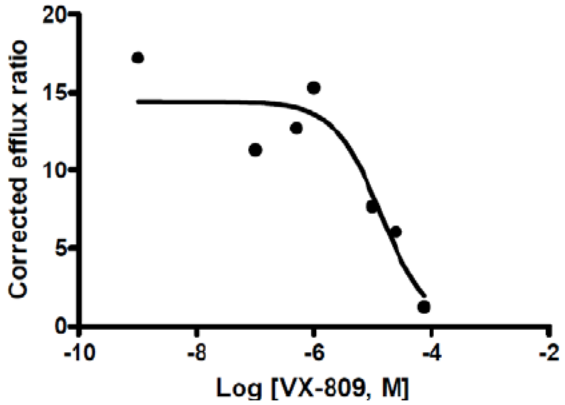


Figure 30. The Inhibitory Effect of VX-809 on Digoxin Transport
(source: Figure 1, study report DM020)

Conclusions: VX-809 is a high permeability and low solubility compound according to the BCS (i.e. a class 2 compound). VX-809 is not a P-gp substrate. VX-809 is a P-gp inhibitor.

Distribution

LUM

Report # D152

Title: *In Vitro* Binding of VRT-826809 to Plasma Proteins in Mouse, Rat, Dog, Monkey, and Human Plasma

Objective: To determine the binding of VRT-826809 to plasma proteins in the mouse, rat, dog, monkey, and human plasma *in vitro*.

Method: In the plasma protein-binding experiments where the plasma was dialyzed against buffer, VRT-826809 at initial concentrations of 0.5, 1, 5 and 10 µM, were incubated in the donor chamber of the equilibrium dialysis block with plasma from the mouse, rat, dog, monkey, or human at room temperature for 16 hr. VRT-826809 was measured by LC/MS/MS.

Results and Conclusion: VX809 shows high plasma protein binding for mouse, rat, dog, monkey and human (**Table 53**).

Table 53. *In vitro* Binding of VRT-826809 to Plasma Proteins Following Equilibrium Dialysis of Plasma Against Buffer.

VRT-826809 (µM)	Percent Protein Bound (Mean ± SD)				
	Mouse	Rat	Dog	Monkey	Human
0.5	99.7[a]	99.6 ± 0.5	98.5[a]	99.3[a]	99.4 ± 0.1
1	99.8 ± 0.1	99.7[a]	98.9 ± 0.3	99.5 ± 0.1	99.2 ± 0.2
5	99.8 ± 0.3	99.0 ± 0.5	99.0 ± 0.5	99.4 ± 0.3	99.3 ± 0.1
10	99.8 ± 0.2	99.9 ± 0.0	99.4[a]	99.3[a]	99.4 ± 0.1

Positive controls: glipizide (89.6 ± 4.0)
[a]n=2
(Source – Table 8-1, Report D152)

Conclusion: Plasma protein binding of LUM is above 99% and is not concentration dependent.

Report # DM-021

Title: *In Vitro* Protein Binding of [14C]VX-809 to Mouse, Rat, Rabbit, Dog, and Human Plasma, HSA, AGG, and HGG, and Protein Binding Displacement Interactions between VX-809 and Warfarin

Objective:

- To determine the extent of protein binding of [14C]VX-809 to mouse, rat, rabbit, dog, and human plasma.
- To determine the extent of binding of [14C]VX-809 to isolated human plasma proteins [i.e. human serum albumin (HSA), human α1-acid glycoprotein (AAG), and human gamma globulin (HGG)].
- To determine the potential for protein binding interactions between VX-809 and warfarin in human plasma.

Method: Protein binding of [14C]VX-809 was determined at six concentrations in mouse, rat, dog, rabbit, and human plasma and at six concentrations in multiple solutions of HSA, AAG, and HGG by equilibrium dialysis using a rapid equilibrium dialysis (RED) device. The potential interactions for protein binding in human plasma between [14C]VX-809 and warfarin and between [3H]warfarin and VX-809 were also determined by equilibrium dialysis. Radiolabeled warfarin and VX-809 were analyzed by liquid scintillation counting (LSC). A summary of the experimental design is presented in the following table.

Table 54. Experimental Design Summary Table

Matrix	Experiment	Concentrations	Ligand
Plasma (mouse, rat, rabbit, dog, and human)	Time-to-Equilibrium	5 µM (0, 1, 3, 5, and 18 hours)	[^{14}C]VX-809
Plasma (mouse, rat, rabbit, and dog)	Concentration Dependence	1, 5, 10, 50, 100, and 500 µM	[^{14}C]VX-809
Plasma (human)	Concentration Dependence	0.5, 1, 5, 10, 50, and 100 µM	[^{14}C]VX-809
HSA, AAG, and HGG	Concentration Dependence	0.5, 1, 5, 10, 50, and 100 µM	[^{14}C]VX-809
Plasma (human)	Interactions	0, 0.5, 1, 5, 10, 50, and 100 µM	VX-809
		4 µg/mL	[^{3}H]Warfarin
Plasma (human)	Interactions	0, 2, 4, and 6 µg/mL	Warfarin
		5 µM	[^{14}C]VX-809

(Source – experimental design summary table, Report DM021)

Results and Conclusion:

Protein binding in plasma

Individual and mean percentages of radioactivity bound to plasma from each species and the percentage of radioactivity recovered are presented in Table 55. [14C]VX-809 was highly bound to proteins in mouse, rat, rabbit, dog, and human plasma. No increase in unbound percentage was observed in human plasma at the highest test article concentration (100 µM).

Protein binding to Human Serum Albumin (HAS)

Protein binding of [14C]VX-809 to various concentrations of HSA was high, with mean protein binding values ranging from 98.85% to 99.84% dependent on HAS concentrations (Table 55). At normal physiological concentrations of HSA (45 mg/mL), protein binding was independent of [14C]VX-809 concentration, indicating that binding sites were not saturated.

Protein binding to Human α 1-Acid Glycoprotein (AAG)

Protein binding of [14C]VX-809 to solutions of AAG was low (Table 55).

Protein binding to Human Gamma-Globulin (HGG)

Protein binding of [14C]VX-809 to solutions of HGG was low (Table 55).

Protein binding interactions with warfarin

- VX809 did not affect the protein binding of warfarin.
- The protein binding of [14C]VX-809 in human plasma was 99.95% in the absence of warfarin and decreased to 97.91% at the highest warfarin concentration (6 µg/mL). Correspondingly, unbound concentrations of [14C]VX-809 increased from 0.05% in the absence of warfarin to 2.09% in the presence of 6 µg/mL warfarin. From these *in vitro* findings, warfarin appears to be able to increase noticeably the free plasma concentration of VX-809 in humans (Table 55).

Table 55. Mean percentages of bound and unbound radioactivity in mouse, rat, rabbit, dog, and human plasma, HSA, AAG, and HGG, and protein binding displacement interactions between VX-809 and warfarin after fortification of [14C]VX-809 at various concentrations and after dialysis at 37°C

Matrix	Incubation Time (Hours)	Range of Mean Percentages Bound	Unbound
	[^{14}C]VX-809[a]		
Mouse Plasma[b]	18	97.02-99.91	0.09-2.98
Rat Plasma	18	98.65-100.00	0.00-1.35
Rabbit Plasma	18	98.84-99.93	0.07-1.16
Dog Plasma	18	98.85-99.85	0.15-1.15
Human Plasma	18	99.97-100.00	0.00-0.03
Human Plasma (Interaction with Warfarin[c])	18	97.91-99.91	0.09-2.09
HSA (25 mg/mL)	18	98.85-99.61	0.39-1.15
HSA (45 mg/mL)	18	99.74-99.82	0.18-0.26
HSA (65 mg/mL)	18	99.82-99.84	0.16-0.19
AAG (0.5 mg/mL)	18	2.84-6.15	93.85-97.16
AAG (1.0 mg/ mL)	18	2.82-7.90	92.10-97.18
AAG (1.5 mg/mL)	18	7.59-13.47	86.53-92.41
HGG (7 mg/mL)	18	3.86-8.58	91.42-96.14
HGG (15 mg/mL)	18	8.35-16.21	83.79-91.65
HGG (22 mg/mL)	18	12.75-26.85	73.15-87.25
	[^{3}H]Warfarin[d]		
Human Plasma[e]	3	99.09[f]	0.91[f]
Human Plasma[g] (Interaction with VX-809)	3	98.98-99.08	0.92-1.02

AGG Human α_1-Acid Glycoprotein
HGG Human Gamma Globulin
HSA Human Serum Albumin
a [^{14}C]VX-809 concentrations were 1, 5, 10, 50, 100, and 500 µM for mouse, rat, rabbit, and dog plasma, and 0.5, 1, 5, 10, 50, and 100 µM for human plasma and plasma proteins.
b Time-to-equilibrium was not fully established in mouse plasma.
c Warfarin concentrations were 2, 4, and 6 µg/mL; [^{14}C]VX-809 concentration was 5 µM. These ranges do not include values for the incubations conducted in the absence of warfarin (zero concentration).
d [^{3}H]Warfarin concentration was 4 µg/mL.
e Incubation in human plasma with [^{3}H]warfarin only, in the absence of test article (VX-809).
f Value listed is the mean from the 3 individual replicates conducted for this concentration. A range is not applicable since there was only one concentration.
g VX-809 concentrations were 0.5, 1, 5, 10, 50, and 100 µM.
(Source – Table 4, Report DM021)

Conclusion:
Plasma protein binding of LUM is above 99% and is not concentration dependent for human plasma.

In vitro, HSA was observed to be the major plasma component in [14C]VX-809 binding, whereas AAG and HGG only appeared to play a minimal role. Protein binding of [14C]VX-809 to HSA appeared to be dependent on HSA concentrations

.

The protein binding of [14C]VX-809 in human plasma was affected by warfarin. An increase in the free fraction of [14C]VX-809 was observed at all warfarin concentrations tested (from approximately 2-fold at 2 to 4 µg/mL up to approximately 40-fold at 6 µg/mL).

M28-LUM:

Report # G085

Title: *In Vitro* Binding of VRT-0995096 to Plasma Proteins in Mouse, Rat, Dog, Monkey, and Human Plasma

Objective: To determine the binding of VRT-0995096 to plasma proteins in the mouse, rat, dog, monkey, and human plasma *in vitro*.

Method: In the plasma protein-binding experiments where the plasma was dialyzed against buffer, VRT- 0995096 at initial concentrations of 1, 5 and 10 µM, were incubated in the donor chamber of the equilibrium dialysis block with plasma from the mouse, rat, dog, monkey, or human at room temperature at 37°C for 4 hr. VRT-0995096 was measured by LC/MS/MS.

Results and Conclusion: VRT- 0995096 shows high plasma protein binding for mouse, rat, dog, monkey and human (Table 56).

Table 56. *In vitro* Binding of VRT-0995096 to Plasma Proteins Following Equilibrium Dialysis of Plasma Against Buffer.

VRT-0995096 (µM)	Percent Protein Bound (Mean ± SD)				
	Mouse	Rat	Dog	Monkey	Human
1	99.40 ± 0.16	99.79 ± 0.02	> 99.99	99.44 ± 0.16	99.84 ± 0.14
5	99.77 ± 0.07	99.87 ± 0.02	99.88 ± 0.03	99.41 ± 0.14	99.93 ± 0.06
10	99.60 ± 0.17	99.89 ± 0.01	99.76 ± 0.07	99.43 ± 0.11	99.92 ± 0.05

n=3, Mean ± SD (standard deviation)
(Source – Table 1, Report G085)

Conclusion: Plasma protein binding of VRT-0995096 (M28-LUM) is above 99% and is not concentration dependent.

In vitro Metabolism

LUM

Report # D072

Title: *In Vitro* Assessment of Metabolic Stability of VRT-826809 in Hepatocytes from Rat, Dog, Monkey, and Human

Objective: To evaluate the extent of metabolism of VRT-826809 in hepatocytes from multiple species *in vitro*.

Method: 1µM VRT-826809 was incubated with human hepatocyte (37°C). Samples were analyzed by LC/MS/MS.

Results: The metabolic stability of VRT-826809 was evaluated in cryopreserved hepatocytes from rat, dog, monkey, and human. The rate of metabolism of VRT-826809 at 1 µM was slow in hepatocytes from dog, monkey, and human, with 84% to 89% remaining after 240 minutes incubation (Table 57, Figure 31).

Table 57. Metabolic Stability Parameters for VRT-826809 at 1 µM Initial Concentration in Hepatocytes Isolated from Rat, Dog, Monkey, and Human

Species	Mean (SD) Percent Remaining at 240 min	$t_{1/2}$ (min)	Intrinsic Clearance (mL/min/kg)	Predicted Hepatic Clearance (mL/min/kg)
Rat	115[a] (6)	Stable	NC[b]	NC
Dog	89[a] (4)	754	3.5	3.2
Monkey	85 (8)	766	3.5	3.3
Human	84 (5)	1240	1.7	1.6

[a]Incubation time = 225 minutes

[b]NC: not calculated

(Source – Table 8-1, study report D072)

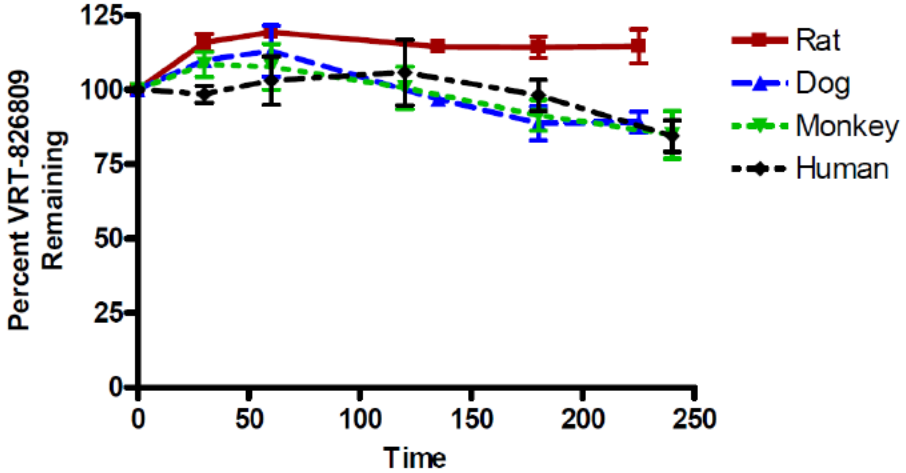


Figure 31. Stability of VRT-826809 at 1 µM Initial Concentration in Hepatocytes from Rat, Dog, Monkey, and Human

(Source – Figure 8-1, study report D072)

Conclusion: The rate of metabolism of VRT-826809 at 1 µM in human hepatocytes was slow.

Study # D071

Title: The *In Vitro* Stability of VRT-826809 in Human Recombinant CYP450 Isozymes

Objective: To predict the potential involvement of various human CYP450 isozymes in the metabolism of VRT-826809

Method: VRT-826809 was incubated at initial concentrations of 2 or 20 µM with recombinant human isozymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The extent of metabolism was determined by measuring the concentration of VRT-826809 remaining at the end of the incubations using LC/MS/MS.

Results: The only CYP450 isozyme that was active at metabolizing VRT-826809 after 1 hour incubation at 37°C was CYP3A4, with 87% and 92% of VRT-826809 remaining at 0.2 and 2 µM initial concentrations, respectively. There was no detectable reduction in VRT-826809 after incubation at 2 and 20 µM with CYP1A2, CYP2C9, CYP2C19, and CYP2D6 (Table 58).

Table 58. Summary of Stability Data (Percent Remaining) for VRT-826809 and Control Compounds after 1 Hour Incubation at 37°C with Human CYP450 Isozymes

Initial VRT-826809 concentration	Mean (SD) Percent of VRT-826809 Remaining (%)				
	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
2 µM	99 (7)	103[a]	99 (3)	106 (1)	87 (3)
20 µM	102 (2)	107 (16)	128 (22)	124 (6)	92 (4)
	Mean (SD) Percent of Control Compound Remaining (%)				
Positive Control	Phenacetin	Diclofenac	Amitriptyline	Dextromethorphan	Quinidine
2 µM	45 (4)	0.2 (0.1)	4 (2)	1 (1)	13 (2)
20µM	29 (1)	1 (1)	32 (1)	3 (2)	42 (3)

n = 3
[a] n = 2
(Source – Table 8-1, Report D071)

Conclusion: LUM is slowly metabolized by CYP3A4.

Study # D083

Title: Characterization of VRT-826809 Putative Metabolites from *In Vitro* and *In Vivo* Matrices

Objective: To characterize putative metabolites of VRT-826809 formed after incubation with rat, dog, monkey, and human liver microsomes and cryopreserved hepatocytes.

Method: VRT-826809 was administered by oral gavage in dogs and rats *in vivo* studies. Plasma, bile and urine samples were collected from 0 to 72 hours after administration. VRT-826809 was incubated with rat, dog, monkey, and human liver microsomes and cryopreserved human hepatocytes at 37ºC. Supernatants were collected at different time points. All samples were analyzed using LC/MS/MS.

Results:

Metabolite of VRT-826809 Formed in Liver Microsomal Incubations

The primary metabolite observed after incubation of VRT-826809 for 60 minutes with liver microsomal preparations from the rat, dog, monkey, and human was M1, the mono-oxidation product. A comparison of the relative amounts of M1 across species is provided in Table 59.

Table 59. Metabolite (M1) of VRT-826809 Detected after Incubation with Liver Microsomes

Metabolite	Mass Shift/ Modification	$[MH]^+$	Retention Time	% Parent Peak Area[a]			
				Rat	Dog	Monkey	Human
Parent	--	453	20.1	100	100	100	100
M1	+16/ Methyl hydroxylation	469	17.8	4	1	5	1

[a]Peak area normalized to parent peak area present in 0 minute samples
VRT-826809 initial concentration = 10μM.
(Source – Table 8-1, Report D083)

Metabolite of VRT-826809 Formed in Hepatocyte Incubations

After incubation of VRT-826809 for 120 minutes with hepatocytes from rat, dog, monkey, and human, both phase I and phase II pathway metabolites were detected. The major metabolite identified for all species examined was M2, a direct glucuronide conjugate. The mono-oxidation metabolite, M1, was produced to a much lesser extent than in liver microsomal preparations. A comparison of metabolites across species is provided in Table 60.

Table 60. Metabolites of VRT-826809 Detected after Incubation with Hepatocytes

Metabolite	Mass Shift/ Modification	$[MH]^+$	Retention Time (min)	% Parent Peak Area[a]			
				Rat	Dog	Monkey	Human
Parent	--	453	20.1	100	100	100	100
M1	+16/ Methyl hydroxylation	469	17.8	0.03	0.05	0.07	0.08
M2	+176/ Acyl glucuronide	629	17.6	0.5	2.6	5	2

[a]Peak area normalized to parent peak area present in 0 minute samples
VRT-826809 initial concentration = 30μM
(Source – Table 8-2, Report D083)

VRT-826809 and its metabolite in bile in rat

A very low percentage (1.1 %) of the orally administered dose of VRT-826809 was excreted intact in rat bile (Table 61). The methyl hydroxylation metabolite (M1) was detected in rat bile at about half the levels of the parent compound. The acyl glucuronide (M2) was present in rat bile at much higher levels than the parent, ~72-fold higher by relative peak area (standards for the glucuronide were not available).

Table 61. Metabolites of VRT-826809 in Urine and Bile Following Oral Administration to Male Sprague Dawley Rats and Male Beagle Dogs

Metabolite	Mass Shift/ Modification	$[MH]^+$	Retention Time (min)	Rat Bile	Rat Urine	Dog Urine
				% Dose Administered		
Parent	--	453	20.1	1.1	0.3	0.8
				% Parent Peak Area[a]		
M1	+16/ Methyl hydroxylation	469	17.8	52	219	2
M2	+176/ Acyl glucuronide	629	17.6	7266	434	11

[a] % metabolism expressed as peak area divided by VRT-826809 peak area x 100%

(Source – Table 8-4, Report D083)

Conclusion: Direct glucuronidation (M2) was the primary metabolic transformation observed after incubation with hepatocytes from multiple species and after oral administration to rat and dog. Majority of the oral dose of LUM was excreted as M2 in rat bile at much higher levels than the parent. The primary Phase I metabolite was the oxidation of the aromatic methyl group (M1), and it is a minor metabolite based on microsome incubation data.

M28-LUM

Report # H060

Title: The *In Vitro* Stability of VRT-0995096 in Human Recombinant CYP Isozymes

Objective: To predict the potential involvement of various human CYP isozymes in the metabolism of VRT-0995096

Method: VRT-0995096 (final concentration of 1 or 10 µM) was incubated with various human recombinant isozymes at 50 pmol/mL for 1 hour. The extent of metabolism was determined by measuring the remaining VRT-0995096 using LC-MS/MS.

Results: The results from *in vitro* phenotyping experiments with VRT-0995096 in human recombinant CYPs are shown in Table 62. Results are expressed as the percent of parent remaining unchanged after 1 hour of incubation.

Table 62. Summary of Human Recombinant CYP Isozyme Stability Data for VRT-0995096 at 1µM and 10µM after 1 hour incubation at 37°C

VRT-0995096 Initial Concentration	Percent of VRT-0995096 Remaining (Mean ± SD)						
	CYP1A2	CYP 2B6	CYP2C8	CYP 2C9	CYP2C19	CYP2D6	CYP3A4
1 µM	79 ± 6	94 ± 6	90 ± 2	84 ± 4	95 ± 3	79 ± 4	83 ± 6
10 µM	101 ± 6	94 ± 3	96 ± 5	100 ± 9	98 ± 7	103 ± 6	97 ± 5

(Source – Table 1, Report H060)

Conclusion: M28-LUM is stable (>79 % remaining) in all CYPs tested (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4) at 1 and 10 µM concentrations tested.

In vitro Enzyme Induction

LUM

Study # K027

Title: Human PXR/SXR Activation on Compounds VX-809, VX-661,VXC-874, VRT-0926930, VRT-0928580, and VRT-0922563

Objective: to investigate whether VX-809 has the potential to activate human PXR/SXR *in vitro*.

Method: Incubation (pH 7.4, 37°C) of VX-809, positive control, and other compounds with DPX2 cells for 24 hours. Following viability determination, 50 µL of ONE-Glo substrate (Promega) was added to each well. The plates were incubated at RT for 5 minutes and luminescence read on a BMG luminometer. In this manner, PXR activation of the CYP3A4 promoter is directly proportional to luciferase activity (RLUs), and is a measure of transcriptional activation of the CYP3A4 gene.

Inducing Agent	DPX2 Cells
	Concentrations Tested
Rifampicin (RIF)	0.1, 0.5, 1, 5, 10 & 20 µM
VX-809, VX-661, VXC-874	0.5, 3, 5, 10, 20 & 30 µM
VRT-0926930, VRT-0928580 VRT-0922563	0.3, 0.5, 1, 3, 5 & 10 µM

Results: Percent turnover of probe substrate relative to positive control (rifampin) is shown in Table 63. These data show strong induction of PXR by VX809 at therapeutic concentrations.

Table 63. Summary of the Effects of PXR activation in PURACYP DPX2 cells

Compound	% of 10 µM RIF	EC_{50} (µM)	Induction Potency[a]
VX-809	86	2.74[b]	Strong
VX-661	7	nd	Negative
VXC-874	8	nd	Negative
VRT-0926930	21	nd	Weak
VRT-0928580	62	nd	Moderate
VRT-0922563	47	nd	Moderate

a. Induction potency is defined as negative, weak, moderate and strong. Negative, weak, moderate and strong inducers are those that give < 15%, <40%, <69% and >70%, respectively, of the response produced by 10 µM RIF (rifampicin) at an equimolar concentration. In this experiment, 10 µM RIF elicited 21.7-fold induction above DMSO-treated cells, and gave an EC50 value of 1.47 µM.

(Source – page 10, Report K027)

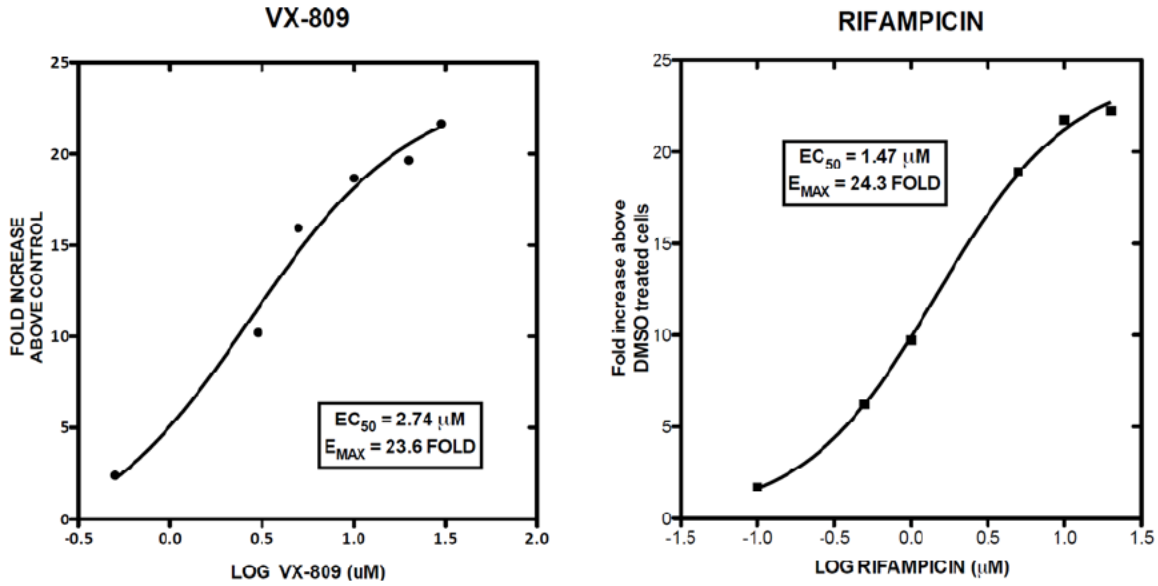


Figure 32. Summary of the Effects of PXR activation by VX-809 and Rifampicin in PURACYP DPX2 cells
(Source – page 13-14, Report K027)

Conclusion: LUM is a strong PXR inducer, and therefore has the potential to induce CYP2C and CYP3A subfamilies as well as P-gp.

Study # DM019

Title: Induction Potential of VX-809 on Cytochromes P450, Assessment of the Cytotoxicity of VX-809, and Induction Potential of VX-661 and VRT-0995096 (M28) on Cytochrome P450 3A4/5 in Human Hepatocyte Cultures

Objective:

- Determination of the induction potential of VX-809 on the activities of human CYP1A2 (phenacetin O-deethylase), CYP2A6 (coumarin 7-hydroxylase), CYP2B6 (bupropion hydroxylase), CYP2C8 (amodiaquine N-deethylase), CYP2C9 (diclofenac 4 -hydroxylase), CYP2C19 (mephenytoin 4 -hydroxylase), and CYP3A4/5 (testosterone 6β-hydroxylase);
- Determination of the cytotoxicity of VX-809;
- Determination of the induction potential of VRT-0995096 (M28) and VX-661 on the activities of human CYP3A4/5; and
- Determination of the expression of mRNA for CYP3A4/5 following incubation with VX-809, VRT-0995096 (M28), or VX-661.

Method: Fresh or cryopreserved hepatocytes from individual human donors were separately incubated for 72 or 48 hours with test article [(VX-809, VRT-0995096 (M28), or VX-661], a prototypical inducer for each enzyme, and an appropriate solvent control for test article [0.5% dimethylsulfoxide (DMSO)] or each prototypical inducer [(0.5% acetonitrile (ACN)]. Following treatment, the hepatocyte cytochrome P450 activities were determined by incubating the cultures with specific probe substrates and measuring

the rates of production of relevant metabolites utilizing liquid chromatography with tandem mass spectrometric (LC-MS/MS) detection. Real-Time reverse transcriptase polymerase chain reaction (RT-PCR) was used to assess mRNA induction.

Results:
Effect of VX-809 on CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 3A4/5
Exposure of the cultures to VX-809 resulted in >2-fold increases in CYP2C9, CYP2C19 and CYP3A4/5 enzyme activities for one or more of the donors. The observed increases were >40% compared to the increases observed with prototypical inducers. These data confirmed induction of CYP2C9, 2C19 and 3A4/5 by VX809 at therapeutic concentrations.

Exposure of the cultures to VX-809 resulted in >2-fold increases in CYP1A2 and CYP2B6 enzyme activities for one or more of the donors. However, the observed increases were <40% compared to the increases observed with prototypical inducers. Therefore, induction of CYP1A2 and CYP2B6 activities by VX-809 was considered to have a low potential for developing clinical interactions.

The enzyme activities for CYP2A6 following treatment with VX-809 were <2-fold compared to the vehicle controls and <40% compared to prototypical inducers. Thus, CYP2A6 was not considered inducible by VX-809.

Data for CYP2C8 were inconclusive as the positive control fails to induce CYP2C8.

Conclusion:
VX-809 appears to be a potential inducer of CYP2C9, CYP2C19, and CYP3A4/5 activities under the conditions of the study.

VX-809 is not an inducer for CYP2A6. Induction potential for CYP1A2 and CYP2B6 were low. VRT-0995096 (M28) does not appear to induce CYP3A4/5. Data for CYP2C8 were inconclusive.

Study # J174
Title: Evaluation of VRT-0826809 as an Inducer of CYP3A4 using Primary Cryopreserved Human Hepatocytes

Objective: to evaluate the effect of VRT-0826809 on the mRNA expression and functional activity of CYP3A4 in human hepatocytes following two day exposure to VRT-0826809 at 0.1, 0.3, 1, 3, 10, 30 and 60 μM.

Method: Cryopreserved human hepatocytes were used to determine activities and relative mRNA expression levels of CYP3A4. Plated hepatocytes were incubated with either a prototypical chemical inducer of CYP3A4 (rifampicin), the test article (VRT-0826809), or vehicle (0.1% DMSO). Following treatment, the hepatocyte cytochrome P450 activities were determined by incubating the cultures with testosterone. mRNA expression levels were assessed by real-time PCR.

Results: A significant dose-dependent increase was observed in CYP3A4 mRNA expression in lots LMP, 8123 and 8127 after 48- hours of exposure to VRT-0826809 (up to 60 µM concentration) relative to the vehicle control (Table 64).

Table 64. Changes in CYP3A4 mRNA and Enzyme Activity in Cryopreserved Human Hepatocytes Treated with VRT- 0826809

CBDM301898		Lot LMP		Lot 8123		Lot 8127	
Treatment	[µM]	6B-hydroxytestosterone	hCYP3A4 mRNA	6B-hydroxytestosterone	hCYP3A4 mRNA	6B-hydroxytestosterone	hCYP3A4 mRNA
		Fold[a]	Fold[a]	Fold[a]	Fold[a]	Fold[a]	Fold[a]
Rifampicin	10.0	12.5	29.0	18.5	106	2.1	28.7
VRT-0826809	0.1	1.14	1.48	1.92*	1.26	0.718	2.21
	0.3	1.70	2.66	1.96	3.25	1.01	2.90
	1	3.61	5.55	3.79*	9.69	1.35	6.76
	3	6.55	10.6	7.52	38.1	1.61	21.2
	10	10.2	16.9	10.1*	73.1	2.27	24.9
	30	9.47	14.6	12.9	65.7	1.97	16.8
	60	7.15	18.0	5.88	44.8	1.23	11.5

(Source – Table 8-1, Report J174)

Conclusion: The *in vitro* data indicate that VRT-0826809 induces CYP3A4 mRNA and CYP3A4 enzyme activity in a concentration dependent manner after 48-hour exposure in human hepatocyte.

Study # K020

Title: Evaluation of VX-809 as an Inducer of CYP2C8, CYP2C9 and CYP2C19 using Primary Cryopreserved Human Hepatocytes

Objective: To evaluate the induction-based DDI risk of VX-809 by assessing the change in mRNA expression of CYP2C8, CYP2C9 and CYP2C19 in human hepatocytes following 72-hour exposure to VRT-0826809 at 0.1, 0.3, 1, 3, 10, 30, and 60 µM.

Method: Cryopreserved human hepatocytes were used to determine activities and relative mRNA expression levels of CYP2C8, CYP2C9 and CYP2C19. Plated hepatocytes were incubated with either a prototypical chemical inducer of CYP2C8, CYP2C9 and CYP2C19 (phenobarbital and rifampicin), the test article (VRT-0826809), or vehicle (0.1% DMSO). Following treatment, the hepatocyte mRNA expression levels were assessed by real-time PCR.

Results Of the three lots of hepatocytes, VX-809 caused a dose-dependent increase in CYP2C8 mRNA up to a VX-809 concentration of 10 or 30 µM in two lots. The CYP2C8 inductive response was significant (>3-fold) in the third lot but was not dose-dependent.

Of the three lots of hepatocytes, a significant inductive response (≥3-fold) was observed only in one lot for CYP2C9 and 2C19, and it is not dose dependent. Data from the other

two lots were not interpretable as the positive control failed to induce CYP2C9 and 2C19 mRNA.

Conclusion: Overall, these data suggest that VX-809 has the potential to induce CYP2C8. The data were inconclusive for CYP2C9 and 2c19.

Study # K028

Title: Evaluation of VRT-0826809 as an Inducer of CYP1A2 and CYP2B6 using Primary Cryopreserved Human Hepatocytes

Objective: to evaluate the potential of VRT-0826809 to induce CYP1A2 and CYP2B6 in human hepatocytes, as measured by relative changes in mRNA expression and metabolic activity.

Method: Cryopreserved human hepatocytes were used to determine activities and relative mRNA expression levels of CYP1A2 and CYP2B6. Plated hepatocytes were incubated with either a prototypical chemical inducer of CYP1A2 and CYP2B6 (omeprazole and phenobarbital), the test article (VRT-0826809), or vehicle (0.5% DMSO). Following treatment, the hepatocyte cytochrome P450 activities were determined by incubating the cultures with bupropion. mRNA expression levels were assessed by real-time PCR.

Results: There was no observed increase in CYP1A2 activity or mRNA in response to VRT-0826809. However, a concentration-dependent induction of CYP2B6 was observed, in each lot of hepatocytes (Table 65). The calculated EC50 for CYP2B6 induction ranged from 3.1-14.5 µM, depending on lot and assay readout. The data agree between the three lots of hepatocytes, and are consistent for both activity and mRNA endpoints.

Table 65. The Effect of VRT-0826809 on CYP2B6 Activity and mRNA Expression in Cryopreserved Human Hepatocytes

Treatment	Conc. (µM)	Lot Hu8123		Lot Hu8127		Lot LMP	
		Bupropion hydroxylation (Fold)	CYP2B6 mRNA (Fold)	Bupropion hydroxylation (Fold)	CYP2B6 mRNA (Fold)	Bupropion hydroxylation (Fold)	CYP2B6 mRNA (Fold)
Phenobarbital	1000	11.7	15.8	8.88	9.06	4.93	5.26
VRT-0826809	0.3	1.06	1.42	.690	1.03	1.27	1.01
	1	1.22	1.41	1.18	1.37	1.38	1.03
	3	1.24	1.29	2.31	2.37	1.98	1.70
	10	1.99	2.61	3.41	3.76	2.32	2.42
	30	4.09	4.58	5.05	4.72	3.04	2.55
	60	4.40	4.64	4.06	4.29	2.66	2.39

(Source – Table 8-2, Report K028)

Conclusion: The *in vitro* data indicate that VRT-0826809 is a CYP2B6 inducer with EC50 predicted to be 3-15µM.

In vitro Enzyme Inhibition

LUM

Study # DM018

Title: Inhibitory Potential of VX-809 on Human Hepatic Microsomal Cytochromes P450

Objective: to characterize, *in vitro*, the direct and metabolism-dependent inhibition potential of VX-809 on human isoenzyme-selective cytochrome P450 activities.

Method: This study assessed the direct (Part I) and metabolism-dependent (Part II) inhibition potential of VX-809 on the isoenzyme-selective cytochrome P450 marker activities of phenacetin O-deethylase for CYP1A2, coumarin 7-hydroxylase for CYP2A6, bupropion hydroxylase for CYP2B6, amodiaquine N-deethylase for CYP2C8, diclofenac 4′-hydroxylase for CYP2C9, S-mephenytoin 4′-hydroxylase for CYP2C19, bufuralol 1′-hydroxylase for CYP2D6, chlorzoxazone 6-hydroxylase for CYP2E1, and testosterone 6β-hydroxylase and midazolam 1′-hydroxylase for CYP3A4/5. For cytochrome P450 activity assays that were significantly inhibited by VX-809, the concentration of VX-809 that inhibited 50% of the activity (IC50 value) was calculated. For selected cytochrome P450 activity assays that were inhibited by VX-809 (Part I), the inhibition kinetics and type of inhibition were also determined (Part III). All sample and control incubations were conducted in triplicate and were analyzed by high-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS).

Results: A summary of IC50 and Ki values for each cytochrome P450 activity in human hepatic microsomes after incubation with VX-809 is shown in Table 66. VX-809 inhibited bupropion hydroxylase (CYP2B6), amodiaquine N-deethylase (CYP2C8), and diclofenac 4′-hydroxylase (CYP2C9) activities, with apparent IC50 values of 102, 12.1, and 32.1 μM, respectively. No IC50 values were calculated for activities representing cytochromes P450 CYP1A2, CYP2A6, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. Percent activity remaining at multiple concentrations of VX-809 for CYP2C8 and CYP2C9 are presented in Table 67.

Kinetic analysis of amodiaquine N-deethylase (CYP2C8) activities showed that VX-809 was a competitive-type inhibitor with an apparent Ki value of 2.4 μM. Kinetic analysis of diclofenac 4′-hydroxylase activities in the presence of VX-809 showed nonlinear competitive inhibition of cytochrome P450 CYP2C9 and an apparent Ki value of 34.7 μM.

Table 66. Inhibition of cytochrome P450 activities by VX-809 in human hepatic microsomal Incubations

Cytochrome P450	Cytochrome P450 Activity	IC_{50} (μM)	Ki (μM)	α Value	Type of Inhibition
CYP1A2	Phenacetin *O*-deethylase	NC	NC	NC	NA
CYP2A6	Coumarin 7-hydroxylase	NC	NC	NC	NA
CYP2B6	Bupropion hydroxylase	102	NC	NC	NA
CYP2C8	Amodiaquine *N*-deethylase	12.1	2.4	NA	Competitive
CYP2C9	Diclofenac 4′-hydroxylase	32.1	34.7	NA	Competitive
CYP2C19	*S*-Mephenytoin 4′-hydroxylase	NC	NC	NC	NA
CYP2D6	Bufuralol 1′-hydroxylase	NC	NC	NC	NA
CYP2E1	Chlorzoxazone 6-hydroxylase	NC	NC	NC	NA
CYP3A4/5	Testosterone 6β-hydroxylase	NC	NC	NC	NA
CYP3A4/5	Midazolam 1′-hydroxylase	NC	NC	NC	NA

IC_{50} Concentration of test article that inhibits 50% of the cytochrome P450 activity.
K_i Inhibition constant.
NA Not applicable.
NC Not calculated.
α Kiu/Kic.
(Source – Table 1, Report DM018)

Table 67. Mean percent of Activity remaining of CYP enzymes after VX-809 treatment

VX809 Concentration (μM)	**Mean Percent of Activity Remaining (%)**	
	CYP2C8 (amodiaquine N-deethylase)	**CYP2C9 (diclofenac 4'-hydroxylase)**
Solvent control (methanol)	100	100
Positive control*	47.2	33.9
0.01	64.6	123
0.1	91.9	123
0.5	92.2	122
1	90.0	120
5	67.0	107
10	52.1	87.6
50	19.7	36.4
100	8.89	18.7

*Positive control: Montelukast for CYP2C8, Sulfaphenazole for CYP2C9
(Source – Reviewer summary based on Table 5 and 6, Report DM018)

Conclusion: The Cmax at steady-state following administration of LUM 400 mg bid dose for 28 days in fed state was 24.2 μg/mL (~53.5 μM). Based on the results with human liver microsomes, LUM is a CYP2C8 and CYP2C9 inhibitor at therapeutic concentrations. As LUM is also a CYP2C8 and CYP2C9 inducer, the net effect of LUM on CYP2C8 and 2C9 substrates is not clear.

M28-LUM

Study # G140

Title: Assessment of VRT-995096 Reversible Inhibition Potential of Human Cytochrome P450 Isozymes

Objective: to evaluate the potential of VRT-995096 to inhibit human CYPs 1A2, 2C9, 2C19, 2D6 and CYP3A4 in a reversible manner using human liver microsomes.

Method: The human liver microsome (HLM) reversible inhibition study was conducted by incubation of pooled human liver microsomal protein for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 with 0-90μM M28-LUM and marker substrates. Following treatment, the cytochrome P450 activities were determined by measuring the rates of production of relevant metabolites utilizing liquid chromatography with tandem mass spectrometric (LC-MS/MS) detection.

Results: VRT-995096 caused less than 50% inhibition at all concentrations tested (to 30 μM) for CYPs 1A2, 2C9, 2C19, 2D6, and 3A4 (w/testosterone or midazolam).

Conclusion: M28-LUM showed little or no inhibition of all isozymes tested.

In vitro Transporter Substrate potential and Inhibition

LUM

Study # K112

Title: Evaluation of the Substrate Potential of VX-809 of Organic Anion Transporting Polypeptide 1B1 and 1B3

Objective: To assess if VX-809 is a substrate of the following transporters: organic anion transporting polypeptide 1B1 and 1B3 (OATP1B1 and OATP1B3).

Method: Human embryonic kidney epithelial cells (HEK293) transfected with individual uptake transporters (OATP1B1 or OATP1B3) were used to assess the substrate potential of VX-809 toward the corresponding transporter. After incubation with VX-809 for different periods of time, the cell lysates were collected for analysis of test compound concentration.

Results and Conclusion: The uptake rate ratio of VX-809 was less than 2.0 in both OATP1B1- and OATP1B3- transfected cells at all tested conditions. Therefore, VX-809 is not a substrate of OATP1B1 and OATP1B3.

Study # K111

Title: Evaluation of the Inhibitor Potential of VX-809 of Uptake Transporters

Objective: To assess if VX-809 is an inhibitor of the following transporters: organic anion transporting polypeptide 1B1 and 1B3 (OATP1B1 and OATP1B3).

Method: Human embryonic kidney epithelial cells (HEK293) transfected with individual uptake transporter (OATP1B1, OATP1B3) were used to assess the inhibitor potential of VX-809 toward the corresponding transporter. After incubation with probe substrate (atorvastatin) in the absence and presence of VX-809, the cell lysates were collected for analysis of test compound concentration.

Results and Conclusion: VX-809 showed a concentration-dependent inhibition towards OATP1B1 and OATP1B3. The IC50 values of VX-809 towards OATP1B1 and OATP1B3 were 83.0 and 276 μM, respectively. Therefore, the inhibitory effect is not significant at clinical relevant concentrations.

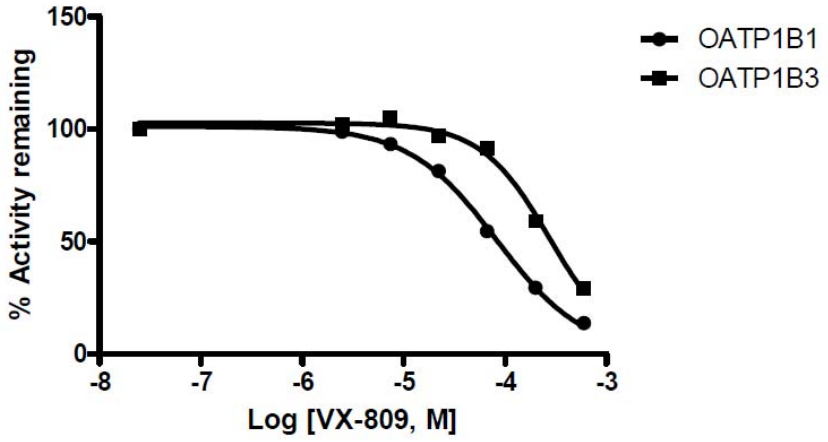


Table 17. R Value

Fraction unbound (%)	C_{max} (μM)	Transporter	IC_{50} (μM)	R value
1	62	OATP1B1	83.0	1.02
		OATP1B3	276	1.01

Figure 33. Effect of VX-809 on OATP1B1 and OATP1B3
(Source: Figure 1, report K111)

PHARMACOKINETICS

1. Mass Balance Study (LUM)

LUM
Study # VX08-809-004

Title: A Phase 1 Open-Label Mass Balance Study to Investigate the Absorption, Metabolism and Excretion of [^{14}C]-Lumacaftor Following Single Oral Administration to Healthy Male Volunteers

Objective:
Primary: To characterize the PK, route(s) and rate of elimination, and total recovery of lumacaftor and total radioactivity after a single, oral dose of [^{14}C]-lumacaftor in healthy male volunteers.
Secondary: To profile and identify, if possible, the major metabolites of lumacaftor in the

urine, plasma, and feces of healthy male subjects following administration of a single oral dose of [^{14}C]-lumacaftor.

Study design: This was an open-label, non-randomized, mass balance study. Each subject (n=6) received a single, oral dose of [^{14}C]-LUM 200 mg as a suspension, containing approximately 100 μCi of carbon-14.

Samples and methods: Blood, urine and faecal samples were to be collected for a minimum of 96 hours, or until discharge. Discharge criteria were met when the radioactivity levels in the blood and plasma contained less than 3 times background radioactivity; and 90% of the total radioactive dose administered was recovered from all matrices; or less than 1% was excreted in the previous 24 hour period.

The [14C]-radioactivity levels in plasma, urine, and feces were determined by means of liquid scintillation counting (LSC). Metabolite profiles in plasma, urine, and feces were determined using HPLC with fraction collection and LSC. Selected plasma, urine, and feces samples were submitted for LC/MS/MS to determine the metabolite composition of each matrix.

Results: Most of the administered radioactivity was recovered in the first 216 hours postdose (range of 89% to 100%; mean of 96%). The overall mean recovery of radioactivity in urine and feces samples ranged from 94% to 100% (mean of 98%) over the 480-hour study period.

Absorption:
After oral administration of [14C] VX-809 as a suspension, plasma ^{14}C-radioactivity and VX-809 concentration slowly peaked, with a median tmax value of 4 hours postdose. In plasma, unchanged VX-809 accounted for a mean of 86% of the total radioactivity at Cmax and for a mean of 59% of the total radioactivity AUC0-tlast values. These results suggest that the majority of circulating total radioactivity was related to unchanged VX-809.
From the amount of parent drug measured in the feces (approximately 24% to 53%) and assuming that VX-809 is not degraded in the gut lumen, VX-809 appears to be quite well absorbed (approximately 47% to 76%). The amount of unchanged VX-809 found in the feces may be due to non-absorbed material from the gut, but also from drug being absorbed
and released in the gut via the bile. In bile-cannulated rats dosed orally with VX-809, a large
amount of parent drug (26% to 30% of the dose) was observed in the bile. Therefore, the absorption of VX-809 in humans may be even higher than these estimated values.

Distribution:
Mean Cmax, AUC0-tlast, and AUCinf values for the total radioactivity in plasma were higher than those observed in whole blood indicating that VX-809 and its metabolites are not highly associated with red blood cells.

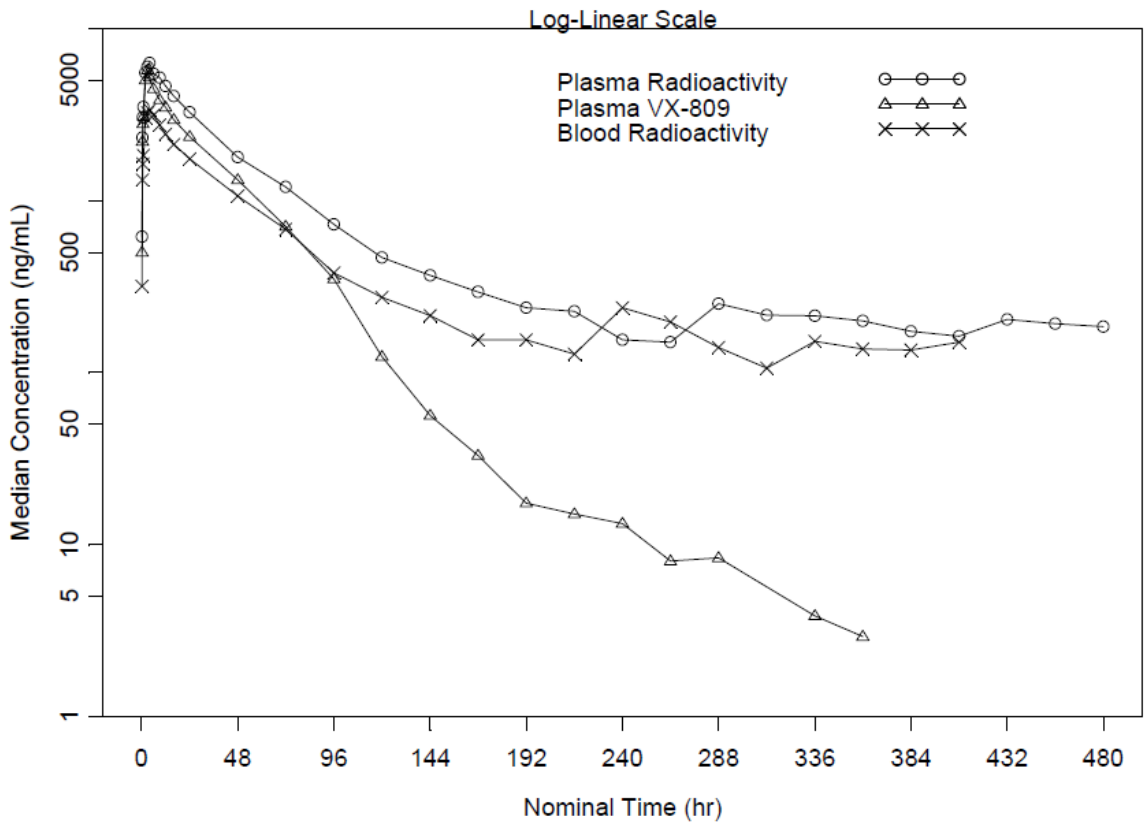


Figure 34. Median Concentrations of Plasma VX-809, Plasma Total Radioactivity and Whole Blood Radioactivity in the Log-Linear Scales
(source: Figure 11-1, VX08-809-004 study report)

Metabolism:
As proposed in the biotransformation pathway (Figure 35), [14C] VX-809 is converted in humans to several metabolites. The metabolism of [14C] VX-809 involved mainly oxidation and glucuronidation, and to a much lesser extent, sulfation.

In plasma, most of the circulating radioactivity was associated with parent drug and metabolite hydroxy-pyrrolidone-VX-809 (M28). The PK parameters for mean concentrations of total radioactivity, parent drug, and metabolites in plasma are listed in Table 68. Comparison of area under the concentration versus time curve (AUC) values in plasma for parent drug versus total radioactivity suggests that approximately 52% of the radioactivity was associated with unchanged VX-809. M28 was the major metabolite in plasma which represented 13% of the total radioactivity and a metabolite: parent AUC ratio of 25%. No other metabolite ratio exceeded 5.4%.

Table 68. Pharmacokinetic Parameters for Mean concentrations of Total Radioactivity, Parent Drug, and Selected Metabolites in Plasma Collected from Healthy Male Subjects Following a Single Oral Administration (200 mg) of [14C]-VX-809

Metabolite Number	Analyte/ Metabolite Identification	t_{max} (hr)	C_{max} (ng/g)[a]	$t_{1/2,\lambda z}$ (hr)	$AUC_{0\text{-}t264\ hr}$ (ng*hr/g)[a]	$AUC_{0\text{-}\infty}$ (ng*hr/g)[a]	$AUC_{0\text{-}t264\ hr}$ of Radioactivity (%)[b]	$AUC_{0\text{-}t264\ hr}$ of Parent (%)[c]
NA	Total radioactivity	3	6450	99.3	298000	325000	100	NA
VX-809	VX-809	3	5630 ~~5010~~	27.2 ~~19.6~~	184291 ~~156000~~	184430 ~~156000~~	61.8 ~~52.4~~	100
M14	O-VX-809-glucuronide-1	24	136 ~~119~~	46.9 ~~25.7~~	8745 ~~7020~~	8952 ~~7030~~	2.93 ~~2.36~~	4.74 ~~4.5~~
M16	O-VX-809-glucuronide-2	6	176 ~~151~~	51.1 ~~30.4~~	8767 ~~6730~~	8991 ~~6740~~	2.94 ~~2.26~~	4.76 ~~4.31~~
M21	VX-809-glucuronide-2	6 ~~3~~	338 ~~295~~	36.6 ~~27~~	9935 ~~8410~~	10273 ~~8530~~	3.33 ~~2.82~~	5.39 ~~5.38~~
M22[d e]	O-VX-809-1	6	139 ~~117~~	34.2 ~~25.7~~	6482 ~~5460~~	6754 ~~5560~~	2.17 ~~1.83~~	3.52 ~~3.49~~
M28	Hydroxy-pyrrolidone-VX-809	72	340 ~~291~~	186 ~~47.9~~	63708 ~~38500~~	103455 ~~39100~~	21.4 ~~12.9~~	34.6 ~~24.6~~
~~M34~~	~~Unknown~~	~~12~~	~~23.4~~	~~43~~	~~1010~~	~~1010~~	~~0.34~~	~~0.64~~

Source: Metabolite Profiling and Identification Report [redacted] (b) (4) Amended Final Report, Version 2, Table 1.
NA: Not applicable.

[a] For total radioactivity, concentrations are ng equivalents [^{14}C]-VX-809/g.

[b] Values were calculated by: $AUC_{0\text{-}t264\ hr}$ (metabolite)/$AUC_{0\text{-}t264\ hr}$ (plasma total radioactivity) × 100.

[c] Values were calculated by: $AUC_{0\text{-}t264\ hr}$ (metabolite)/$AUC_{0\text{-}t264\ hr}$ (parent) × 100.

[d e] M22 (M469A, O-VX-809-1) was the major metabolite of VX-809 found in rat plasma in [redacted] (b) (4) Study No. 6536-451.

(source: Table 11-3, VX08-809-004 study report Errata)

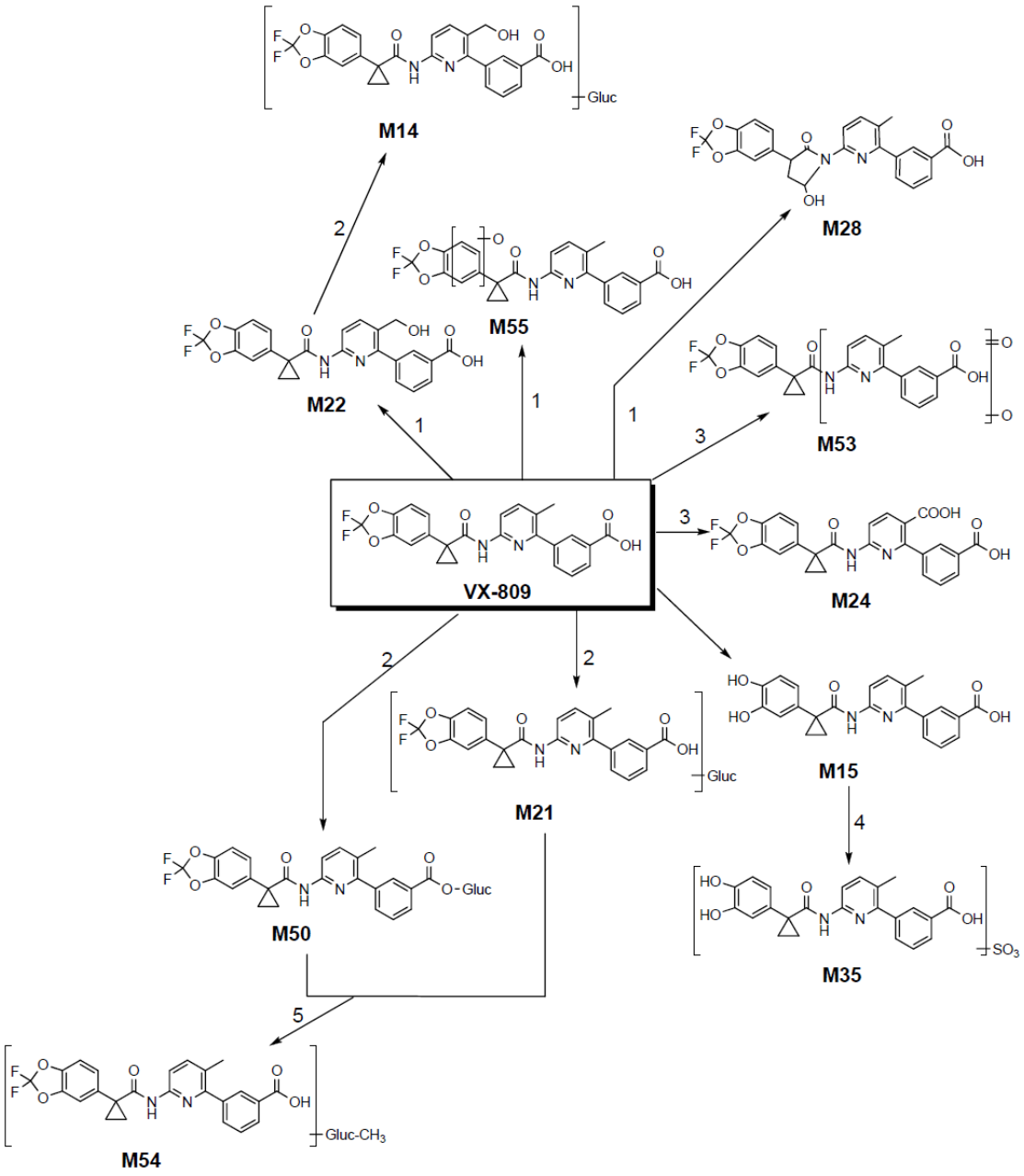


Figure 35 Proposed Metabolic Pathway of VX-809 in Humans
(source: Figure 11-6, VX08-809-004 study report)

Elimination:
The mean apparent terminal half-life (t1/2,□z) for VX-809 was approximately 26 hours. Most of the radioactivity was recovered in feces; accounting approximately 89.5% after oral administration. The total recovery in urine following oral administration was <2%.

Unchanged VX-809 contributed to a combined total in excreta of 24% to 53% of the dose, with only 0.10% to 0.25% in urine. These findings indicate that the renal clearance of VX-809 is negligible.

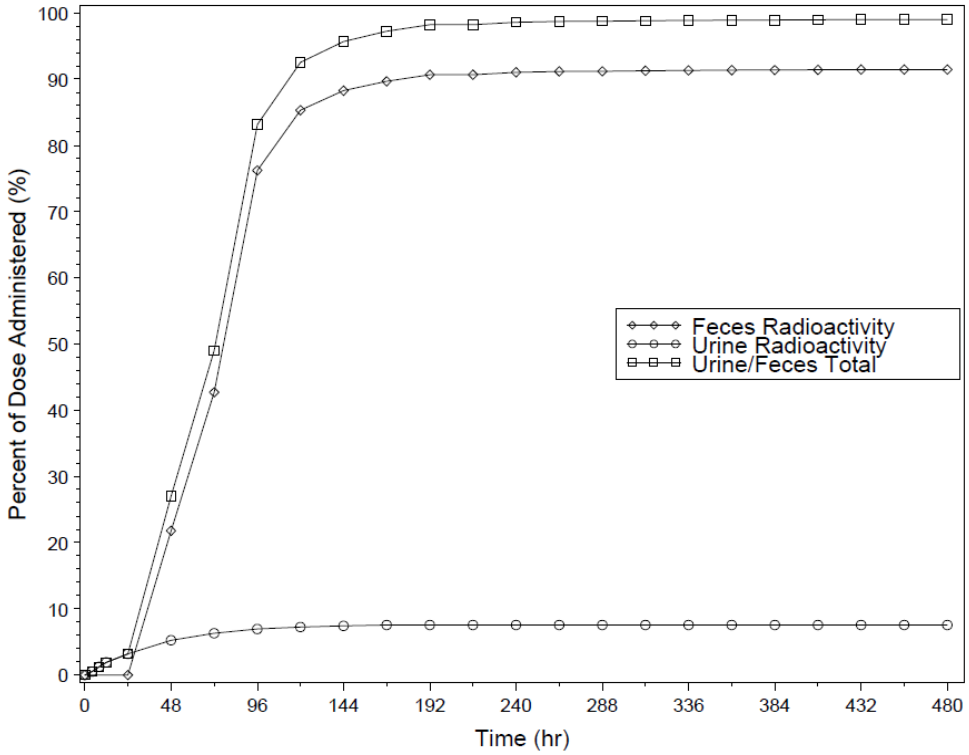


Figure 36. Median Cumulative Percent of Radioactive Dose Recovered in Urine and Feces over 480 Hours Following Oral Administration of a Single 200 mg Dose of [14C]LUM.
(source: Figure 11-5, VX08-809-004 study report)

Percentage of total dose recovered as parent drug on metabolites in urine and feces are shown in Table 69. Most of the radioactivity excreted in feces was associated with unchanged VX-809 and a monohydroxylated metabolite (M22), accounting for means of 42% and 14% of the radioactive dose, respectively, through 216 hours postdose. These findings showed that the majority of VX-809 was excreted unchanged from the body into the feces.

Table 69: VX-809 and Major Metabolites in Human Plasma, Urine and Feces Expressed as Percent of Total Administered Radioactivity

Metabolite Number	Metabolite Identification	Percent of Administered Dose (Mean) Matrix: Plasma	Urine	Feces	Total
VX-809	VX-809	D	0.18 ~~0.17~~	50.7 ~~42.2~~	50.9 ~~42.4~~
M12	Unknown	ND	0.41 ~~0.39~~	ND	0.41 ~~0.39~~
M14	O-VX-809-glucuronide-1	D	0.73 ~~0.68~~	ND	0.73 ~~0.68~~
M15	Desdifluoromethylene-VX-809	ND	ND	0.54 ~~0.42~~	0.54 ~~0.42~~
M16	O-VX-809-glucuronide-2	D	0.77 ~~0.71~~	ND	0.77 ~~0.71~~
M20	Urea adduct of VX-809 glucuronide ~~Unknown~~	ND	3.39 ~~3.18~~	ND	3.39 ~~3.18~~
M21	VX-809-glucuronide-2	D	ND	ND	NA
M22[a e]	O-VX-809-1	D	0.68 ~~0.64~~	17.2 ~~13.5~~	17.9 ~~14.1~~
M24	VX-809 carboxylic acid	D ~~ND~~	0.16 ~~0.15~~	0.27 ~~0.21~~	0.43 ~~0.36~~
M28	Hydroxy-pyrrolidone-VX-809	D	0.07	ND	0.07
M34	Unknown	D	0.01	0.03 ~~0.02~~	0.04 ~~0.03~~
M35	Desdifluoromethylene-VX-809 sulfate	ND	0.01 ~~0.00~~	ND	0.01 ~~0.00~~
M44	Unknown	ND	ND	0.97 ~~0.77~~	0.97 ~~0.77~~
M45	Unknown	ND	ND	0.68 ~~0.51~~	0.68 ~~0.51~~
M46	Unknown	ND	ND	0.53 ~~0.42~~	0.53 ~~0.42~~
M47	Unknown	ND	ND	0.82 ~~0.64~~	0.82 ~~0.64~~
	Total	NA	6.41 ~~6.00~~	71.7 ~~58.7~~	78.1 ~~64.7~~

Source: Metabolite Profiling and Identification Report [redacted] (b) (4) Amended Final Report, Version 2, ~~Table 1. Summary of Metabolites~~, Table 26, Table 28, Table 44, and Table 57.
D: Detected by high performance liquid chromatography (HPLC) analysis; NA: Not applicable; ND: Not detected by HPLC analysis.
[a e] M22 (M469A, O-VX-809-1) was the major metabolite of VX-809 found in rat plasma in [redacted] (b) (4) Study No. 6536-451.

(source: Table 11-4, VX08-809-004 study report Errata)

Conclusion:

Systemic plasma exposure following oral administration of [14C]-VX-809 is mostly due to the parent drug and its major metabolite, hydroxy-pyrrolidone-VX-809 (M28). [14C]-VX-809 is mainly excreted unchanged in feces following oral administration. The renal route plays a minimal role in the elimination of VX-809.

2. Single and multiple dose rising(LUM)

Trial # vx07-809-001

Title: A Phase 1, Randomized, Double-Blinded, Single-Dose Escalation Study in Healthy Subjects Followed by a Multiple-Dose Escalation Study of VX-809 in Healthy Subjects

Objective:
Part A and B: To evaluate the pharmacokinetics (PK) of VX-809 following administration of single ascending and descending doses of VX-809 suspension administered to healthy male (part A) and female subjects (part B) in the fasted state.
Part C: To evaluate the effect of food on the PK of single doses of VX-809 suspension administered to healthy male subjects.
Part D: To evaluate the PK of VX-809 following multiple ascending doses of VX-809 suspension administered for 14 days to healthy male and female subjects in the fed state.

Study design and treatment schedule:
This was a Phase 1, 4-part, double-blind, placebo-controlled, randomized, dose-escalation, food-effect and gender-effect study in healthy subjects. It was designed to evaluate the pharmacokinetics (PK), safety, and tolerability of VX-809 and to evaluate the effect of food and gender on VX-809 PK, safety, and tolerability. A total of 64 subjects were randomized and received at least 1 dose of study drug (placebo or VX-809): 16 in the Part A panels (8 in each dosing panel), 9 in Part B, 9 in Part C, and 30 in Part D.

For the first 3 parts (Parts A through C), single doses of VX-809 or placebo were administered and each dosing occasion was followed by at least a 14-day washout period before administration of the next scheduled dose in a crossover scheme. For the last part (Part D), subjects were randomized to receive VX-809 or placebo once a day for 14 days.

- Part A/Panel 1a, single doses of placebo or 75, 200, or 400 mg of VX-809 were administered.
- Part A/Panel 1b, single doses of placebo or 25, 75, 200, or 400 mg of VX-809 were administered.
- Part B, Single doses of placebo or 75, 200, or 400 mg of VX-809 were administered.
- Part C, Single doses of placebo or 200 mg of VX-809 were administered with or without food.
- Part D, Multiple doses of placebo or 50, 100, or 200 mg of VX-809 were administered

Test Product: The VX-809 formulation used in the study was a powder reconstituted as an aqueous suspension for oral administration at the clinical site.

PK Sampling Schedule

- **Blood –** Blood PK samples were drawn predose (0 hour) and 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, 72, 120, 168, 216, and 264 hours postdose following

each single-dose administration. A PK sample was also taken at the Follow-up visit.

- **Urine –** Urine samples were collected and pooled for PK analysis of VX-809 at predose (0 hour), between 0 – 4 hours, 4 – 8 hours, 8 – 12 hours, 12 – 24, 24 - 48, and 48 - 72 hours for subjects enrolled in Part A (Panels 1a and 1b) following each single dose administration. Urine samples were not collected for Parts B (Panel 2) or C (Panel 3).

Results

Single dose PK

- Mean serum lumacaftor concentration vs. time profiles are shown in Figure 37. After a single oral administration under fasting conditions in healthy male subjects, VX-809 was slowly absorbed with a median time to peak concentration in plasma of approximately 3 hours. The elimination of VX-809 displayed 2 exponential phases. The PK parameter estimates suggested a relatively low clearance of VX-809 (1.1 to 1.5 L/hr), limited distribution within the body (mean apparent volume of distribution of 37 to 54 L), and a rather long terminal half-life (23 to 28 hours) over the 25- to 400-mg dose range tested.

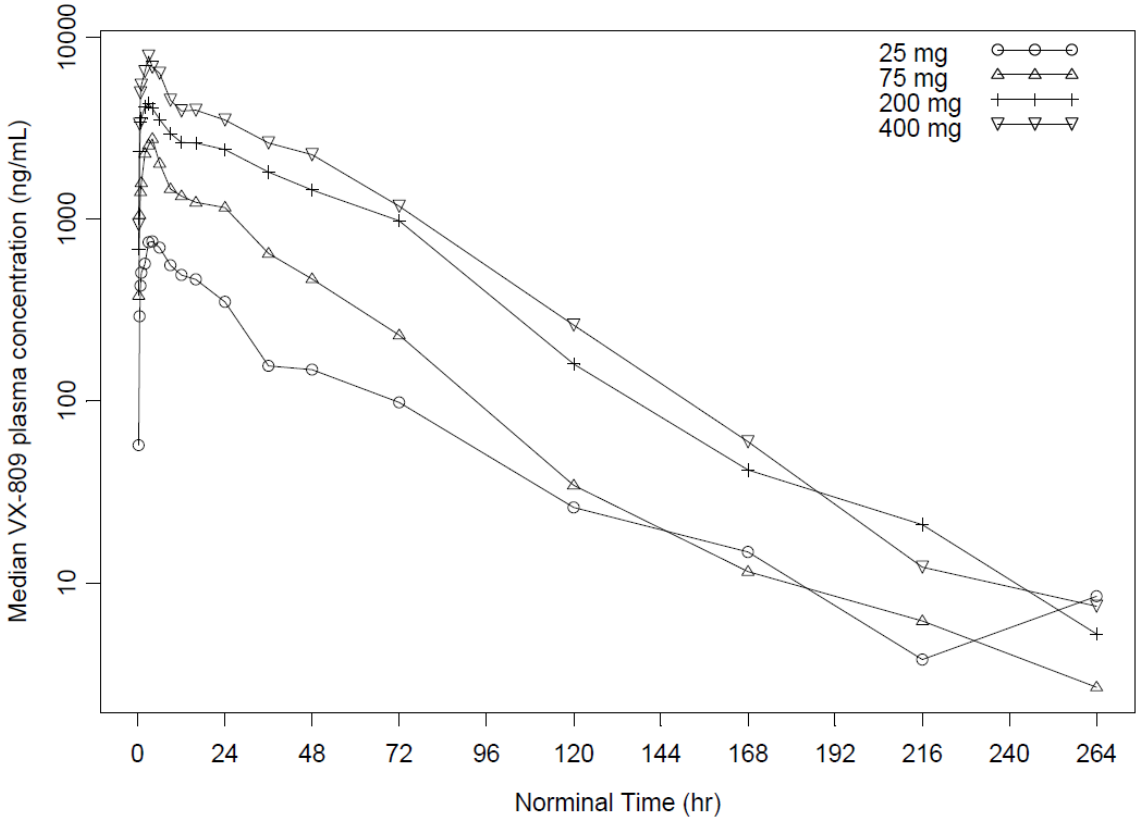


Figure 37. Median VX-809 Concentration (ng/mL) Versus Nominal Time (hours), Part A (Healthy Male Subjects)

(Source – Figure 11-2, Study 809-001 report)

- In healthy female subjects, a slight increase in plasma concentrations was observed compared to healthy male subjects and the increase in dose-normalized Cmax and AUC0-∞ was approximately 37% and 16% (Table 70).

Table 70. Summary of Selected LUM Pharmacokinetic Parameters following a Single dose of LUM suspension, mean(CV%)

Gender	Dose (mg)	N	Tmax* (h)	Cmax (ng/mL)	AUCinf (ng.h/mL)	T1/2 (h)
Male	25	5	4.0 (3.0, 6.1)	886.4 (23.8%)	24606 (35.5%)	28.3 (47.4%)
	75	12	4.0 (2.0, 4.1)	2942.5 (28.5%)	76199 (37.8%)	24.4 (26.8%)
	200	11	3.0 (1.0, 6.0)	4930.0 (26.4%)	185001 (34.3%)	24.7 (33.8%)
	400	11	4.0 (0.75, 4.1)	8332.7 (38.8%)	286789 (31.3%)	25.0 (34.8%)
Female	75	6	3.5 (2.0, 4.0)	3505.0 (25.5%)	85929 (15.3%)	29.5 (13.3%)
	200	5	2.0 (0.3, 6.0)	8060.0 (19.6%)	243986 (33.9%)	29.8 (11.9%)
	400	4	2.5 (2.0, 3.0)	10785 (25.1%)	376565 (18.9%)	25.5 (5.0%)

***median (range)**
(Source: Table 11-1, Table 11-2, study 809-001 report)

- Systemic exposure of lumacaftor as measured by AUC(0–∞), was close to dose proportional, while peak exposure (Cmax) increased in a less than proportional manner over the 75 mg to 400 mg dose range (35% less than unity). Overall, linear elimination kinetics in the terminal phase were observed over a dose range of 25 to 400 mg in male and 75 to 400 mg in female subjects, with the mean terminal half-life ranging from 23 to 28 hours and from 26 to 30 hours, respectively (Table 70 and Table 71).

Table 71. Statistical Assessment of Dose Proportionality (Parts A and B)

Pharmacokinetic Parameter		Estimate	95% Confidence Interval	P-Value
$LN(AUC_{0-\infty})$	Intercept	7.6391	7.3754, 7.9029	<0.0001
	LN(Dose) Slope	0.8384	0.7889, 0.8880	<0.0001
$LN(C_{max})$	Intercept	4.7876	4.4178, 5.1574	<0.0001
	LN(Dose) Slope	0.7264	0.6556, 0.7972	<0.0001

(Source: Table 11-4, study 809-001 report)

- Administration of VX-809 as a suspension with a high-fat breakfast resulted in a tmax delay (from 3 to 6 hours) and an increase in drug exposure (approximately 47% for Cmax and 32% for AUC0-inf) compared to VX-809 administration under fasting conditions (Table 72). The terminal half-life was comparable (approximately 23 hours) regardless of the presence of food during study drug administration. Therefore, food significantly increased the absorption of VX-809 when VX-809 was given as a suspension.

Table 72. Statistical Assessment of Food Effect, Part C

Pharmacokinetic Parameter	Food Condition	N	Least Square Mean	Ratio (%)	90% Confidence Interval	P-value
$AUC_{0-\infty}$	200 – Fast	7	164,084.16	100	ND	ND
(ng*hr/mL)	200 – Fed	7	216,541.16	131.97	112.59, 154.69	0.0152
C_{max}	200 – Fast	7	5365.00	100	ND	ND
(ng/mL)	200 – Fed	7	7890.76	147.08	123.17, 175.63	0.0067

(Source: Table 11-4, study 809-001 report)

- After a single oral dose administration, the mean fraction of VX-809 excreted unchanged in urine ranged from 0.04% to 0.09% across dose ranges, suggesting that the renal clearance of the parent drug is a minor route of VX-809 elimination.

Multiple dose PK

- After repeated oral daily dosing for 14 days with a standard breakfast in male and female subjects, VX-809 dose-independent PK parameters were in agreement with those observed after a single oral dose. Steady state was reached after 5 to 14 days of treatment, with a mean accumulation ratio ranging from 1.9 to 2.2 over the tested dose range (Table 73), which was consistent with a dosing interval (24 hours) close to VX-809 terminal half-life.

Table 73. Summary of Selected LUM Pharmacokinetic Parameters following Mutiple doses of LUM suspension, mean(CV%)

Dose (mg)	Day	N	t_{max} (hr)	C_{max} (ng/mL)	C_{0h} (ng/mL)	AUC_{0-24h} (ng*hr/mL)	V_z/F (L)	CL/F (L/hr)	$t_{1/2\lambda z}$ (hr)	AR
50	1	8	6.00 (3, 12)	1958.75 (324)	-	30,083 (5502)	-	-	-	-
	5	8	6.00 (4, 6)	3631.25 (956)	1703.13 (670)	64,500 (1905)	-	-	-	-
	14	8	6.00 (4, 12)	3598.75 (1040)	2074.13 (1014)	68,117 (24,559)	34.04 (1052)	0.82 (0.28)	29.97 (8.11)	2.25 (0.61)
100	1	8	6.13 (6, 12)	4565.00 (952)	-	69,923 (13,790)	-	-	-	-
	5	8	6.00 (4, 9)	7171.25 (1227)	3450.00 (1310)	123,988 (33,455)	-	-	-	-
	14	8	6.00 (3, 9)	7368.75 (1938)	4382.50 (1806)	130,938 (39,244)	32.03 (6.66)	0.83 (0.25)	28.75 (9.93)	1.87 (0.42)
200	1	8	6.00 (4, 6)	8098.75 (1665)	-	116,718 (37,385)	-	-	-	-
	5	8	6.00 (4.07, 6.05)	12,481.25 (5053)	5931.25 (3508)	222,870 (104,663)	-	-	-	-
	14	8	6.00 (6, 12)	13,027.50 (4366)	7528.75 (3869)	237,770 (97,778)	31.08 (13.05)	0.97 (0.39)	23.14 (7.44)	2.00 (0.30)

AR: accumulation ratio measured by AUC0-24 (day 14) /AUC0-24 (day 1)

Note: t_{max} expressed as median (minimum, maximum) value and C_{max}, C0h, AUC_{0-24}, V_z/F, CL/F, $t_{1/2\lambda z}$ and AR expressed as mean (SD) value.

(Source: Table 11-7, study 809-001 report)

Conclusion: Overall lumacaftor exposure was dose proportional. The pharmacokinetics of lumacaftor is not time-independent.

3. Multiple Rising Dose (LUM/IVA, 7 days)

Trial # vx12-809-008

Title: A Phase 1, Randomized, Placebo- and Active-Controlled, Double-Blind, Parallel, Electrocardiogram Study to Evaluate the Effect of Lumacaftor in Combination With Ivacaftor on the QT/QTc Interval in Healthy Subjects

Objective:
Primary:

- To evaluate the effects of a therapeutic and a supratherapeutic dose of lumacaftor in combination with ivacaftor administered for 7 days on the QT/QTc interval in healthy subjects

Secondary:

- To evaluate the pharmacokinetics (PK) of lumacaftor and its metabolite, M28 (M28-lumacaftor), following multiple ascending doses of lumacaftor administered for 7 days in healthy subjects

Only results related to multiple dose PK are reviewed here. For QT results, please refer to QT-IRT review.

Study design and treatment schedule:
This study was conducted in 2 parts (Parts A and B). Part B was initiated once the supratherapeutic dose had been selected from Part A.

Part A was a sequential, double-blind, randomized, placebo-controlled, multiple-dose escalation, single-center study. Part A was to consist of a maximum of 4 cohorts, but only 3 cohorts were completed with 30 subjects enrolled. There were no dose-limiting safety findings in Part A. However, review of the data from Cohort 2 and Cohort 3 indicated that drug exposure had been saturated at the 1000-mg dose level.
• Cohort 1: LUM 600 mg qd for 7 days (n=8)/placebo (n=2)
• Cohort 2: LUM 1000 mg qd for 7 days (n=8)/placebo (n=2)
• Cohort 3: LUM 1200 mg qd for 7 days (n=8)/placebo (n=2)

Part B of the study was a parallel, double-blind, randomized, placebo- and active-controlled, multiple-dose, single-center ECG study. A total of 170 subjects were randomized in 3 cohorts:
• Cohort A: therapeutic dose (LUM 600mg qd/IVA 250 mg q12h) for 7 days (Days 1 through 7) followed by the supratherapeutic dose (LUM 1000mg qd/IVA450 mg q12h) for an additional 7 days (Days 8 through 14) (n=55)
• Cohort B: Placebo for 14 days (n=58)
• Cohort C: single dose of moxifloxacin on day 14 (n=55)

Test Product: Lumacaftor was supplied as 200 mg tablets. Ivacaftor was supplied as 100 mg and 150 mg tablets.

PK Sampling Schedule

- **Part A –** On Day 1, a plasma sample was collected before study drug dosing. On Day 7, plasma samples were collected before study drug dosing and 1, 2, 3, 4, 6, 8, 10, and 12 hours after study drug dosing. On Days 8 through 11, plasma samples were also collected 24 (Day 8), 48 (Day 9), 72 (Day 10), and 96 (Day 11) hours after study drug dosing.
- **Part B –** On Days 7 (Cohorts A and B) and 14 (all cohorts), plasma samples were collected before study drug dosing and 0.5, 1, 2, 3, 4, 6, 9, 12, and 24 hours after

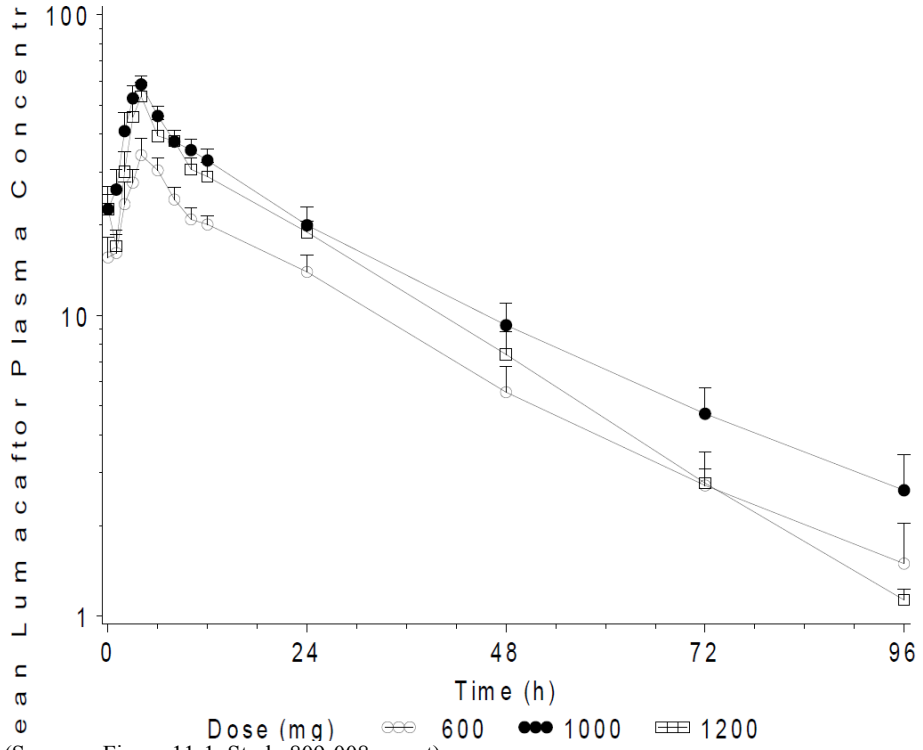
study drug dosing. Additional plasma samples matching the 0- to 24-hour time points (on Days 7 and/or 14) were collected on Day -1 (i.e., at -24, -23.5, -23, -22, -21, -20, -18, -15, -12, and 0 hours before the first dose of study drug on Day 1).

Results

Part A-Lumacaftor PK

After multiple ascending doses of lumacaftor qd for 7 days, the mean lumacaftor plasma concentration versus time profiles after lumacaftor administration on Day 7 are shown in Figure 38 (semi-log scale).

Figure 38. Mean Lumacaftor Plasma Concentrations Versus Time Profiles After Lumacaftor Administration on Day 7



(Source – Figure 11-1, Study 809-008 report)

The lumacaftor exposure, represented by AUCτ and Cmax, was approximately dose proportional from LUM 600 mg qd to LUM 1000 mg qd (1.6-fold increase in AUCτ and 1.7-fold increase in Cmax versus 1.7-fold increase in dose); the lumacaftor exposure was slightly decreased when the lumacaftor dose was increased from 1000 to 1200 mg qd (Figure 38, Table 74).

Table 74. Mean (SD) Lumacaftor Pharmacokinetic Parameters After Lumacaftor Administration on Day 7 (Part A)

	Treatment Group		
Parameter	**LUM 600 mg qd [N = 8]**	**LUM 1000 mg qd [N = 8]**	**LUM 1200 mg qd [N = 8]**
AUC_{τ} (µg·h/mL)	497 (132)	798 (209)	708 (179)
C_{max} (µg/mL)	35.6 (12.6)	60.4 (10.5)	59.2 (14.2)
t_{max} (h)[a]	4.00 (3.00, 8.00)	3.50 (2.00, 4.07)	4.00 (3.00, 6.00)
$t_{1/2}$ (h)	20.98 (5.96)	20.79 (4.73)[b]	20.55 (3.34)
CLss/F (h/L)	1.27 (0.275)	1.33 (0.367)	1.79 (0.420)
V_z/F (L)	36.9 (5.23)	40.0 (11.9)[b]	52.4 (12.5)

n*=Number of subjects for whom parameter cannot be derived because of non-calculable concentrations.
(Source – Table 2-3, Study 809-008 report)

The mean (SD) values for selected PK parameters for lumacaftor and ivacaftor on Day 7 following the therapeutic dose regimen (LUM 600 mg qd/IVA 250 mg q12h) and on Day 14 following the supratherapeutic dose regimen (LUM 1000 mg qd/IVA 450 mg q12h) are shown in Table 75.

The systemic exposure of both LUM and IVA as measured by AUCτ increased in a less than dose-proportional manner from LUM 600 mg qd/ IVA 250 mg q12h to LUM 1000 mg qd/IVA 450 mg q12h. The mean lumacaftor AUCτ was similar (525 to 566 µg·h/mL) and Cmax increased (35.9 to 41.1 µg/mL) when the therapeutic dose regimen was changed to the supratherapeutic regimen; the median tmax was the same (4.00 hours) for the 2 dose regimens.

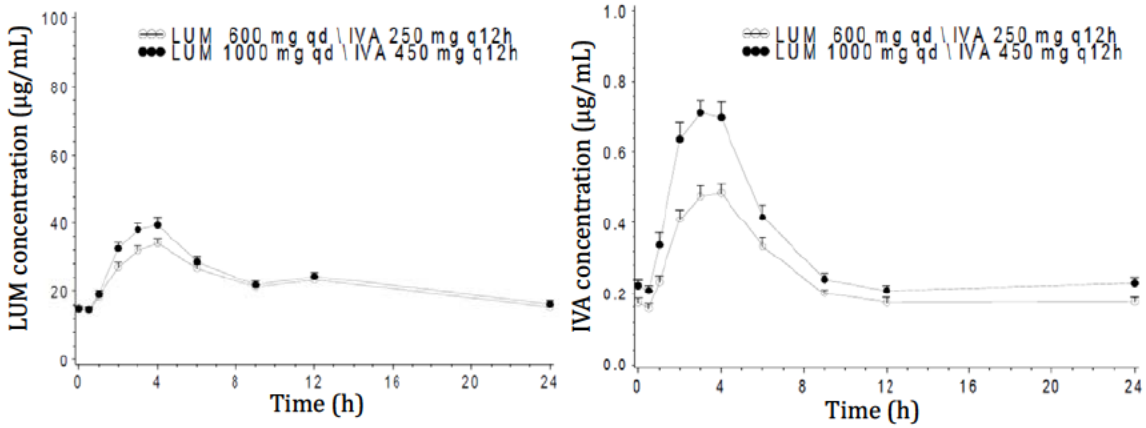
The mean AUCτ and Cmax were increased by approximately 1.3- to 1.4-fold for ivacaftor when the therapeutic dose regimen was changed to the supratherapeutic dose regimen, in which the ivacaftor dose was increased by 1.8-fold; the median tmax was similar between the 2 dose regimens.

Table 75. Mean (SD) Pharmacokinetic Parameters of Lumacaftor and Ivacaftor After Administration of Lumacaftor in Combination With Ivacaftor in Therapeutic Dose and Supratherapeutic Dose in Cohort A (Part B)

	Treatment	
Parameter	Therapeutic Dose Regimen, Day 7 [N = 50]	Supratherapeutic Dose Regimen, Day 14 [N = 36]
Lumacaftor		
AUC_τ (µg·h/mL)	525 (157)	566 (154)
C_{max} (µg/mL)	35.9 (9.69)	41.1 (10.9)
t_{max} (h)[a]	4.00 (0.52, 6.00)	4.00 (2.00, 4.00)
M28-lumacaftor		
AUC_τ (µg·h/mL)	43.9 (11.2)[b]	60.5 (14.8)
C_{max} (µg/mL)	2.02 (0.522)	2.77 (0.751)
t_{max} (h)[a]	11.92 (0.52, 23.92)	11.92 (0.00, 24.00)
Ivacaftor		
AUC_τ (µg·h/mL)	3.58 (1.35)	4.83 (1.77)
C_{max} (µg/mL)	0.573 (0.197)	0.797 (0.286)
t_{max} (h)[a]	3.52 (2.00, 6.00)	3.00 (1.05, 4.00)
M1-ivacaftor		
AUC_τ (µg·h/mL)	12.3 (3.90)	16.2 (4.54)
C_{max} (µg/mL)	2.02 (0.559)	2.88 (0.714)
t_{max} (h)[a]	4.00 (2.00, 6.00)	4.00 (2.00, 4.00)
M6-ivacaftor		
AUC_τ (µg·h/mL)	40.5 (14.1)	60.1 (22.9)
C_{max} (µg/mL)	4.61 (1.44)	7.16 (2.57)
t_{max} (h)[a]	6.00 (3.00, 9.00)	4.02 (4.00, 6.10)

Sources: Table 14.4.2.7, Table 14.4.2.8, Table 14.4.2.9, Table 14.4.2.10, and Table 14.4.2.11.
AUC_τ: area under the concentration versus time curve from the time of dosing to the end of dosing interval, τ = 24 hours for lumacaftor and M28-lumacaftor and τ = 12 hours for ivacaftor, M1-ivacaftor, and M6-ivacaftor; C_{max}: maximum observed concentration; h: hours; IVA: ivacaftor; LUM: lumacaftor; N: data set sample size; q12h: every 12 hours; qd: daily; SD: standard deviation; t_{max}: time of C_{max}.
Note: Supratherapeutic dose regimen: LUM 1000 mg qd/IVA 450 mg q12h; Therapeutic dose regimen: LUM 600 mg qd/IVA 250 mg q12h.
[a] Median (minimum, maximum) values are presented for t_{max}.
[b] n = 49; one AUC_τ value was not estimated due to insufficient data in the dosing interval.
(Source – Table 2-4, Study 809-008 report)

Figure 39. Mean Lumacaftor and Ivacaftor Plasma Concentrations Versus Time Profiles After Administration of Lumacaftor in Combination With Ivacaftor in Cohort A (Part B)



(Source –Figure 11-5, Figure 11-7, Study 809-008 report)

Conclusion: Overall LUM/IVA exposure increased less than dose proportional beyond therapeutic dose.

SPECIFIC POPULATION

4. Hepatic Impairment (LUM/IVA)

Trial # VX13-809-010

Title: A Phase 1, Open-Label Study to Assess the Pharmacokinetics and Safety of Multiple Doses of Lumacaftor in Combination With Ivacaftor in Subjects With Moderate Hepatic Impairment and in Matched Healthy Subjects

Objective:

Primary:

- To compare the pharmacokinetics (PK) of multiple doses of lumacaftor in combination with ivacaftor in subjects with moderate hepatic impairment to the PK in matched healthy subjects

Secondary:

- To compare the PK of a lumacaftor metabolite, M28 (M28-lumacaftor), following multiple doses of lumacaftor in combination with ivacaftor in subjects with moderate hepatic impairment to the PK in matched healthy subjects
- To compare the PK of ivacaftor metabolites, M1 and M6 (M1-ivacaftor and M6-ivacaftor), following multiple doses of lumacaftor in combination with ivacaftor in subjects with moderate hepatic impairment to the PK in matched healthy subjects
- To assess the safety and tolerability of multiple doses of lumacaftor in combination with ivacaftor in subjects with moderate hepatic impairment and in matched healthy subjects

Study design: Open-label, multiple-dose, multicenter study

Treatment groups and sample size:

- moderate hepatic impairment (N=12, group A)
- healthy normal liver function (N=12, group B)

Duration of Treatment: Lumacaftor (200 mg every 12 hours [q12h]) in combination with ivacaftor (250 mg q12h) was administered orally on Days 1 through 9 and with only a morning dose on Day 10.

Reviewer's comment:

As LUM exposure is twice as high in healthy volunteers as in CF patients, the dose of LUM used in this study is half of the proposed dose in CF patients.

PK Sampling Schedule

- **Blood – Day 1 at** pre-dose, 1, 2, 4, 5, 6, 8, and 12 hours after the morning dose of study drug. **Days 2, 3, 4, 5, 6, and 8:** A single blood sample was collected before the morning dose of study drug. **Day 10 at** pre-dose, 1, 2, 4, 5, 6, 8, 12, 24 (Day 11), 48 (Day 12), 96 (Day 14), and 144 (Day 16) hours after the last dose of study drug.

Pharmacogenomic evaluation
Optional samples were collected for potential exploratory analysis.

Results:
Pharmacokinetic results

Day 1 Pharmacokinetics:
Summary statistics of PK parameters on Day 1 are presented in Table 76. On Day 1, the exposure to parent lumacaftor and ivacaftor was comparable in subjects with moderate hepatic impairment and matched healthy subjects. The metabolite (M28-lumacaftor, M1-ivacaftor, and M6-ivacaftor) exposures (Cmax and area under the concentration versus time curve from time 0 to last measurable concentration [AUC0-last]) were lower in subjects with moderate hepatic impairment than healthy subjects. Lumacaftor and ivacaftor reached peak plasma concentrations at 2 to 4 hours after dosing.

Table 76. Summary of Pharmacokinetic Parameters for Total Lumacaftor, Ivacaftor, M28-lumacaftor, M1-ivacaftor, and M6-ivacaftor in Subjects With Moderate Hepatic Impairment and in Matched Healthy Subjects on Day 1

Analyte	Group	N	t_{max}[a] (h)	C_{max}[b] (ng/mL)	$AUC_{0\text{-last}}$[b] (ng•h/mL)
Lumacaftor	A	11	4.00 (2.00, 5.00)	11800 (3040)	90100 (30200)
	B	11	2.00 (1.97, 4.95)	11900 (2220)	79100 (18000)
Ivacaftor	A	11	4.00 (2.00, 6.00)	1260 (541)	9900 (4970)
	B	11	4.00 (4.00, 4.95)	1460 (429)	9750 (2910)
M28-lumacaftor	A	11	11.98 (11.95, 12.00)	163 (65.8)	1170 (563)
	B	11	11.97 (11.95, 12.00)	265 (69.8)	2120 (616)
M1-ivacaftor	A	11	5.00 (4.00, 8.00)	2280 (835)	15800 (5630)
	B	11	4.00 (4.00, 5.02)	3240 (735)	19900 (4760)
M6-ivacaftor	A	11	8.00 (6.00, 12.00)	1090 (619)	7650 (4310)
	B	11	6.00 (4.95, 8.00)	1410 (661)	10300 (4670)

Sources: Table 14.4.1.6 through Table 14.4.1.10.
$AUC_{0\text{-last}}$: area under the concentration versus time curve from the time 0 to last measurable concentration; C_{max}: maximum observed concentration; N: total sample size; SD: standard deviation; t_{max}: time of maximum concentration.
Note: Group A: Subjects with moderate hepatic impairment; Group B: Healthy subjects.
[a] Median (minimum, maximum).
[b] Mean (SD).
(Source –Table 11-1, Study 809-010 report)

Day 10 Pharmacokinetics:

The PK parameters of lumacaftor, ivacaftor, M28-lumacaftor, M1-ivacaftor, and M6-ivacaftor are summarized in Table 77. Both lumacaftor and ivacaftor total exposures (Cmax and AUC) were higher in subjects with moderate hepatic impairment than in healthy subjects. M1-ivacaftor and M6-ivacaftor exposures were comparable between subjects with moderate hepatic impairment and healthy subjects. The M28-lumacaftor exposures were lower in subjects with moderate hepatic impairment compared with healthy subjects. Plots for mean concentration versus nominal time (0 to 12 hours) in subjects with moderate hepatic impairment and healthy subjects are shown in Figure 40.

When dosed in combination with lumacaftor, the half-life of ivacaftor is approximately 9.3 hours in healthy volunteers. The $t_{1/2}$ was prolonged for ivacaftor and its metabolites M1-ivacaftor and M6-ivacaftor in subjects with moderate hepatic impairment compared with healthy subjects. The $t_{1/2}$ for lumacaftor was similar in subjects with moderate hepatic impairment and healthy subjects (Table 77).

For comparison of C_{max} and AUC_{τ} between subjects with moderate hepatic impairment and healthy subjects, the GLSMRs for lumacaftor were 1.33 (90% CI: 1.04, 1.68) for C_{max} and 1.47 (90% CI: 1.14, 1.88) for AUC_{τ}. The GLSMRs for ivacaftor were 1.26 (90% CI: 0.91, 1.75) for C_{max}, and 1.61 (90% CI: 1.12, 2.34) for AUC_{τ} (Table 78).

Table 77. Summary of Pharmacokinetic Parameters for Total Lumacaftor, Ivacaftor, M28-lumacaftor, M1-ivacaftor, and M6-ivacaftor in Subjects With Moderate Hepatic Impairment and in Matched Healthy Subjects on Day 10

Analyte	Group	N	t_{max}[a] (h)	C_{max}[b] (ng/mL)	AUC_{τ}[b]	$t_{½}$[b] (h)	CL_{ss}/F[b]	V_z/F[b]
Lumacaftor	A	11	4.00 (0.98, 5.00)	23000 (6120)	219000 (68100)	24.34 (9.91)	0.987 (0.289)	36.9 (24.9)
	B	11	2.00 (0.00, 6.00)	18000 (6320)	153000 (56800)	25.20 (9.94)	1.48 (0.540)	50.1 (17.4)
Ivacaftor	A	11	4.00 (1.98, 5.00)	773 (369)	6700 (3710)	13.34 (5.29)	52.4 (32.6)	870 (428)
	B	11	2.00 (1.98, 6.00)	580 (218)	3710 (1270)	9.34 (3.81)	74.7 (24.6)	1000 (550)
M28-lumacaftor	A	11	2.00 (0.00, 6.00)	1250 (457)	14200 (5180)	NR	NR	NR
	B	11	4.00 (2.00, 6.00)	1560 (536)	17600 (6210)	NR	NR	NR
M1-ivacaftor	A	11	4.00 (3.98, 6.05)	2100 (1070)	16200 (8310)	19.39 (4.09)	20.5 (11.9)	547 (259)
	B	11	4.00 (4.00, 6.00)	2280 (629)	13900 (3760)	14.69 (2.00)	19.2 (5.00)	400 (92.6)
M6-ivacaftor	A	11	5.00 (0.00, 6.05)	4000 (1590)	38400 (16900)	16.64 3.70)	7.85 (3.61)	184 (82.2)
	B	11	5.00 (0.00, 7.98)	3790 (1800)	30100 (14800)	13.94 (3.54)	10.7 (6.01)	199 (85.6)

Sources: Table 14.4.1.6 through Table 14.4.1.10.

AUC_{τ}: area under the concentration versus time curve from time 0 to time τ, the dosing interval 12 hours; CL_{ss}/F: apparent steady-state clearance; C_{max}: maximum observed concentration; N: total sample size; NR: not reported; SD: standard deviation; $t_{½}$: terminal phase half-life; t_{max}: time of maximum concentration; Vz/F: apparent volume of distribution.

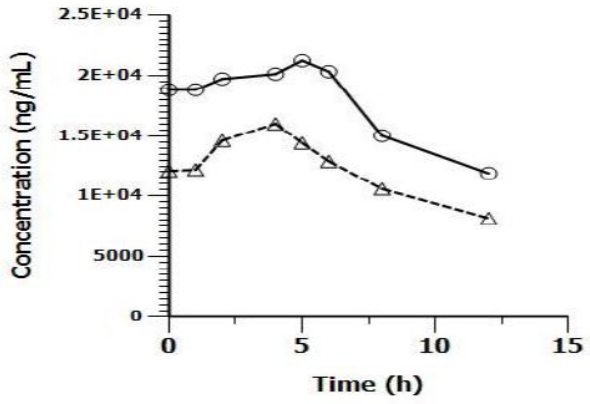
Note: Group A: Subjects with moderate hepatic impairment; Group B: Healthy subjects.

[a] Median (minimum, maximum).

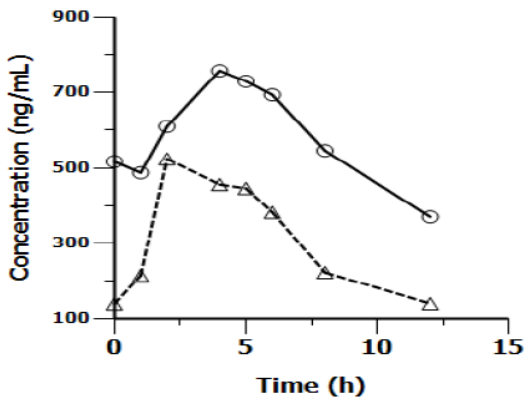
[b] Mean (SD).

(Source –Table 11-2, Study 809-010 report)

Lumacaftor



Ivacaftor



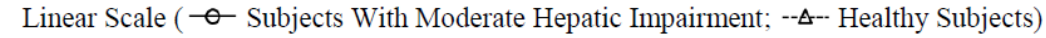


Figure 40. Mean LUM/IVA Plasma Concentration-Time Profiles Following Repeat Dose (LUM/IVA 200/250 mg q12h for 10 Days)
(Source – Figure 11-1, Study 809-010 report)

Table 78. Summary of Results of LUM/IVA Pharmacokinetic Parameters in Subjects with Moderate Hepatic Impairment Compared with Healthy Subjects

Day	Analyte	Parameter	Group comparison	Mean	Ratio	90% CI of the ratio
Day 10	LUM	AUCτ (ng.h/mL)	Moderate hepatic impairment/healthy	219000/153000	1.31	(1.04, 1.65)
		Cmax (ng/mL)	Moderate hepatic impairment/healthy	23000/18000	1.47	(1.14, 1.88)
	IVA	AUCτ (ng.h/mL)	Moderate hepatic impairment/healthy	6700/3710	1.26	(0.91, 1.75)
		Cmax (ng/mL)	Moderate hepatic impairment/healthy	773/580	1.62	(1.12, 2.34)

(Source –Table 11-1, Table 11-2, Table 11-3, Study 809-010 report)

Plasma Protein Binding:

- Lumacaftor, ivacaftor, and their metabolites (M28-lumacaftor, M1-ivacaftor, and M6-ivacaftor) were tightly bound to plasma proteins; overall, the unbound fraction was less than 1%.
- The extent of protein binding was similar in subjects with moderate hepatic impairment and healthy subjects.

Table 79. Summary of Unbound Percentage of Lumacaftor, M28-lumacaftor, Ivacaftor, M1-ivacaftor, and M6-ivacaftor in Plasma by Nominal Time and Group

			Group A		Group B	
Analyte	Dose Day	Time (h)	N	Mean (CV%)	N	Mean (CV%)
Lumacaftor	1	0	11	0.33 (22.4)	11	0.27 (8.4)
	10	4	11	0.25 (30.2)	11	0.18 (12.2)
	10	12	11	0.36 (13.3)	11	0.27 (14.0)
M28-lumacaftor	1	0	10	0.13 (15.8)	8	0.10 (14.5)
M1-ivacaftor	1	0	11	0.12 (32.5)	11	0.10 (17.4)
	10	4	8	0.17 (27.6)	7	0.14 (20.6)
M6-ivacaftor	1	0	10	0.11 (0.30)	7	0.08 (0.10)

(Source –Table 11-4, Study 809-010 report)

Conclusions:

Patients with moderate hepatic impairment (Child-Pugh Class B) had approximately 50% higher exposures (AUC0-12h) than matched healthy subjects. The ORKAMBI dose should be reduced to 2 tablets (400/250 mg) in the morning and 1 tablet(200/125) in the evening (lumacaftor 600 mg/ivacaftor 375 mg total daily dose) for these subjects.

The impact of mild hepatic impairment (Child-Pugh Class A) on pharmacokinetics of lumacaftor has not been studied, but the increase in exposure is expected to be less than 50%. Therefore, no dose adjustment is necessary for patients with mild hepatic impairment.

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, use with caution at a maximum dose of 1 tablet in the morning and 1 tablet in the evening (lumacaftor 400 mg /ivacaftor 250 mg total daily dose), or less, in patients with severe hepatic impairment after weighing the risks and benefits of treatment.

5. Pancreatic insufficiency (LUM)

Trial # VX07-809-002

Title: A Phase 1, Open-Label, Randomized, Single-Dose Pharmacokinetic Study of VX-809 in Pancreatic-Insufficient Subjects with Cystic Fibrosis

Objective:

Primary:

- To evaluate the pharmacokinetics (PK) of VX-809 in pancreatic-insufficient subjects with cystic fibrosis (CF)

Secondary:

- To evaluate the effect of food on the PK of VX-809 in pancreatic-insufficient subjects with CF

Study design: Open-label, randomized, single-dose, 2-period crossover, PK study. There were 8 subjects (male or female) with CF who were pancreatic-insufficient. Each subject received a single oral dose of VX-809 on 2 separate occasions, once in the fasted state and once after the intake of a standard high-fat, high-calorie CF breakfast taken with oral enzyme supplements.

To be enrolled, CF Patients must have a history of exocrine pancreatic insufficiency by clinical symptomatology, fecal elastase ≤200 µg/g or fecal fat collection (must have been on pancreatic enzyme replacement therapy).

Subjects were randomly assigned to 1 of 2 treatment sequences:
• Treatment Sequence 1:
Dosing Period 1: Single oral dose of 200-mg VX-809 in the fasted state, followed by
Dosing Period 2: Single oral dose of 200-mg VX-809 in the fed state
• Treatment Sequence 2:
Dosing Period 1: Single oral dose of 200-mg VX-809 in the fed state, followed by
Dosing Period 2: Single oral dose of 200-mg VX-809 in the fasted state

Test Product: Oral dose of 200 mg (as 4x 50-mg capsules)

PK Sampling Schedule
Blood samples were collected for PK analysis predose and 0.5, 1, 2, 3, 4, 6, 9, 15, 24, 48, 72, and 168 hours after dosing.

Results:
Pharmacokinetic results
After a single-dose administration of VX-809 200 mg following an overnight fast, VX-809 rapidly reached systemic circulation in CF subjects who were pancreatic-insufficient. Plasma concentration peaked at 4 hours. The mean Cmax and total plasma exposure (AUC0-∞) values were 9880 ng/mL and 189,230 ng*hr/mL, respectively. Mean oral clearance was 1.2 L/hr and apparent volume of distribution was 35.7 L. The mean terminal half-life was 23.4 hours.
Single-dose administration of VX-809 200 mg with a standard high-fat, high-calorie CF breakfast to the same cohort of subjects resulted in a longer median time to peak plasma concentration compared to the fasting condition (6 hours vs. 4 hours). Cmax decreased significantly by 23% with food, whereas total plasma exposure increased by 12% compared to the fasting condition. However, the difference in total exposure (AUC0-∞) was not statistically significant and the 90% CI (0.98-1.28) was close to the acceptance range of 0.80-1.25. These results suggest that food might affect the rate of absorption of VX-809 without modifying the extent when VX-809 is administered as a capsule. The elimination of VX-809 was not affected by food condition.

Table 80. Summary of LUM Pharmacokinetic Parameters in Subjects with pancreatic insufficiency, by food status

DOSE (mg)		T_{max} (hr)	C_{max} (ng/mL)	AUC_{last} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	Vz/F (L)	CL/F (L/hr)	Half-life (hr)
200	N	7	7	7	7	7	7	7
Fast	NObs	7	7	7	7	7	7	7
	Mean	3.99	9880	185213	189230	35.66	1.19	23.37
	SD	1.00	1080	72601	77051	12.64	0.380	11.69
	Min	3.00	8920	121133	122490	21.97	0.610	10.67
	Median	4.00	9440	152219	155064	31.02	1.29	23.41
	Max	6.00	12000	310624	326067	54.29	1.63	42.14
	CV%	25.11	10.95	39.20	40.72	35.44	32.22	50.02
200	N	7	7	7	7	7	7	7
Fed	NObs	7	7	7	7	7	7	7
	Mean	6.30	7820	212165	216564	33.30	1.05	23.41
	SD	2.69	1970	79734	83677	17.90	0.400	11.30
	Min	3.00	4810	116634	118017	19.00	0.600	11.13
	Median	6.10	7840	192291	192338	30.60	1.04	22.81
	Max	9.10	10000	330561	333176	69.80	1.69	42.88
	CV%	42.69	25.15	37.58	38.64	53.82	38.25	48.28

(Source –Table 11-1, Study 809-002 report)

Table 81. Statistical Assessment of Food Effect

PK Parameter	Food Status	Least Square Mean	Ratio (%)	90% CI	Pvalue
$AUC_{0-\infty}$	Fast	173010	-	-	-
(ng*hr/mL)	Fed	193891	1.12	0.98, 1.28	0.1448
AUC_{0-last}	Fast	170193	-	-	-
(ng*hr/mL)	Fed	190990	1.12	0.98, 1.29	0.1585
C_{max}	Fast	9845	-	-	-
(ng/mL)	Fed	7589	0.77	0.61, 0.97	0.0734

(Source –Table 11-2, Study 809-002 report)

Conclusions:
No significant food effect was observed with LUM capsules in CF patients with pancreatic insufficiency. LUM/IVA was administered with high fat food in later efficacy/safety studies to optimize the exposure of IVA.

6. Pediatric, 6-11 yr

Trial # VX13-809-011

Title: A Phase 3, Open-Label Study to Evaluate the Pharmacokinetics, Safety, Tolerability, and Efficacy of Lumacaftor in Combination With Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation

Objective:
Primary: To evaluate the PK of multiple doses of lumacaftor in combination with ivacaftor.

Study design: Open-label, multiple-dose, multicenter study. A total of 5 subjects in Cohort 1 (6 through 8 years of age) and 5 subjects in Cohort 2 (9 through 11 years of age) were enrolled, completed dosing, and completed Part A. All 10 subjects were administered LUM 200 mg q12h/IVA 250 mg q12h for 14 days. (Figure 41)

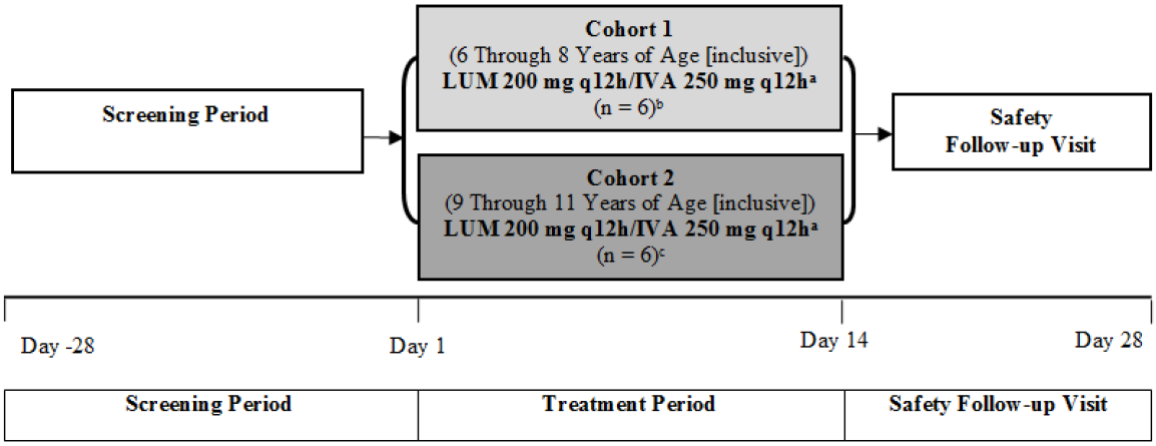


Figure 41. Schematic of study design for part A.
(Source: Figure 2-1, study report 809-011)

Test Product: LUM 200 mg q12h/IVA 250 mg q12h (1 × LUM 200-mg/IVA 125-mg fixed-dose tablet q12h + 1 × IVA 125-mg tablet q12h) was administered orally

PK Sampling Schedule
For the evaluation of plasma concentrations of lumacaftor, M28-lumacaftor, ivacaftor, M1-ivacaftor, and M6-ivacaftor for Part A, blood samples were collected from all subjects as follows:

- Day 1: before the morning dose, and at 2, 4, 6, and 12 hours after the morning dose
- Day 7: before the morning dose
- Day 14: before the morning dose, and at 4, 6, and 12 hours after the morning dose
- Day 15: any time between 24 to 96 hours after the morning dose on Day 14

Pharmacogenomic evaluation
Optional buccal swab samples were collected for potential exploratory analysis.

Results:
Pharmacokinetic results
The summary of PK parameters stratified by the age groups (Cohort 1: 6 through 8 years of age; Cohort 2: 9 through 11 years of age) generated from NCA of lumacaftor, ivacaftor, and their associated metabolites data are presented in Table 82.

Following a LUM 200 mg q12h regimen given in combination with IVA 250 mg q12h for 14 days, the steady state concentration of lumacaftor appeared to be reached by approximately Day 7, which is consistent with the adult CF population (Study 005 and Study 006). The mean lumacaftor C12h value on Day 14 in this study was modestly higher than those of the adults in Study 102 (C12h mean [range] on Day 56: 10400 [4210 to 20500] ng/Ml) When evaluated by age cohorts, Cohort 1 (6 through 8 years of age) appeared to have higher concentration levels of lumacaftor than those in Cohort 2 (9 through 11 years of age) on both Day 1 and Day 14. The difference in exposures between Cohort 1 versus Cohort 2 is likely

due to the differences in weight between the 2 groups. Similar to lumacaftor, the levels of M28-lumacaftor in Cohort 1 was higher relative to Cohort 2.

Following an IVA 250 mg q12h regimen given in combination with LUM 200 mg q12h for 14 days, the steady state concentration of ivacaftor appeared to be reached by approximately Day 7, which is consistent with the adult CF population (Study 005 and Study 006). The ivacaftor trough concentration over 14 days of dosing demonstrated the highest concentration on Day 1, and much lower levels on Day 7 and Day 14. This shape of the trough concentration versus time profile is consistent with previous lumacaftor and ivacaftor interaction studies in adults, which showed a rapid decrease in the levels of ivacaftor due to the induction of its metabolism by lumacaftor (Study 005 and Study 006). The mean ivacaftor C12h values on Day 14 in this study are higher than those of the adults in Study 102 (C12h mean [range] on Day 56: 98.0 [37.2 to 324] ng/mL for ivacaftor). When evaluated by age cohorts, Cohort 1 (6 through 8 years of age) appeared to have modestly lower concentration levels of ivacaftor on Day 1, but substantially lower concentration levels of these analytes than those in Cohort 2 (9 through 11 years of age) on Day 14. The large difference observed on Day 14 relative to Day 1 may be due to the greater magnitude of induction in subjects in Cohort 1 because they have much high levels of lumacaftor than subjects in Cohort 2.

The cross-study and age cohort comparison should be interpreted with caution due to the small number of subjects in this study and Study 102.

Table 82. Summary of Pharmacokinetic Parameters by Age Cohort

			Day 1			Day 14		
			Median (min, max)	Arithmetic Mean (SD)		Median (min, max)	Arithmetic Mean (SD)	
Analyte	Age Cohort (years)	N	t_{max} (h)	C_{4h} (ng/mL)	C_{12h} (ng/mL)	t_{max} (h)	C_{4h} (ng/mL)	C_{12h} (ng/mL)
Lumacaftor	Cohort 1 (6 to 8)	5	4.10 (2.08, 11.13)	15600 (7650)	10600 (3910)	4.08 (0.00, 6.17)	29900 (10600)	16700 (9310)
	Cohort 2 (9 to 11)	5[a]	4.05 (1.98, 6.03)	14800 (6570)	6080 (1930)	4.07 (0.00, 6.47)	17700 (5330)	8600 (3110)
M28-lumacaftor	Cohort 1 (6 to 8)	5	11.23 (6.47, 11.82)	191 (81.1)	344 (79.5)	0.00 (0.00, 6.17)	2850 (1090)	2470 (1430)
	Cohort 2 (9 to 11)	5[a]	11.05 (6.42, 11.45)	160 (82.9)	269 (132)	0.00 (0.00, 6.47)	1030 (188)	977 (220)
Ivacaftor	Cohort 1 (6 to 8)	5	4.10 (2.08, 6.47)	1900 (760)	655 (120)	4.08 (3.98, 6.08)	658 (345)	95.6 (17.9)
	Cohort 2 (9 to 11)	5[a]	4.33 (4.05, 6.05)	1940 (780)	921 (426)	4.10 (4.02, 6.47)	578 (337)	379 (465)
M1-ivacaftor	Cohort 1 (6 to 8)	5	4.13 (4.03, 6.47)	4560 (1310)	1760 (567)	4.08 (3.98, 6.08)	2590 (1280)	333 (55.2)
	Cohort 2 (9 to 11)	5[a]	6.03 (4.13, 6.05)	3320 (1270)	1780 (357)	4.10 (4.02, 6.47)	2130 (1610)	1170 (1150)
M6-ivacaftor	Cohort 1 (6 to 8)	5	6.23 (5.95, 11.13)	2360 (780)	3340 (977)	4.08 (0.00, 6.08)	5270 (1860)	2200 (420)
	Cohort 2 (9 to 11)	5[a]	11.03 (6.05, 11.10)	1250 (883)	2260 (1700)	4.18 (0.00, 6.47)	2950 (1400)	2530 (1350)

(Source –Table 11-3, Study 809-011 report)

Conclusions:
The time required to achieve steady state plasma concentration of lumacaftor, ivacaftor, and their associated metabolites in subjects 6 through 11 years of age with CF is comparable to that of adult subjects with CF. Based on Ctrough, both LUM and IVA exposures are higher in 6-11yr old who took 200/250 mg BID compared to that of adult with 400/250 mg BID regimen.

DRUG-DRUG INTERACTIONS

7. DDI with Ciprofloxacin, Itraconazole, and Rifampin

Trial # VX12-809-009

Title: A Phase 1, Open-label Study to Examine the Effect of Ciprofloxacin, Itraconazole, and Rifampin on the Pharmacokinetics of Lumacaftor in Combination With Ivacaftor in Healthy Adult Subjects

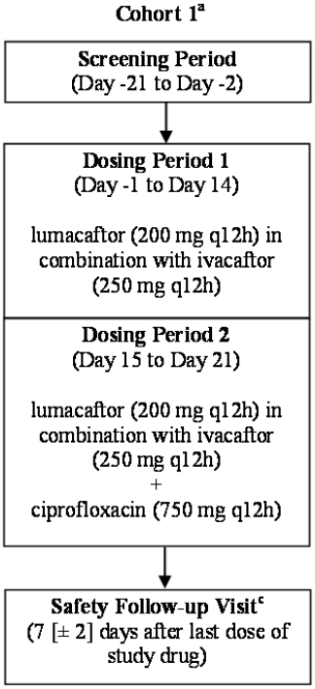
Test Product: Lumacaftor, 200-mg tablet; Ivacaftor, 100-mg tablet and 150-mg tablet.

Cohort 1. Ciprofloxacin

Objective: Primary: To assess the pharmacokinetics (PK) of lumacaftor and ivacaftor in the absence and presence of ciprofloxacin in healthy adult subjects.

Study design and treatment schedule: This was a single-center, Phase 1, open-label, drug-drug interaction (DDI) study to evaluate the effects of ciprofloxacin (750 mg every 12 hours [q12h]) on the PK of LUM (200 mg q12h) /IVA (250 mg q12h). 17subjects was enrolled for cohort 1.

Table 83. Study design for Cohort 1



(Source – Figure 2-1, Study 809-009 report)

Reviewer's comment:
Ivacaftor is metabolized extensively by CYP3A. Ciprofloxacin is a moderate inhibitor of CYP3A. Ciprofloxacin is a medication commonly used by CF patients, therefore it is reasonable to assess the effect of ciprofloxacin on LUM/IVA. The given schedule of ciprofloxacin 750 mg BID is the highest approved dose. Seven days of dosing is sufficient for ciprofloxacin to achieve steady-state and is sufficient for evaluating its maximal CYP3A inhibition potential.

The product and dosing regimen tested in this study (LUM (200 mg q12h) /IVA (250 mg q12h)) is not the to-be-marketed product and is not used in phase 3 trials. As LUM exposure is twice as high in healthy volunteers as in CF patients, the dose of LUM used in this study is half of the proposed dose in CF patients. Therefore, the information learned in this study could be extrapolated to the to-be-marketed product.

PK Sampling Schedule
Lumacaftor and ivacaftor plasma PK –Before the morning dose on Days 7, 10, 19, and 20; before the morning dose, and 0.5, 1, 2, 3, 4, 6, 9, and 12 hours after the morning dose on Days 14 and 21

Ciprofloxacin plasma PK – Before the morning dose on Day 21

Results:
Lumacaftor mean plasma concentrations over time were slightly lower in the presence of ciprofloxacin. However, the M28-lumacaftor concentration versus time profiles were similar in the absence and presence of ciprofloxacin. Ivacaftor mean plasma concentrations were higher (approximately 28%) in the presence of ciprofloxacin. The mean plasma concentrations for the metabolites M1-ivacaftor and M6-ivacaftor were also higher in the presence of ciprofloxacin. The statistical results in the absence and presence of ciprofloxacin are summarized in (Table 84).

Table 84: PK parameters and statistical summary for comparison of plasma LUM/IVA with and without Ciprofloxacin

Cohort	Analyte	Parameter	GLSMR	90% CI Lower	90% CI Upper
1	Lumacaftor	C_{max} (µg/mL)	87.97	80.15	96.57
		AUC_τ (h·µg/mL)	86.29	78.58	94.76
	M28-lumacaftor	C_{max} (µg/mL)	98.60	93.40	104.1
		AUC_τ (h·µg/mL)	101.4	96.28	106.7
	Ivacaftor	C_{max} (µg/mL)	128.5	110.6	149.3
		AUC_τ (h·µg/mL)	128.5	111.5	148.0
	M1-ivacaftor	C_{max} (µg/mL)	140.5	120.8	163.3
		AUC_τ (h·µg/mL)	125.6	110.6	142.6
	M6-ivacaftor	C_{max} (µg/mL)	118.7	104.5	134.9
		AUC_τ (h·µg/mL)	112.1	93.37	127.7

$AUC_\tau = AUC_{0\text{-}12}$: area under the curve from the time of last dose to 12 hours after last dose; CI: confidence interval, C_{max}: maximum observed concentration; GLSMR: geometric least squares mean ratio (with ciprofloxacin GLSM/without ciprofloxacin GLSM).
(Source – Table 2-1, Study 809-009 report)

A single trough sample was collected from each subject to analyze the ciprofloxacin plasma concentrations. The concentrations observed in this study (Table 85) are similar to concentrations in literature, thus indicating no effect of lumacaftor in combination with ivacaftor on ciprofloxacin PK.

Table 85: Ctrough (12h post-dose) of Ciprofloxacin after 750mg BID for 7 days, coadministered with LUM/IVA

Analyte	Cohort	Day	NRT (h)	N	N_{BQL}	Mean (ng/mL)	SD (ng/mL)
CPROFLXN	1	21	0	17	0	500.71	200.14

(Source – Table 14.4.1.1.1.6, Study 809-009 report)

Reviewer's comment:

The reference ciprofloxacin exposure is based on the approved ciprofloxacin label. The mean Ctrough at steady-state with 500mg BID ciprofloxacin was approximately 200 ng/mL, comparable to the dose normalized Ctrough observed in this study. Therefore, ciprofloxacin could be coadministered with LUM/IVA without dose adjustment.

Conclusions:

No significant change in exposure (AUC and Cmax) of lumacaftor and ivacaftor was observed following co-administration with ciprofloxacin. Therefore, no dose adjustment recommended.

No significant change in steady state trough concentrations of ciprofloxacin was observed following co-administration with LUM/IVA. Therefore, ciprofloxacin could be coadministered with LUM/IVA without dose adjustment.

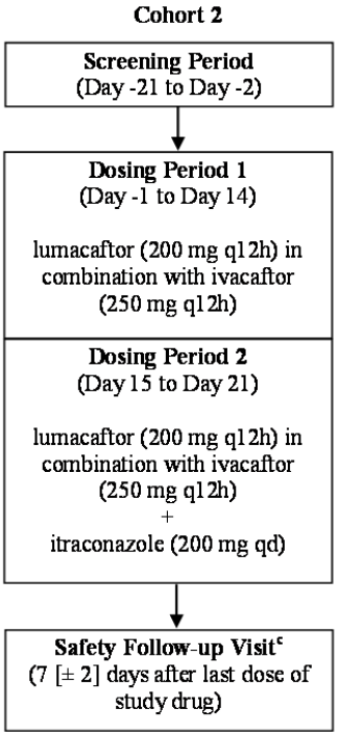
Cohort 2. Itraconazole

Objective:

- Primary: To assess the pharmacokinetics (PK) of lumacaftor and ivacaftor in the absence and presence of itraconazole in healthy adult subjects.
- Secondary: To assess the safety and tolerability of lumacaftor and ivacaftor in the absence and presence of itraconazole in healthy adult subjects.

Study design and treatment schedule: This was a single-center, Phase 1, open-label, drug-drug interaction (DDI) study to evaluate the effects of itraconazole (200 mg once daily [qd]) on the PK of LUM (200 mg q12h) /IVA (250 mg q12h). 18subjects was enrolled for cohort 2.

Table 86. Study design for Cohort 2



(Source – Figure 2-1, Study 809-009 report)

Reviewer's comment:

The given schedule of itraconazole 200 mg QD is the highest approved dose. Seven days of dosing is sufficient for itraconazole to achieve steady-state and is sufficient for evaluating its maximal CYP3A inhibition potential in liver and intestine.

The product and dosing regimen tested in this study (LUM (200 mg q12h) /IVA (250 mg q12h)) is not the to-be-marketed product and is not used in phase 3 trials. As LUM exposure is twice as high in healthy volunteers as in CF patients, the dose of LUM used in this study is half of the proposed dose in CF patients. Therefore, the information learned in this study could be extrapolated to the to-be-marketed product.

PK Sampling Schedule

Lumacaftor and ivacaftor plasma PK –Before the morning dose on Days 7, 10, 19, and 20; before the morning dose, and 0.5, 1, 2, 3, 4, 6, 9, and 12 hours after the morning dose on Days 14 and 21

Itraconazole plasma PK –Before the morning dose, and 0.5, 1, 2, 3, 4, 6, 9, and 12 hours after the morning dose on Day 21

Results:

Lumacaftor and M28-lumacaftor mean plasma concentrations were similar in the absence and presence of itraconazole. Ivacaftor mean plasma concentrations were higher (approximately 4.2-fold) in the presence of itraconazole. The mean plasma concentration of the metabolite M1-ivacaftor was higher (2.4-fold) in the presence of itraconazole;

however, there was no change for M6-ivacaftor. The statistical results in the absence and presence of itraconazole are summarized in Table 87.

Table 87: PK parameters and statistical summary for comparison of plasma LUM/IVA with and without Itraconazole

Cohort	Analyte	Parameter	GLSMR	90% CI Lower	90% CI Upper
2	Lumacaftor	C_{max} (µg/mL)	98.56	92.22	105.3
		AUC_{τ} (h·µg/mL)	96.45	90.90	102.3
	M28-lumacaftor	C_{max} (µg/mL)	109.1	106.7	111.6
		AUC_{τ} (h·µg/mL)	109.0	105.7	112.3
	Ivacaftor	C_{max} (µg/mL)	364.3	318.5	416.6
		AUC_{τ} (h·µg/mL)	429.5	378.4	487.5
	M1-ivacaftor	C_{max} (µg/mL)	170.8	152.7	190.9
		AUC_{τ} (h·µg/mL)	240.5	216.6	267.1
	M6-ivacaftor	C_{max} (µg/mL)	82.17	73.82	91.48
		AUC_{τ} (h·µg/mL)	99.84	91.05	109.5

AUC_{τ} = AUC_{0-12}: area under the curve from the time of last dose to 12 hours after last dose; CI: confidence interval, C_{max}: maximum observed concentration; GLSMR: geometric least squares mean ratio (with itraconazole GLSM/without itraconazole GLSM).

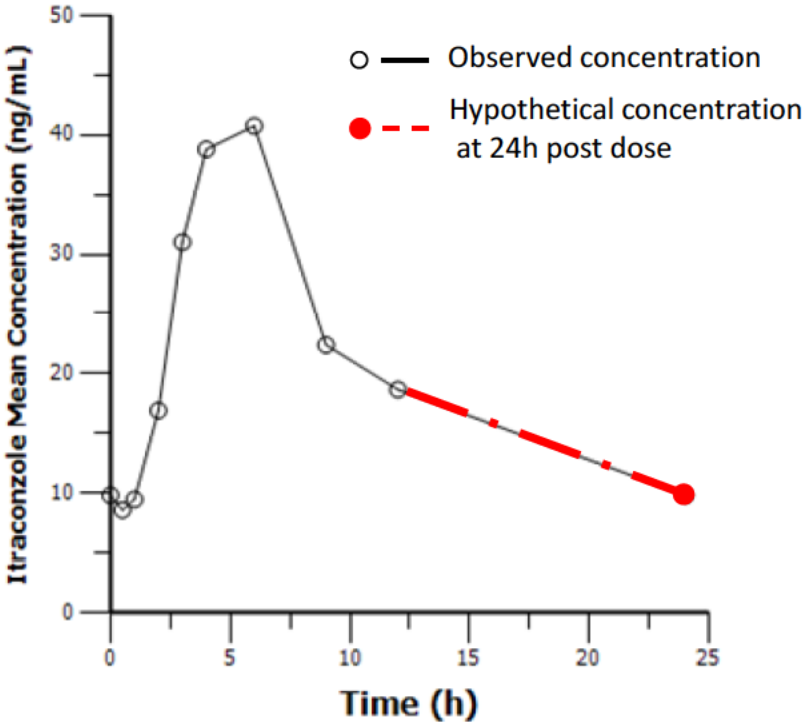
(Source – Table 2-2, Study 809-009 report)

The study also measured concentrations of itraconazole and its major metabolite, hydroxy-itraconazole, because they are known substrates of CYP3A. The conversion of itraconazole to hydroxy-itraconazole and the conversion of hydroxy-itraconazole to the subsequent metabolite keto-itraconazole are predominantly mediated by CYP3A4. The observed exposures of both itraconazole and hydroxy-itraconazole were lower than expected (Table 88). This is likely due to the induction of CYP3A by lumacaftor.

Table 88. Summary of plasma itraconazole concentration with and without LUM/IVA

Analyte	Treatment	n	$AUC_{(0-24h)}$ (ng.h/mL)	Cmax (ng/mL)
Itraconazole	Itraconazole	30	2682	504
	LUM/IVA+Itraconazole	18	488.5*	49.1
Hydroxy-Itraconazole	Itraconazole	30	7293	302
	LUM/IVA+Itraconazole	18	527**	84.7

*AUCτ (0-24h) calculated by reviewer based on hypothetical concentration at 24h post dose
**AUC0-12h
(Source – Table 11-21, Study 809-009 report, after repeated doses of itraconazole +LUM/IVA for 7 days; SPORANOX label, clinical pharmacology section, capsules fed data after single dose of itraconazole 200 mg)



(Source – reviewer analysis)

Reviewer's comment:

This study was not designed as a 2-way study to assess the combined effect of lumacaftor and ivacaftor on the PK of itraconazole; hence the study did not include dosing itraconazole in the absence of lumacaftor and ivacaftor. The reference itraconazole exposure is based on the approved itraconazole label, AUC0-24h with a single dose of 200mg itraconazole capsule administered with food. In this study, the itraconazole concentration was measured to 12 hour post dose after coadministration with LUM/IVA for 7 days. Assuming that the itraconazole concentration at 24 hour post-dose is similar to the pre-dose concentration, this reviewer did independent calculation, and AUC0-24h for itraconazole is approximately 488.5ng.h/mL. Therefore, Itraconazole exposure (AUC) was decreased by more than 80% when coadministered with LUM/IVA. This is consistent with the DDI study between LUM and IVA, where LUM decreased IVA exposure by more than 80%.

Conclusions:

When coadministered with itraconazole, exposure for ivacaftor increased by 4 fold. Nevertheless, the absolute concentration of ivacaftor is still within the range with adequate safety data/margin. Therefore no dose adjustment was necessary for ivacaftor.

On the other hand, the exposure of itraconazole decreased by more than 80% when coadministered with LUM/IVA. Therefore, administration of LUM/IVA with itraconazole is not recommended as itraconazole may not be effective in patients concomitantly taking LUM/IVA.

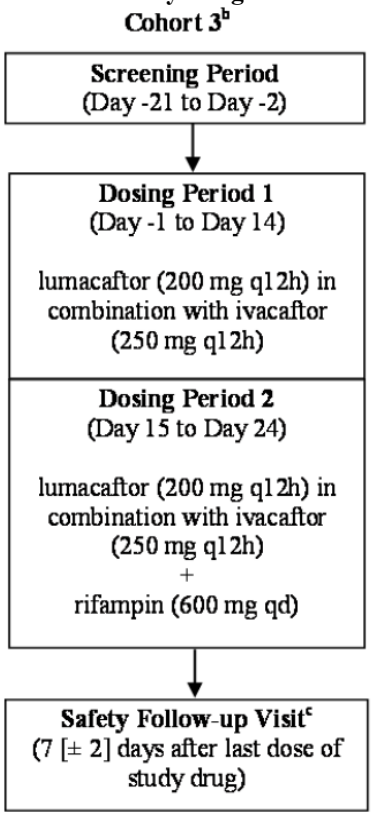
Cohort 3. Rifampin

Objective:

- Primary: To assess the pharmacokinetics (PK) of lumacaftor and ivacaftor in the absence and presence of rifampin in healthy adult subjects.
- Secondary: To assess the safety and tolerability of lumacaftor and ivacaftor in the absence and presence of rifampin in healthy adult subjects.

Study design and treatment schedule: This was a single-center, Phase 1, open-label, drug-drug interaction (DDI) study to evaluate the effects of rifampin (600 mg qd) on the PK of LUM (200 mg q12h) /IVA (250 mg q12h). 18subjects was enrolled for cohort 2.

Table 89. Study design for Cohort 3



(Source – Figure 2-1, Study 809-009 report)

Reviewer's comment:

The given schedule of rifampin 600 mg QD is the highest approved dose. Seven days of dosing is sufficient for rifampin to achieve steady-state and is sufficient for evaluating its maximal CYP3A induction potential in liver and intestine.

The product and dosing regimen tested in this study (LUM (200 mg q12h) /IVA (250 mg q12h)) is not the to-be-marketed product and is not used in phase 3 trials. As LUM exposure is twice as high in healthy volunteers as in CF patients, the dose of LUM used in this study is half of the proposed dose in CF patients. Therefore, the information learned in this study could be extrapolated to the to-be-marketed product.

PK Sampling Schedule

Lumacaftor and Ivacaftor plasma PK –Before the morning dose on Days 7, 10, 22, and 23; before the morning dose, and 0.5, 1, 2, 3, 4, 6, 9, and 12 hours after the morning dose on Days 14 and 24.

Results:

There was no substantial change in lumacaftor mean plasma concentrations in the presence of rifampin. The mean plasma concentrations of M28-lumacaftor were higher (approximately 35%) in the presence of rifampin. Ivacaftor mean plasma concentrations were substantially lower (approximately 50%) in the presence of rifampin. The mean plasma concentrations of M1-ivacaftor were also lower (approximately 35%); however, the mean plasma concentrations of M6-ivacaftor were higher (approximately 29%) in the presence of rifampin. The statistical results in the absence and presence of rifampin are summarized in Table 90.

Table 90: PK parameters and statistical summary for comparison of plasma LUM/IVA with and without Rifampin

Cohort	Analyte	Parameter	GLSMR	90% CI Lower	90% CI Upper
3	Lumacaftor	C_{max} (µg/mL)	95.66	87.15	105.0
		AUC_τ (h·µg/mL)	87.01	81.48	92.92
	M28-lumacaftor	C_{max} (µg/mL)	135.3	130.7	140.0
		AUC_τ (h·µg/mL)	135.6	131.5	139.8
	Ivacaftor	C_{max} (µg/mL)	49.81	42.69	58.11
		AUC_τ (h·µg/mL)	43.15	38.32	48.59
	M1-ivacaftor	C_{max} (µg/mL)	92.90	81.00	106.5
		AUC_τ (h·µg/mL)	65.96	59.78	72.79
	M6-ivacaftor	C_{max} (µg/mL)	189.1	163.2	219.0
		AUC_τ (h·µg/mL)	129.2	115.1	144.9

$AUC_\tau = AUC_{0\text{-}12}$: area under the curve from the time of last dose to 12 hours after last dose; CI: confidence interval, C_{max}: maximum observed concentration; GLSMR: geometric least squares mean ratio (with rifampin GLSM/without rifampin GLSM).

(Source – Table 2-3, Study 809-009 report)

Conclusions:

Co-administration with the CYP3A4 inducer rifampin, decreased exposure to ivacaftor by 57% based on AUC and 50% based on Cmax. Therefore, coadministration with rifampin or other CYP3A inducers is not recommended.

PD: Effect of lumacaftor on spirometry assessment Cohort 1-3

A review of spirometry data from Cohort 1, Cohort 2, and Cohort 3 revealed an asymptomatic, decline in FEV1 within 4 hours of treatment with LUM/IVA 200/250 mg. None of the subjects had an SAE, required treatment with concomitant medications, or had long term sequelae as a result of the decline in FEV1.

Table 91: Summary of Spirometry Absolute Change From Baseline for Percent Predicted FEV1, Safety Set (Cohort 1, Cohort 2, and Cohort 3)

	Day 1, 4 hours Postdose	Day 2, Predose	Day 2, 4 hours Postdose	Day 14, Predose	Day 16, Predose	Day 21/24, Predose[a]	Safety Follow-up Visit[b]
Cohort 1							
n	18	18	18	17	17	17	ND
Mean	-5.08	-3.97	-5.21	-6.60	-5.62	-4.13	ND
SD	4.349	5.663	5.859	9.989	13.025	4.370	ND
Median	-5.10	-3.30	-3.45	-4.20	-1.80	-5.40	ND
Minimum	-13.8	-16.6	-21.9	-39.0	-52.4	-10.0	ND
Maximum	2.4	5.2	4.0	3.7	4.6	3.5	ND
Cohort 2							
n	18	18	18	18	18	18	18
Mean	-4.63	-5.41	-7.34	-3.91	-5.76	-5.87	-4.64
SD	2.735	5.083	5.515	4.714	6.042	5.562	5.352
Median	-4.40	-4.80	-6.25	-3.15	-5.10	-5.45	-3.75
Minimum	-11.4	-15.1	-19.7	-13.5	-18.9	-17.5	-21.8
Maximum	1.0	5.6	3.9	4.4	5.8	3.5	1.8
Cohort 3							
n	18	18	18	18	18	17	ND
Mean	-4.94	-5.69	-4.24	-3.16	-2.52	-0.44	ND
SD	4.151	5.259	5.789	5.791	6.083	5.726	ND
Median	-4.45	-3.45	-2.65	-2.50	-2.30	0	ND
Minimum	-19.0	-20.1	-20.9	-16.3	-14.4	-15.5	ND
Maximum	0	-0.7	2.7	5.4	11.1	8.1	ND

Sources: Table 14.3.5.4a, Table 14.3.5.4b, and Table 14.3.5.4c.

FEV_1: forced expiratory volume in 1 second; n: size of subsample; ND: not determined; SD: standard deviation.

Note: Days 1, 2, and 14 were for Period 1 and Days 16, 21, 24, and Follow-up were for Period 2.

[a] Spirometry was performed on Day 21 for Cohort 1 and Cohort 2 and on Day 24 for Cohort 3.

[b] Spirometry was performed at the Safety Follow-up Visit for Cohort 2 only.

(Source – Table 12-16, Study 809-009 report)

Reviewer's comment:

LUM/IVA (200/250 mg) reduced PPFEV1 in healthy volunteers by approximately 5% in all three cohorts. This FEV1 reducing effect took place by 4 hours post first dose, and last through the whole study period, to 21/24 day as last tested. The time profile and extent of FEV1 decline is consistent with the observed FEV1 decline with LUM monotherapy in study 809-102. Notably, the first post-dose spirometry assessment in phase 3 studies (103 and 104) was on day 15, and LUM/IVA showed a positive effect for

PPFEV1 in CF patients in general. Therefore, LUM/IVA seems to reduce PPFEV1 in healthy volunteers, but increase PPFEV1 in CF patients.

Cohort 4. Bronchodilator

Objective:

- Primary: To evaluate the ability of short- and long-acting bronchodilators to block or reverse the FEV1 decline induced by LUM/IVA

Study design and treatment schedule: This was a single-center, Phase 1, open-label, drug-drug interaction (DDI) study to evaluate the effects of short- and long-acting bronchodilators on lung function following treatment with lumacaftor in combination with ivacaftor. 24 subjects were enrolled for cohort 4. LUM/IVA 200/250mg was dosed on day 1 (period 1), day 8 (period 2), and day 15 (period 3). Short-acting bronchodilators were administered 4 hours after the dose of study drug on Days 1, 8, and 15, and at the appropriate time-matched times on Day -1, Days 2, 7, 9, 14, and 16. Long-acting bronchodilators were administered on Days 7 and 14 at 12 hours before the dose of study drug and on Days 8 and 15 at 12 hours after the dose of study drug.

Table 92. Study design for Cohort 4

Sequence	Period 1	Period 2	Period 3
1 (n=6)	A1 (albuterol + 200 mg LUM + 250 mg IVA)	B (indacaterol + 200 mg LUM + 250 mg IVA) 1 (albuterol)	C (tiotropium + 200 mg LUM + 250 mg IVA) 1 (albuterol)
2 (n=6)	A1 (albuterol + 200 mg LUM + 250 mg IVA)	C (tiotropium + 200 mg LUM + 250 mg IVA) 1 (albuterol)	B (indacaterol + 200 mg LUM + 250 mg IVA) 1 (albuterol)
3 (n=6)	A2 (ipratropium + 200 mg LUM + 250 mg IVA)	B (indacaterol + 200 mg LUM + 250 mg IVA) 2 (ipratropium)	C (tiotropium + 200 mg LUM + 250 mg IVA) 2 (ipratropium)
4 (n=6)	A2 (ipratropium + 200 mg LUM + 250 mg IVA)	C (tiotropium + 200 mg LUM + 250 mg IVA) 2 (ipratropium)	B (indacaterol + 200 mg LUM + 250 mg IVA) 2 (ipratropium)

(Source – Figure 9-2, Study 809-009 report)

Spirometry Schedule

Spirometry was performed before the dose of study drug and at 2, 4, 5, and 8 hours after LUM/IVA administration on Days 1, 8, and 15. Time-matched spirometry was performed on Day -1, Days 2, 7, 9, 14, and 16. A single spirometry was collected on Day -2, Day 6, Day 13, and the Safety Follow-up Visit.

Results:

In Cohort 4, treatment with long-acting bronchodilators (indacaterol and tiotropium) largely prevented the mild decline observed in FEV1 following dosing with lumacaftor in combination with ivacaftor (Table 93, Treatment B and C compared to Treatment A), and treatment with short-acting bronchodilators (albuterol and ipratropium) led to a reversal of the decline (Table 94, Treatment A).

The mean (SD) of the difference in the absolute change in percent predicted FEV1 from period baseline to 4 hours after dosing in the presence versus the absence of a long-acting bronchodilator was 3.41 (9.511) percentage points for indacaterol and 2.53 (6.892) percentage points for tiotropium (Table 93).

Table 93: ANCOVA Analysis of the Difference in the Absolute Change in Percent Predicted FEV1 From Period Baseline to 4 Hours After Dosing in the Presence Versus Absence of Each Long-Acting Bronchodilator, Safety Set (Cohort 4)

	Difference[c]		ANCOVA[d]		
LABD Sequence[a,b]	n	Mean (SD)	LS Mean (SE)	95% 2-sided CI	*P* Value
Indacaterol[e]					
All sequences	24	3.41 (9.511)	3.14 (1.597)	-0.08, 6.36	0.056
Tiotropium[f]					
All sequences	24	2.53 (6.892)	2.80 (1.597)	-0.42, 6.02	0.086

(Source – Table 12-17, Study 809-009 report)

The mean (SD) of the absolute change in percent predicted FEV1 from 4 hours after LUM/IVA dose (before receipt of short-acting bronchodilator) to 30 minutes after receipt of short-acting bronchodilator (5 hour post LUM/IVA dose) was 4.01 (5.481) percentage points for albuterol (P = 0.017), 3.51 (6.323) percentage points for ipratropium (P = 0.081), and 3.78 (5.769) percentage points for both short-acting bronchodilators (P = 0.003) in the absence of long-acting bronchodilators (Table 94, Treatment A).

Table 94: Absolute Change in Percent Predicted FEV1 From 4 Hours After Receipt of Lumacaftor in Combination With Ivacaftor to 30 Minutes After Receipt of a Short-Acting Bronchodilator in the Absence of Long-Acting Bronchodilators, Safety Set (Cohort 4)

	Absolute Change			
Treatment	n	Mean (SD)	Median (min, max)	*P* value[a]
Albuterol	14	4.01 (5.481)	4.00 (-8.0, 14.2)	0.017
Ipratropium	12	3.51 (6.323)	5.55 (-11.1, 10.9)	0.081
All SABD[b]	26	3.78 (5.769)	4.55 (-11.1, 14.2)	0.003

Source: Table 14.3.5.4.4d.

FEV_1: forced expiratory volume in 1 second; max: maximum; min: minimum; SABD: short-acting bronchodilator; SD: standard deviation.

[a] T-test was fitted to the absolute change in percent predicted FEV_1 from 4 hours after dosing with lumacaftor in combination with ivacaftor (before receipt of short-acting bronchodilator) to 30 minutes after receipt of short-acting bronchodilator in the absence of long-acting bronchodilators.

[b] Results from subjects who received albuterol (A1) or ipratropium (A2) were pooled.

(Source – Table 12-19, Study 809-009 report)

Reviewer's comment:

In healthy subjects, treatment with long-acting bronchodilators (indacaterol and tiotropium) largely prevented the decline observed in FEV1 following dosing with

LUM/IVA, and treatment with short-acting bronchodilators (albuterol and ipratropium) led to a reversal of the decline.

In CF patients, 80-90% patients had concomitant bronchodilator during study 809-102 (n=157/190), 103 and 104 (n=905/1121), and spirometry assessment for efficacy was performed pre-bronchodilator. In study 102, LUM monotherapy reduced FEV1 in a dose dependent manner despite the concomitant use of bronchodilators in most CF patients.

In phase 3 protocols, there is no specific instruction on concomitant use of bronchodilators to prevent the FEV1 declining effect of LUM, and the bronchodilator use is similar between placebo group and treatment (LUM/IVA) groups.

Conclusions:

In healthy subjects, treatment with long-acting bronchodilators (indacaterol and tiotropium) largely prevented the decline observed in FEV1 following dosing with LUM/IVA, and treatment with short-acting bronchodilators (albuterol and ipratropium) led to a reversal of the decline.

It is not clear whether the bronchodilators have similar protective effects against the FEV1 declining effect of LUM in CF patients.

8. DDI between LUM and IVA

Trial # VX08-809-005

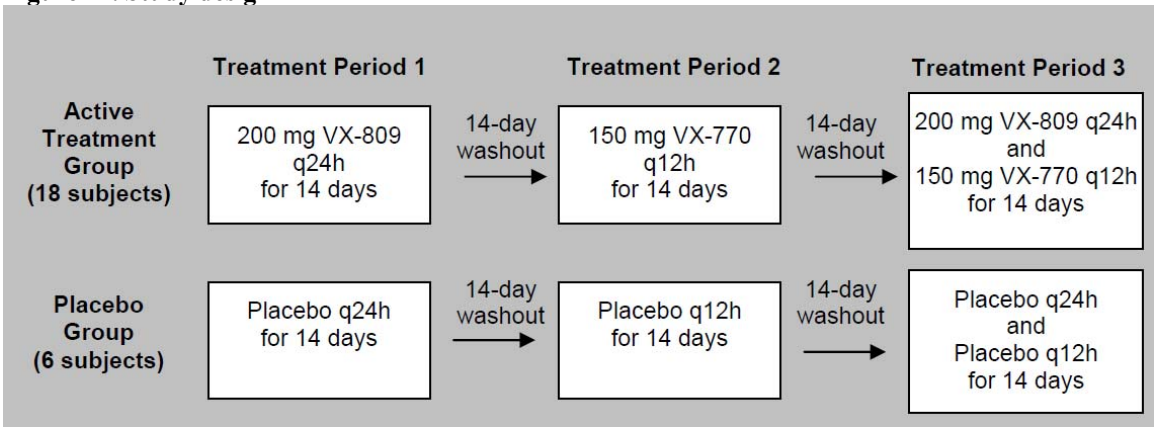
Title: A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Drug-Drug Interaction Study of VX-809 and VX-770 in Healthy Subjects

Objective:

To assess the pharmacokinetics of coadministration of VX-770 and VX-809 in healthy adult subjects

Study design and treatment schedule: Randomized, double-blind, placebo-controlled, multiple-dose, 3-treatment period, Phase 1, drug-drug interaction study investigating VX-809 alone, VX-770 alone, and VX-809 coadministered with VX-770 in healthy subjects. A total of 24 subjects were enrolled, randomized, and received study drug (18) or placebo (6). There was a minimum of a 14-day washout period between Treatment Periods (Figure 42).

Figure 42. Study design



(Source – Figure 9-1, Study 809-005 report)

Reviewer's comment:

LUM 200mg qd/IVA 150 mg q12h is not the final dose of the product, neither is it used in phase 3 programs. This study provides supportive information in the DDI of LUM and IVA. The result of this study is not stated in the label.

Test Product: Lumacaftor was supplied as 50-mg capsules; Ivacaftor was supplied as 50-mg tablets.

PK Sampling Schedule

- **Blood –**0, 5, 15, 30 min, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 32 and 48 hr

Results and Conclusions:

LUM

On Day 1 and Day 14 of Periods 1 and 3, mean VX-809 plasma concentration time profiles were similar after the administration of VX-809 alone or in combination with VX-770. M28 metabolite showed slightly higher concentrations on Day 1 and Day 14 of the combination treatment period relative to the VX-809 alone treatment period. The statistical analysis results for the PK of VX-809 and M28 metabolite when coadministered with VX-770 are summarized below: (Table 95) The relative amount of M28 to VX-809 was not affected by coadministration with VX-770.

Table 95. Effect of VX-770 on VX-809 PK: GLSM Ratio (With/Without VX-770) and Confidence Intervals

Analyte	Parameter	N	Day	GLSM Ratio (%)	90% CI Lower (%)	90% CI Upper (%)
VX-809	C_{max}	17	1	116.6	95.83	141.9
		17	14	119.0	99.44	142.5
	AUC_{0-24}	17	1	100.0	85.46	117.1
		17	14	107.8	91.93	126.4
M28	C_{max}	17	1	110.1	99.06	122.3
		17	14	133.2	116.3	152.6
	AUC_{0-24}	17	1	113.7	103.6	124.8
		17	14	131.9	115.9	150.2

AUC_{0-24}=The area under the plasma concentration-time curve from time 0 to time 24 hours
CI=Confidence interval
C_{max}=Maximum observed plasma concentrations
Day=Day relative to the initial dose of study drug within a treatment period
GLSM=Geometric Least Squares Mean
GLSM Ratio=(VX-809 GLSM with VX-770/VX-809 GLSM without VX-770)
(Source – Table on page 5, Study 809-005 report)

IVA

On Day 1 of Periods 2 and 3, plasma concentration-time profiles of VX-770 and M1 were comparable after the administration of VX-770 alone or in combination with VX-809. On Day 14 of Periods 2 and 3, a massive reduction in VX-770 and M1 plasma concentrations was observed when VX-770 was coadministered with VX-809. The absence of any effect on Day 1 and a profound decrease observed on Days 7 and 14 suggests an induction of VX-770 and M1 metabolism by VX-809 rather than a decrease in the absorption of VX-770. The potential mechanism of this interaction is probably related to the induction of the cytochrome P450 CYP 3A isoenzyme (CYP3A) by VX-809 since VX-770 is mainly metabolized by this isoenzyme. Unlike the parent drug or M1, M6 plasma exposure did not appear to be extensively affected by the coadministration of VX-809 on Day 1 and Day 14. The statistical analysis results for the PK of VX-770, M1, and M6 metabolites when coadministered with VX-809 are summarized below:

Table 96. Effect of VX-809 on VX-770 PK:GLSM Ratio (With/Without VX-809) and Confidence Intervals

Analyte	Parameter	N	Day	GLSM Ratio (%)	90% CI Lower (%)	90% CI Upper (%)
VX-770	C_{max}	17	1	91.84	81.56	103.4
		17	14	24.10	18.58	31.27
	AUC_{0-12}	17	1	98.19	88.16	109.4
		17	14	19.50	15.07	25.22
M1	C_{max}	17	1	80.22	71.54	89.95
		17	14	37.46	31.22	44.94
	AUC_{0-12}	17	1	85.77	77.67	94.72
		17	14	28.25	23.78	33.55
M6	C_{max}	17	1	104.2	92.96	116.9
		17	14	96.57	82.74	112.7
	AUC_{0-12}	17	1	106.1	94.40	119.2
		17	14	89.46	77.97	102.6

AUC_{0-12}=The area under the plasma concentration-time curve from time 0 to time 12 hours
CI=Confidence interval
C_{max}=Maximum observed plasma concentrations
Day=Day relative to the initial dose of study drug within a treatment period
GLSM=Geometric Least Squares Mean
GLSM Ratio=(VX-770 GLSM with VX-809/VX-770 GLSM without VX-809)
(Source – Table on page 6, Study 809-005 report)

In addition to PK samples collected after the morning dose of VX-770 (AM), samples were collected for the evening dose of VX-770 (PM) to provide an assessment of the potential diurnal variation of VX-770. No discernible differences in plasma exposures of VX-770 were observed between the morning and evening doses of VX-770.

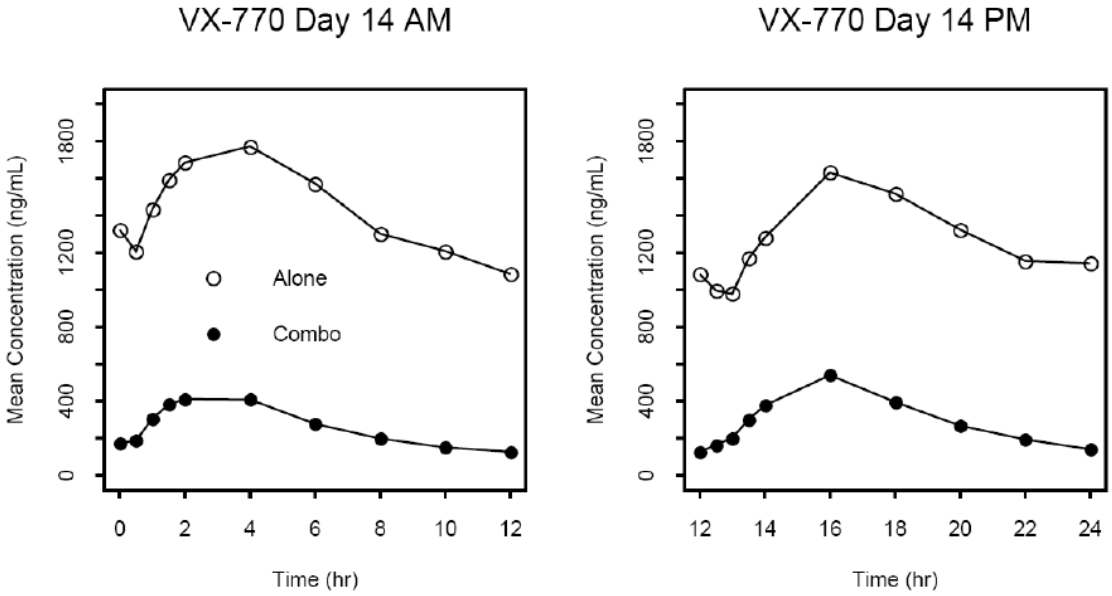


Figure 43. Mean VX-770 Plasma Concentration Time Profiles on Day 14 After AM and PM Dose of VX-770 Alone and With VX-809 for 14 Days
(Source – Figure 11-12, Study 809-005 report)

- **Conclusions:**

There was no major effect of VX-770 on the PK of both VX-809 and its major metabolite M28 when the 2 drugs were coadministered at a dose of 200 mg q24h for VX-809 and 150 mg q12h for VX-770 for 14 days.

There was a profound effect of VX-809 on the PK of VX-770, resulting in a significant decrease in plasma exposures of both VX-770 (by 81%) and metabolite M1 (by 72%), and no major effect on the exposure of metabolite M6 when the 2 drugs were coadministered at a dose of 200 mg q24h for VX-809 and 150 mg q12h for VX-770 for 14 days.

There were no major differences in plasma exposures of VX-770, M1, and M6 between the morning and evening doses of VX-770.

Trial # VX10-809-006

Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation, Drug-Drug Interaction Study of Lumacaftor and Ivacaftor in Healthy Subjects

Objective:

To assess the pharmacokinetics (PK) of lumacaftor (VX-809) and ivacaftor (VX-770) when coadministered in healthy adult subjects

Study design and treatment schedule: Phase 1, randomized, double-blind, placebo-controlled, multiple-dose, 3-treatment period, 3-cohort, dose-escalation, drug-drug interaction (DDI) study investigating lumacaftor alone, ivacaftor alone, and lumacaftor and ivacaftor coadministered in healthy subjects. 48 subjects were enrolled in this study, approximately 24 subjects in each cohort (Cohort 1 and 2), at a single clinical site. All cohorts were studied sequentially. There was a minimum of a 14-day washout period between Treatment Periods.

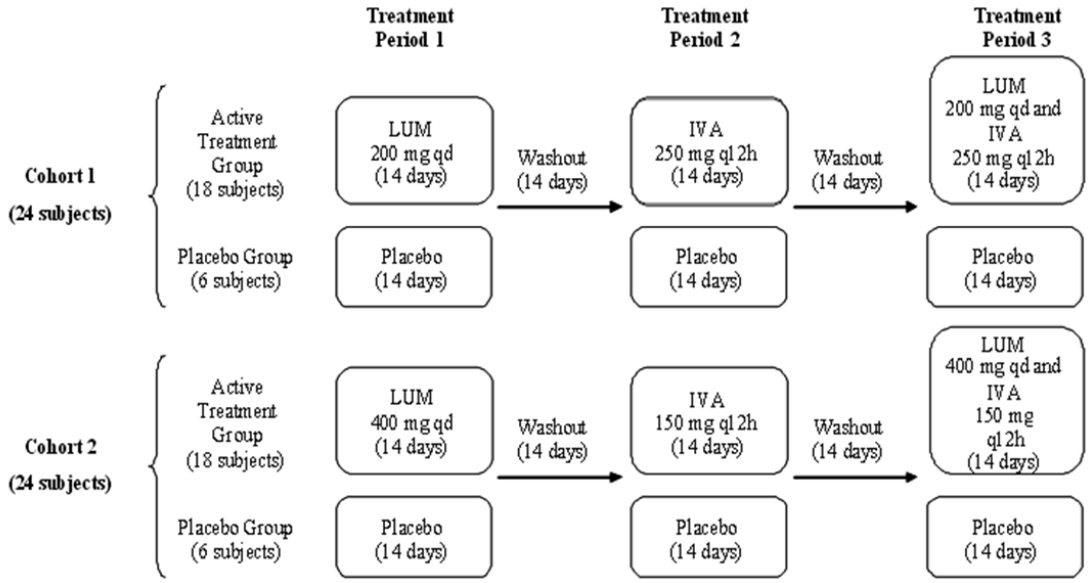


Figure 44. Study design
(Source: Figure 9-1, Study 809-006 report)

Reviewer's comment:

LUM 400mg qd/IVA 150 mg q12h is not the final dose of the product, neither is it used in phase 3 programs. As LUM exposure is twice as high in healthy volunteers as in CF patients, the exposure (AUC24h) of LUM in cohort 2(435 μg.h/mL) is similar to the exposure(AUC24h) of LUM in CF patients (432 μg.h/mL). Therefore, the effect of LUM on IVA exposure learned in this study could be extrapolated to the to-be-marketed product.

Test Product: Lumacaftor was supplied as 50-mg capsules; Ivacaftor was supplied as 100-mg or 150-mg blue film-coated tablets.

PK Sampling Schedule

Lumacaftor alone

Day 1: before dosing, and 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, and 24 hours after the morning dose of lumacaftor alone or placebo
Day 7: before dosing
Day 14: before dosing, and 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, and 168 hours after the morning dose of lumacaftor alone or placebo

Ivacaftor alone

Day 29: before dosing, and 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 12.5, 13, 13.5, 14, 16, 18, 20, 22, and 24 hours after the morning dose of ivacaftor alone or placebo
Day 35: before dosing
Day 42: before dosing, and 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 12.5, 13, 13.5, 14, 16, 18, 20, 22, 24, 48, 72, 96, 120, 144, and 168 hours after the morning dose of ivacaftor alone or placebo

Lumacaftor and ivacaftor coadministration
Day 57: before dosing, and 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 12.5, 13, 13.5, 14, 16, 18, 20, 22, and 24 hours after the morning dose of lumacaftor and ivacaftor or placebo
Day 63: before dosing
Day 70: before dosing, and 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 12.5, 13, 13.5, 14, 16, 18, 20, 22, 24, 48, 72, 96, 120, 144, and 168 hours after the morning dose of lumacaftor and ivacaftor or placebo

Results and Conclusions:
PK parameters were determined for lumacaftor, M28-lumacaftor, ivacaftor, M1-ivacaftor, and M6-ivacaftor for all dose regimens on nominal days (Day 1 and Day 14). PK parameters for lumacaftor and ivacaftor are summarized in Table 97.

Table 97. Summary of Steady State (Nominal Day 14) Pharmacokinetic Parameters for Lumacaftor and Ivacaftor

			Median (min, max)	Arithmetic Mean (SD)				
Analyte	Interacting Drug	N	t_{max} (h)	C_{max} (ng/mL)	AUC_{tau} (h*ng/mL)	CLss/F (L/h)	Vz/F (L)	$t_{1/2}$ (h)
Lumacaftor 200 mg qd	None	18	6.00 (4.00,10.0)	17200 (5130)	242000 (75200)	0.905 (2.72)	33.8 (13.6)	26.4 (8.07)
Lumacaftor 200 mg qd	Ivacaftor 250 mg q12h	16	4.01 (0.00, 8.00)	13200 (5600)	212000 (107000)	1.35 (1.17)	44.1 (37.1)	24.1 (7.16)
Lumacaftor 400 mg qd	None	17	6.00 (4.00, 10.0)	27900 (8900)	435000 (139000)	1.00 (0.304)	38.3 (13.7)	27.3 (10.2)
Lumacaftor 400 mg qd	Ivacaftor 150 mg q12h	13	6.00 (2.00, 11.9)	25000 (8660)	387000 (142000)	1.14 (0.343)	42.4 (17.7)	26.3 (8.95)
Ivacaftor 250 mg q12h	None	17	6.00 (0.500, 6.02)	2140 (1370)	40600 (27400)	15.7 (6.06)	207 (129)	9.13 (4.16)
Ivacaftor 250 mg q12h	Lumacaftor 200 mg qd	16	4.00 (2.00, 6.03)	544 (189)	8530 (2850)	72.9 (29.9)	705 (373)	7.20 (4.62)
Ivacaftor 150 mg q12h	None	15	6.00 (2.00, 10.0)	1330 (438)	23600 (8300)	14.1 (5.11)	187 (96.6)	9.73 (5.98)
Ivacaftor 150 mg q12h	Lumacaftor 400 mg qd	13	4.00 (1.50, 11.9)	572 (312)	6180 (2840)	65.6 (38.6)	515 (536)	4.86 (1.78)

AUC: area under concentration versus time curve; AUC_{tau}: AUC for the dosing interval. Lumacaftor tau = 24 h and Ivacaftor tau = 12 h (AM [0 - 12 h] tau is reported in table); CI: confidence interval; CLss/F: apparent clearance; C_{max}: maximum observed concentration; N: number of subjects; qd: daily; q12h: every 12 hours; t_{max}: time of maximum concentration; $t_{1/2}$: terminal phase half-life; Vz/F: apparent volume of distribution (based on the terminal phase).
(Source – Table on page 8, Study 809-006 report)

LUM

- There was no major effect of ivacaftor on the PK of lumacaftor or M28-LUM.

IVA

- Coadministration of 250 mg ivacaftor q12h with 200 mg lumacaftor qd for 14 days considerably decreased GLSM ratios for ivacaftor Cmax by 74% and AUC0-24h by 78% as compared to ivacaftor administered alone. Coadministration with 400 mg lumacaftor qd for 14 days considerably decreased 150-mg ivacaftor q12h

exposure as compared to administration of ivacaftor alone (GLSM ratios for Cmax by 62% and for AUC0-24h by 75%).

- Coadministration of ivacaftor with lumacaftor for 14 days considerably decreased M1-ivacaftor exposure as compared to ivacaftor administered alone. M1-ivacaftor metabolite to parent ratios on Day 14 were greater with coadministration of lumacaftor 400 mg qd (3.58-fold) than administration of ivacaftor alone (2.54-fold).

- M6-ivacaftor exposures were similar when ivacaftor was administered alone or coadministered with 400 mg lumacaftor qd for 14 days. M6-ivacaftor metabolite to parent ratios on Day 14 were greater with coadministration of lumacaftor 400 mg qd (8.4-fold) than when administered alone (2.5-fold).

- **Conclusions:**

There was no major effect of ivacaftor on the PK of both lumacaftor and its major metabolite M28 when the 2 drugs were coadministered.

Coadministration of lumacaftor (in regimens of either 400 mg lumacaftor qd/ 150 mg ivacaftor q12h or 200 mg lumacaftor qd/ 250 mg ivacaftor q12h, for 14 days) considerably reduced ivacaftor by 75-78%, and reduced M1-ivacaftor concentrations by 59-66%, but has little impact on M6-ivacaftor concentrations.

Trial # VX09-809-102

Title: A Phase 2, Multicenter, Double-Blind, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of Lumacaftor Monotherapy, and Lumacaftor and Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTR Mutation

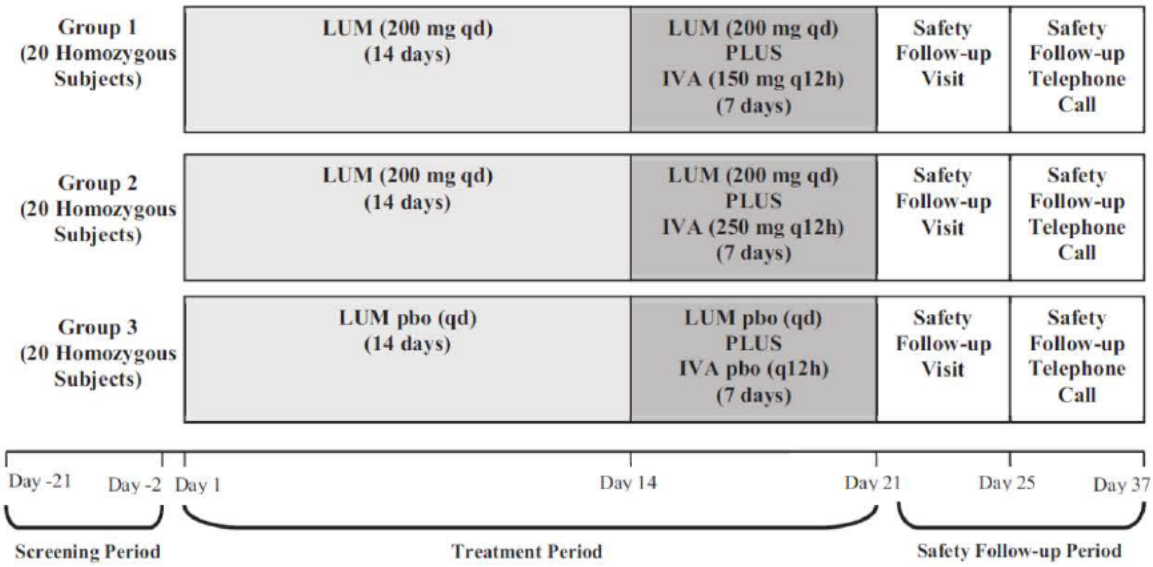
Objective:

To assess the pharmacokinetics (PK) of lumacaftor (VX-809) and ivacaftor (VX-770) when coadministered in CF adult subjects.

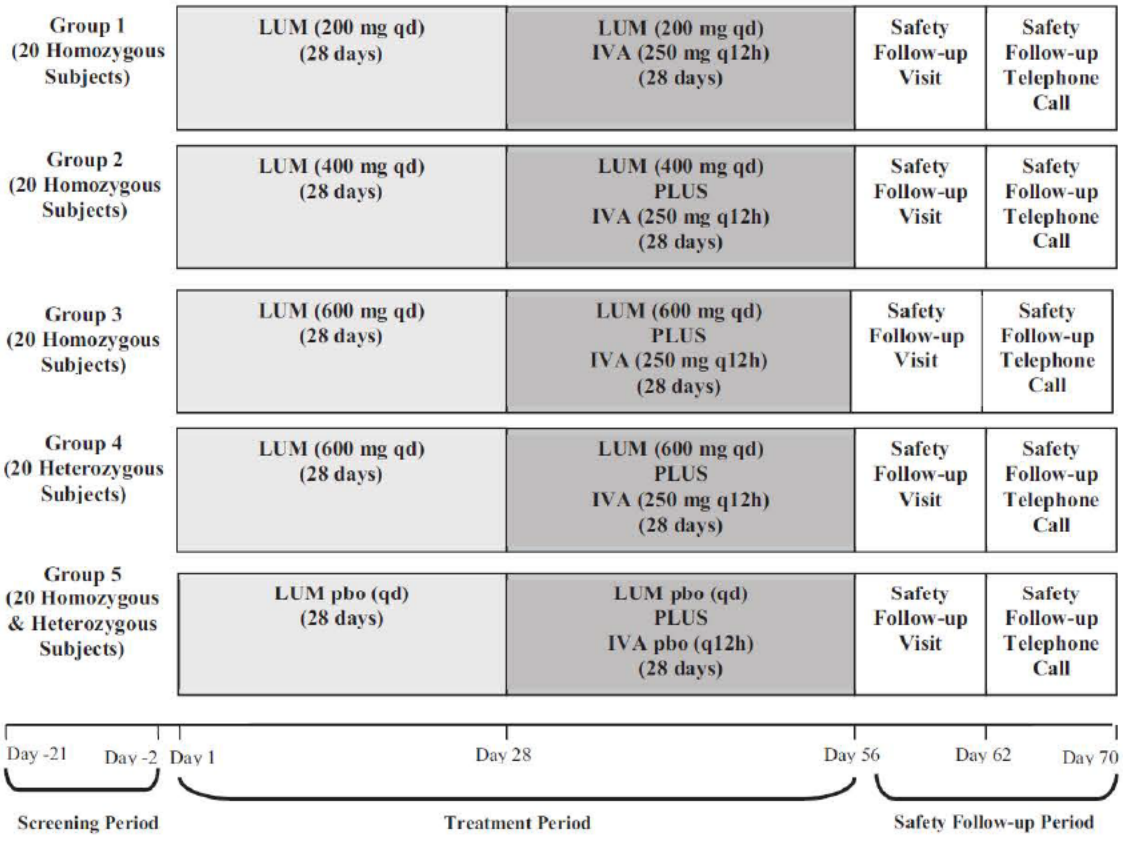
Only results related to LUM/IVA PK are reviewed here. For PD (sweat chloride), efficacy and safety review, please refer to pharmacometrics review (section 4.1) and the review by medical officer Dr. Robert Lim.

Study design and treatment schedule: The multicenter phase 2 study included 4 cohorts, as Figure 45.

Cohort 1 (60 Subjects)



Cohort 2 (100 Subjects)



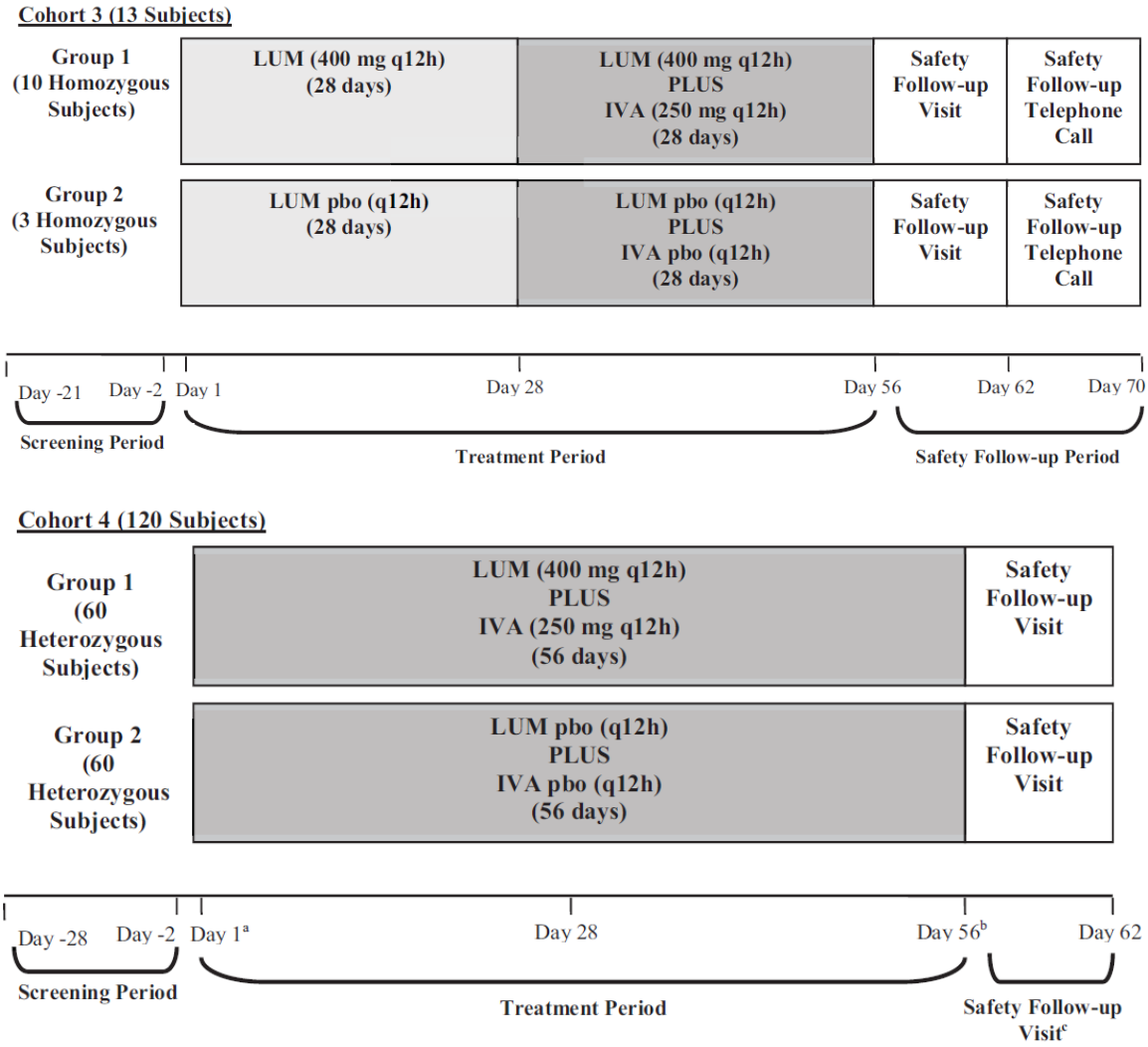


Figure 45. Study design
(Source: Figure 9-1, 9-2 Study 809-102 report)

Test Product:
Cohort 1-3: Lumacaftor 200 mg tablet (Form1), Ivacaftor 150 mg tablet and 100 mg tablet
Cohort 4: Lumacaftor 200/125 mg FDC tablet

PK Sampling Schedule
Cohort 1
Monotherapy period
Day 1: pre-morning dose, 2-3h, 4-5h
Day 7 and 15: pre-morning dose
Day 14: pre-morning dose, and 0.5, 1, 2, 3, 4, 6, 9, and 12 hours after the morning dose

Combination therapy period
Day 21 dose: pre-morning dose, and 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 30, 60 and 120-180 hours after the morning dose

Cohort 2 and 3
Monotherapy period
Day 1: pre-morning dose, 3-5h post dose
Day 14 and 29: pre-morning dose
Day 28: pre-morning dose, and 0.5, 1, 2, 3, 4, 6, 9, and 12 hours after the morning dose

Combination therapy period
Day 42: pre-morning dose
Day 56 dose: pre-morning dose, and 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 30, 60 and 120-180 hours after the morning dose

Cohort 4
Combination therapy
Day 1: pre-morning dose, 2, 4, and 6h post dose
Day 7, 14, 42 and 56: pre-morning dose
Day 28: pre-morning dose, and 0.5, 1, 2, 3, 4, 6, 9, and 12 hours after the morning dose

Results and Conclusions:
LUM
Lumacaftor exposures were minimally affected by ivacaftor administered in combination. Lumacaftor exposure increased slightly less than dose proportional for daily doses of 200-800 mg when lumacaftor was administered alone or in combination with ivacaftor. The metabolite to parent ratio based on AUC(Rauc, met) for M28-lumacaftor showed a decreasing trend with increasing doses of lumacaftor. At steady state (400/250 mg q12h), the metabolite to parent ratio based on AUC(Rauc, met) were 0.08 for M28-lumacaftor.(Table 99)

Table 98. Summary of Lumacaftor PK Parameters by Treatment (Cohort 2 and Cohort 3)

Treatment Group	Period	Statistic	AUC_{0-24h} (ng•h/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	t_{max} (h)[a]	CLss/F (L/h)
200 mg LUM qd / 200 mg LUM qd + 250 mg IVA q12h (Homozygous)	Monotherapy (Day 28)	N	21	21	21	21	21
		Mean (SD)	132000 (34400)	13300 (3040)	2890 (1290)	3.10 (1.00, 4.10)	1.62 (0.467)
	Combination Therapy (Day 56)	N	18	18	18	18	18
		Mean (SD)	122000 (48100)	11400 (2310)	2780 (1780)	3.05 (1.00, 6.30)	1.84 (0.604)
400 mg LUM qd / 400 mg LUM qd + 250 mg IVA q12h (Homozygous)	Monotherapy (Day 28)	N	19[b]	20	20	20	19[b]
		Mean (SD)	226000 (86500)	22000 (7370)	4310 (2490)	3.00 (1.00, 6.00)	2.02 (0.731)
	Combination Therapy (Day 56)	N	20	20	20	20	20
		Mean (SD)	219000 (79400)	21100 (5170)	4080 (1960)	2.55 (2.00, 6.10)	2.09 (0.905)
600 mg LUM qd / 600 mg LUM qd + 250 mg IVA q12h (Homozygous)	Monotherapy (Day 28)	N	19[b]	20	20	20	19[b]
		Mean (SD)	309000 (152000)	32100 (8980)	5460 (4030)	3.10 (2.00, 9.10)	2.28 (0.849)
	Combination Therapy (Day 56)	N	20	20	20	20	20
		Mean (SD)	290000 (127000)	27700 (7510)	5330 (3740)	4.00 (1.00, 8.50)	2.60 (1.59)
600 mg LUM qd / 600 mg LUM qd + 250 mg IVA q12h (Heterozygous)	Monotherapy (Day 28)	N	18	18	18	18	18
		Mean (SD)	344000 (134000)	33100 (9560)	5780 (2980)	3.00 (1.00, 6.20)	1.93 (0.575)
	Combination Therapy (Day 56)	N	17	17	17	17	17
		Mean (SD)	306000 (127000)	29500 (12000)	5320 (2240)	4.00 (0.50, 6.00)	3.01 (4.07)
400 mg LUM q12h / 400 mg LUM q12h + 250 mg IVA q12h (Homozygous)	Monotherapy (Day 28)	N	11	11	11	11	11
		Mean (SD)	331000 (93400)	23700 (6190)	7370 (3160)	3.00 (1.00, 6.20)	2.64 (0.917)
	Combination Therapy (Day 56)	N	10	10	10	10	10
		Mean (SD)	371000 (135000)	24200 (6990)	9760 (4750)	3.10 (1.00, 4.00)	2.40 (0.819)

Sources: Table 14.4.1.2.2.1 and Table 14.4.1.2.3.1.

AUC_{0-24h}: AUC from the time of dosing to the end of dosing interval, τ(24 hours) for qd regimen, and for the lumacaftor q12h regimen, the AUC_{τ} (i.e., AUC_{0-12h}) was multiplied by a factor of 2 to obtain the total daily AUC (equivalent of AUC_{0-24h}); C_{max}: maximum observed concentration; C_{min}: minimum observed concentration; CLss/F: apparent clearance at steady state; IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours; qd: once daily; SD: standard deviation; t_{max}: time of maximum concentration

[a] Median (minimum, maximum) values are presented for t_{max}.

[b] For AUC_{0-24h} and CLss/F, some subjects in the corresponding treatment period had missing values due to insufficient data in the terminal phase.

(Source – Table 11-7, Study 809-102 report)

Table 99. Summary of PK Parameters of Lumacaftor and M28-Lumacaftor in CF(to be marketed formulation, Cohort 4)

Parameter	Treatment 400 mg LUM q12h + 250 mg IVA q12h Day 28 N = 56
Lumacaftor	
AUC_{τ} (ng•h/mL)[a]	198000 (64800) [c]
$AUC_{0\text{-}24h}$ (ng•h/mL)[a]	396000 (130000) [c]
C_{max} (ng/mL)[a]	25000 (7960)
C_{min} (ng/mL)[a]	10 600 (5190)
t_{max} (h)[b]	2.15 (0.00, 12.00)
CLss/F (L/h) [a]	2.22 (0.682) [c]
M28-Lumacaftor	
AUC_{τ} (ng•h/mL)[a]	16600 (7990) [c]
$AUC_{0\text{-}24h}$ (ng•h/mL)[a]	33300 (16000) [c]
C_{max} (ng/mL)[a]	1580 (764)
C_{min} (ng/mL)[a]	1310 (635)
t_{max} (h)[b]	2.05 (0.00, 12.00)
$R_{AUC,met}$ [a]	0.0840 (0.0315) [c]

Sources: Cohort 4 Table 14.4.1.2.4.1 and Cohort 4 Table 14.4.1.1.4.2.

AUC_{τ}: AUC from the time of dosing to the end of dosing interval, τ (12 hours); CLss/F: apparent clearance at steady state; C_{max}: maximum observed concentration; C_{min}: minimum observed concentration; IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours; $R_{auc,met}$: ratio of AUC_{τ} of metabolite to parent; t_{max}: time of maximum concentration.

Note: For the lumacaftor q12h regimen, the $AUC_{0\text{-}24h}$ was the results of AUC_{τ} multiplied by a factor of 2 to obtain the total daily AUC (equivalent of $AUC_{0\text{-}24h}$).

[a] Mean (SD) values are presented.

[b] Median (minimum, maximum) values are presented.

[c] n = 55; a value was missing for these parameters due to insufficient data in terminal phase.

(Source – Table 11-12, Study 809-102 report)

IVA

When administered in combination with lumacaftor, there was a dose-dependent decrease in the ivacaftor exposure, featuring lower ivacaftor exposure with higher lumacaftor doses (Table 100, Figure 46). A similar decreasing trend was observed for M1-ivacaftor , but not M6-ivacaftor. M6-ivacaftor exposure was comparable when ivacaftor was administered in combination with lumacaftor for all dose levels.

Ivacaftor exposure (AUCτ, Cmax, and Cmin) increased more than proportional to dose as ivacaftor doses were increased from 150mg q12h to 250mg q12h. At steady state (400/250 mg q12h), the metabolite to parent ratio based on AUC(Rauc, met) were 3.5 and 7.5 for M1-ivacaftor M6-ivacaftor, respectively.(Table 100)

Table 100. Summary of Ivacaftor, M1-Ivacaftor, and M6-Ivacaftor PK Parameters on Day 56 by Treatment Group (Cohort 2 and Cohort 3)

Analyte Parameter	200 mg LUM qd + 250 mg IVA q12h (Homozygous) N = 19	400 mg LUM qd + 250 mg IVA q12h (Homozygous) N = 20	600 mg LUM qd + 250 mg IVA q12h (Homozygous) N = 20	600 mg LUM qd + 250 mg IVA q12h (Heterozygous) N = 17	400 mg LUM q12h + 250 mg IVA q12h (Homozygous) N = 10
Ivacaftor					
AUC_τ (ng•h/mL)[a]	5840 (2750)	3800 (1330)	3830 (1840)[c]	3450 (2960)	2560 (539)
C_{max} (ng/mL)[a]	903 (651)	598 (213)	668 (342)	558 (445)	493 (242)
C_{min} (ng/mL)[a]	195 (88.2)	125 (67.3)	102 (91.6)	96.9 (92.9)	77.6 (20.8)
t_{max} (h)[b]	3.00 (2.00, 6.00)	3.05 (2.00, 6.10)	3.00 (1.90, 6.00)	3.00 (1.00, 9.00)	4.00 (1.10, 9.10)
CLss/F (L/h)[a]		72.8 (21.8)	83.0 (45.4)[c]	112 (78.4)	102 (24.6)
M1-ivacaftor					
AUC_τ (ng•h/mL)[a]	15700 (6320)	11500 (4570)	11700 (4980)	9920 (8380)[c]	8850 (2430)
C_{max} (ng/mL)[a]	2280 (1380)	1790 (651)	1950 (833)	1630 (1240)	1590 (487)
C_{min} (ng/mL)[a]	593 (250)	366 (203)	298 (168)	345 (376)	223 (55.6)
t_{max} (h)[b]	4.00 (0.00, 6.10)	4.00 (3.00, 9.00)	4.00 (3.00, 6.10)	4.00 (0.00, 9.00)	4.00 (2.80, 11.00)
$R_{auc,met}$[a]	2.77 (0.599)	3.04 (0.707)	3.15 (0.778)[c]	3.09 (0.667)[c]	3.46 (0.653)
M6-ivacaftor					
AUC_τ (ng•h/mL)[a]	19200 (11100)	15900 (9560)	20300 (11900)[c]	22400 (25600)[c]	18800 (9130)
C_{max} (ng/mL)[a]	2390 (1770)	2060 (1200)	2680 (1550)	2780 (3020)	2580 (1560)
C_{min} (ng/mL)[a]	892 (622)	652 (468)	755 (517)	958 (1130)	792 (389)
t_{max} (h)[b]	4.00 (0.00, 9.10)	4.10 (2.00, 9.00)	6.00 (4.00, 11.10)	6.00 (0.00, 9.00)	5.10 (3.00, 11.00)
$R_{auc,met}$[a]	3.63 (2.17)	4.49 (2.90)	5.70 (3.22)[d]	6.55 (4.42)[c]	7.53 (3.41)

Sources: Table 14.4.1.2.2.3, Table 14.4.1.2.2.4, Table 14.4.1.2.2.5, Table 14.4.1.2.3.3, Table 14.4.1.2.3.4, and Table 14.4.1.2.3.5.

AUC_τ: AUC from the time of dosing to the end of dosing interval τ (12 hours); CLss/F: apparent clearance at steady state; C_{max}: maximum observed concentration; C_{min}: minimum observed concentration; IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours; qd: once daily; $R_{auc,met}$: ratio of AUC_τ of metabolite to parent; t_{max}: time of maximum concentration

[a] Mean (SD) values are presented.

[b] Median (minimum, maximum) values are presented.

[c] One subject in the corresponding treatment period had missing values due to insufficient data in the terminal phase; therefore, the number of subjects included in the analysis was 19 for 600 mg LUM qd + 250 mg IVA q12h (Homozygous) and was 16 for 600 mg LUM qd + 250 mg IVA q12h (Heterozygous).

[d] n=18; two subject in the corresponding treatment period had missing values due to insufficient data in the terminal phase.

(Source – Table 11-11, Study 809-102 report)

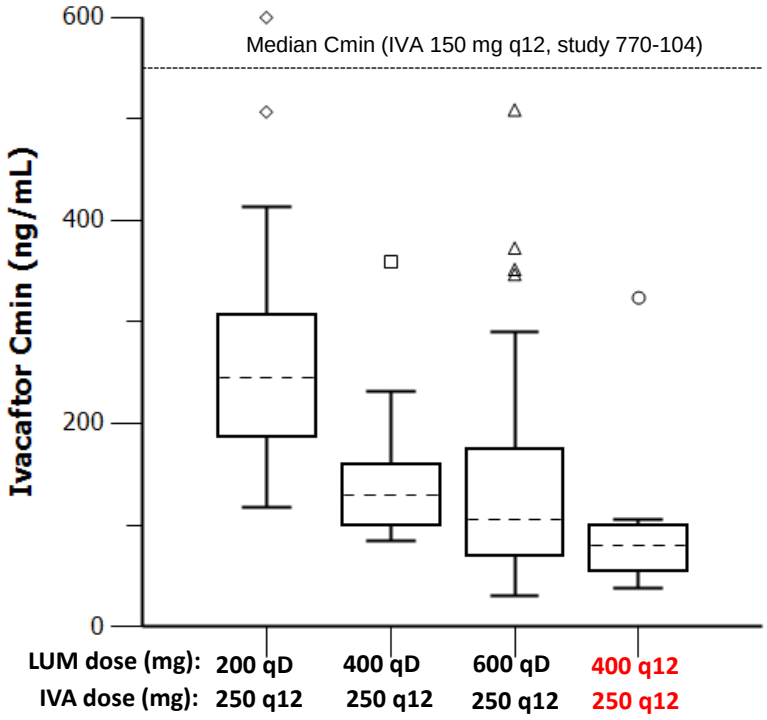


Figure 46. Lower Ivacaftor exposure with increased dose of Lumacaftor (study 102)
(source: reviewer analysis)

Table 101. Summary of Ivacaftor, M1-Ivacaftor, and M6-Ivacaftor PK Parameters on Day 28 in CF patients, (to be marketed formulation, Cohort 4)

Parameter	Number of Subjects	Treatment 400 mg LUM q12h + 250 mg IVA q12h Day 28
Ivacaftor		
AUC_τ (ng•h/mL)[a]	54	3660 (2250)
C_{max} (ng/mL)[a]	56	602 (304)
C_{min} (ng/mL)[a]	56	118 (119)
t_{max} (h)[b]	56	2.10 (0.00, 11.10)
CLss/F (L/h) [a]	54	85.6 (40.3)
M1-Ivacaftor		
AUC_τ (ng•h/mL)[a]	54	12100 (4660)
C_{max} (ng/mL)[a]	56	1960 (673)
C_{min} (ng/mL)[a]	56	368 (284)
t_{max} (h)[b]	56	4.00 (0.00, 11.10)
$R_{AUC,met}$ [a]	54	3.57 (0.897)
M6-Ivacaftor		
AUC_τ (ng•h/mL)[a]	55	24800 (14300)
C_{max} (ng/mL)[a]	56	3370 (1770)
C_{min} (ng/mL)[a]	56	1190 (1080)
t_{max} (h)[b]	56	4.20 (0.00, 11.10)
$R_{AUC,met}$ [a]	54	7.81 (3.98)

Sources: Cohort 4 Table 14.4.1.2.4.3, Cohort 4 Table 14.4.1.1.4.4, and Cohort 4 Table 14.4.1.2.4.5.

AUC_τ: AUC from the time of dosing to the end of dosing interval, τ (12 hours); CLss/F: apparent clearance at steady state; C_{max}: maximum observed concentration; C_{min}: minimum observed concentration; IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours; $R_{auc,met}$: ratio of AUC_τ of metabolite to parent; t_{max}: time of maximum concentration.

[a] Mean (SD) values are presented.

[b] Median (minimum, maximum) values are presented.

(Source – Table 11-13, Study 809-102 report)

- **Conclusions:**

Overall, LUM exposure increased dose proportional for daily dose of 200 mg qd to 600 mg qd. Coadministration with ivacaftor had minimal effects on the exposures of lumacaftor or its metabolite M28-LUM.

When IVA was coadministered with LUM, the daily dose of lumacaftor from 200 mg to 800 mg caused a dose dependent decrease in IVA exposure, with lowest IVA concentrations observed in the 400/250mg q12h treatment group.

BIOPHARMACEUTICS

9. Food effect (LUM/IVA)

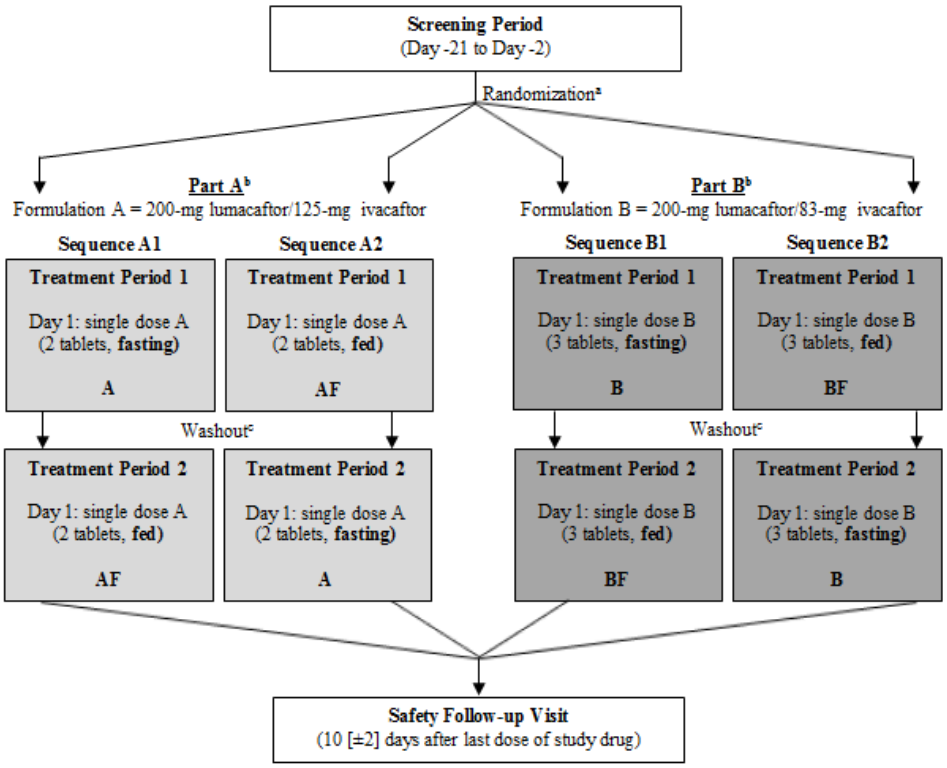
Trial # VX13-809-012

Title: A Phase 1, Randomized, Single-Dose, Open-Label Crossover Study to Investigate the Effect of Food on the Relative Bioavailability of 2 Fixed-Dose Combinations of

Lumacaftor and Ivacaftor Tablet Formulations in Healthy Adult Subjects

Objective:
To evaluate the effect of food on the relative bioavailability of 2 fixed-dose combinations (FDCs) of lumacaftor and ivacaftor tablet formulations.

Study design and treatment schedule:
Randomized, open-label, 2-part (2-sequence, 2-period per part), crossover study in healthy adult subjects. This study was designed to investigate the effect of food on the relative bioavailability of 2 different strengths of FDCs of lumacaftor and ivacaftor tablet formulations which were used in pivotal studies VX809-103 and VX809-104. Each of the 28 subjects was randomized to 1 of 4 dosing sequences. All 14 subjects in Part A received a single oral dose of 400-mg lumacaftor/250-mg ivacaftor in the fed and fasted conditions and completed both treatment periods. All 14 subjects in Part B received a single oral dose of 600-mg lumacaftor/250-mg ivacaftor in the fed and fasted conditions and completed both treatment periods.



A = 2 tablets of Formulation A in the fasting condition; AF = 2 tablets of Formulation A in the fed condition;
B = 3 tablets of Formulation B in the fasting condition; BF = 3 tablets of Formulation B in the fed condition.
[a] Randomization occurred on Day 1 of Treatment Period 1.
[b] Admission and discharge occurred on Day -1 and Day 5 of each treatment period. Treatment Period 1 occurred from Day -1 of Treatment Period 1 until Day -1 of Treatment Period 2. Treatment Period 2 occurred from Day -1 of Treatment Period 2 to the Safety Follow-up Visit.
[c] There was a washout of at least 14 days between each dosing occasion.

Figure 47. Schematic of Study Design
(Source: Figure 2-1 study 809-012 report)

PK Sampling Schedule

Blood (PK) samples were collected at predose and at 0.5, 1, 2, 3, 4, 6, 9, 12 (Day 1), 24 (Day 2), 48 (Day 3), 72 (Day 4), and 96 (Day 5) hours after the dose of study drug in each treatment period.

Results
The effect of food on the bioavailability of 2 FDCs of lumacaftor and ivacaftor tablet formulations, Formulation A (200-mg lumacaftor/125-mg ivacaftor) and Formulation B (200-mg lumacaftor/83-mg lumacaftor), was evaluated. Administration of a single dose of LUM/IVA with food significantly increased the exposures of both lumacaftor and ivacaftor (Table 102).

Table 102. Summary of Results of LUM/IVA Pharmacokinetic Parameters in healthy Subjects administered a single dose of LUM/IVA with or without food

Dose	Analyte	Parameter	Group comparison	Mean	Ratio	90% CI of the ratio
400/ 250 (n=14)	LUM	AUC_{inf} (ng.h/mL)	Fed/fast	565000/ 363000	1.64	(1.42, 1.88)
		Cmax (ng/mL)	Fed/fast	22400/10400	2.22	(1.93, 2.57)
	IVA	AUC_{inf} (ng.h/mL)	Fed/fast	18700/7840	2.53	(2.22, 2.88)
		Cmax (ng/mL)	Fed/fast	1490/475	3.7	(3.00, 4.56)
600/ 250 (n=14)	LUM	AUC_{inf} (ng.h/mL)	Fed/fast	766000/ 440000	1.95	(1.70,2.24)
		Cmax (ng/mL)	Fed/fast	36000/12900	2.82	(2.45, 3.26)
	IVA	AUC_{inf} (ng.h/mL)	Fed/fast	16400/4780	3.39	(3.01,3.83)
		Cmax (ng/mL)	Fed/fast	1540/314	5.18	(4.15,6.48)

(Source – Table 11-1, 11-2, 11-3, 11-4, Study VX809-012 report)

Reviewer's comment:

When a single dose of LUM/IVA was administered with fatty foods, lumacaftor exposure is approximately 2 times higher and ivacaftor exposure is 3 times higher than when taken in a fasting state. The sponsor did not compare the food effect after repeat doses. The food effect is not expected to differ for lumacaftor after repeat doses. For ivacaftor, as its exposure is reduced in a lumacaftor exposure-dependent manner, a higher lumacaftor exposure will further reduce the exposure of ivacaftor after repeated dose. When Lumacaftor dose doubled from 400mg qd to 400 mg q12h under fed condition, the ivacaftor exposure (AUC) was reduced from 3800 to 2560 ng.h/mL (Table 100). As the food effect on single dose IVA is 3 fold increase in exposure, the net food effect is still estimated to be an increase of ivacaftor exposure. Therefore, LUM/IVA should be taken with food.

Conclusions
When a single dose of LUM/IVA was administered with fatty foods, lumacaftor exposure

is approximately 2 times higher and ivacaftor exposure is approximately 3 times higher than when taken in a fasting state.

10. Relative bioavailability

Trial # vx08-809-003

Title: A Phase 1, Randomized, Open-Label Study to Evaluate the Bioavailability and Food Effect of a Capsule Formulation of VX-809 Relative to a Suspension Formulation of VX-809 in Healthy Male Subjects

Objectives

Primary:

- To evaluate the bioavailability (BA) of a capsule formulation of VX-809 relative to the suspension formulation administered in the VX-809 First in Human (FIH) Phase 1 Study (VX07-809-001)
- To assess the effect of food on the pharmacokinetics (PK) of the VX-809 capsule formulation after a single dose of 200 mg

Study design and treatment schedule:

Open-label, 2-formulation, 6-sequence, 3-period crossover study used a Williams' design. Eighteen male subjects were randomly assigned to 1 of 6 sequences with a total of 3 subjects in each sequence. Over the course of this study, each subject received 3 treatments ordered sequentially, with a minimum 13-day washout period between each sequence. The reference formulation was the suspension formulation studied in study VX07-809-001. The test formulation was a capsule formulation of VX-809. A single dose of 200-mg VX-809 was administered orally (PO) per treatment period.

Table 103. A William's Design for 3 Treatment Periods

	Treatment Period		
Sequence	**1**	**2**	**3**
1	R	TF	T
2	T	R	TF
3	TF	T	R
4	T	TF	R
5	TF	R	T
6	R	T	TF

R: reference formulation (suspension formulation); T: test formulation (capsule formulation); TF: test formulation (capsule formulation) with food

(Source – Table 9-1, Study 809-003 report)

PK Sampling Schedule

- Pharmacokinetic samples were collected at the following time points: 0 (predose), 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, 72, 120, 168 and 216 hours postdose. In addition, 1 sample was collected at the follow-up visit.

Results

The capsules given in the fasting condition resulted in statistically significant higher

AUC0-∞ (mean ratio of 141%) and Cmax (mean ratio of 144%) values when compared to the suspension formulation administered in fasting condition.

The capsules given with food (high-fat breakfast) resulted in statistically significant higher AUC0-∞ (mean ratio of 117%) and Cmax (mean ratio of 133%) values when compared to the capsules administered in fasting condition.

Table 104. Geometric Mean Ratios and 90% Confidence Intervals for VX-809 Plasma Pharmacokinetic Parameters (T: capsule; R: suspension; TF: capsule fed)

Pharmacokinetic Parameter	Reference	Test	Mean Ratio (%)	Lower Limit (%)	Upper Limit (%)
$AUC_{0-\infty}$ (ng*hr/mL)	R	T	141.23	131.74	151.41
	T	TF	116.75	108.91	125.17
	R	TF	164.89	153.81	176.77
AUC_0-t_{last} (ng*hr/mL)	R	T	141.23	131.82	151.30
	T	TF	116.75	108.98	125.08
	R	TF	164.88	153.90	176.64
C_{max} (ng/mL)	R	T	143.51	126.01	163.45
	T	TF	132.85	116.64	151.30
	R	TF	190.65	167.40	217.14

(Source – Table 11-2, Study 809-003 report)

- **Conclusions**

The food effect is not significant for lumacaftor capsule formulation. Lumacaftor capsule has higher bioavailability compared to lumacaftor suspension. As lumacaftor capsule is not used in efficacy/safety studies, the relative bioavailability and PK data learned in this study is not reflected in the label.

Trial # vx12-809-007

Title: A Phase 1, Open-Label, Randomized, Single-Dose, Crossover Study to Investigate the Relative Bioavailability of a High Drug Load Lumacaftor Formulation Compared to a Lumacaftor Reference Formulation in Healthy Adult Male Subjects

Objectives:

Part A

Primary: To evaluate the relative bioavailability of a new tablet formulation ((b) (4) of lumacaftor compared to a reference tablet formulation of lumacaftor (b) (4) at 2 different doses

Part B

Primary: To evaluate the relative bioavailability of a new tablet coformulation (200-mg VX-809/125-mg VX-770 cogranulation [CG] tablets) of lumacaftor and ivacaftor compared to codosing as separate tablet formulations (b) (4) of lumacaftor and film-coated ivacaftor tablets)

For Part A, the (b) (4) formulation studied in part A is only used in the QT study, and not used in any efficacy/safety studies. For Part B, (b) (4) of lumacaftor

and film coated ivacaftor tablets were used in study 809-102, the phase 2 dose ranging study for LUM/IVA. The tablet coformulation was used in the pivotal studies 809-103 and 809-104.

Study design and treatment schedule:
Part B was a 3-formulation, 2-sequence, 2-period crossover study in healthy, adult male subjects. Thirty-one subjects were randomized to 1 of 2 sequences on Day 1 of the study as shown in Table 105. All formulations were administered in the fed state.

Table 105. Part B: Dosing Periods

Sequence	Dosing Period 1	Dosing Period 2
1 (N = 15)	Co-Dose 400-mg lumacaftor (b) (4) 250-mg ivacaftor	Coformulation 400-mg VX-809/250-mg VX-770
2 (N = 16)	Coformulation 400-mg VX-809/250-mg VX-770	Co-Dose 400-mg lumacaftor (b) (4) 250-mg ivacaftor

N: number of subjects
Notes: All formulations were administered in the fed state. Coformulation was dosed as 2 tablets of the 200-mg VX-809/125-mg VX-770 CG coformulation. Ivacaftor was dosed as one 100-mg tablet and one 150-mg tablet. Lumacaftor was dosed as 2 × 200-mg tablets.
(Source – Table 2-2, Study 809-007 report)

Test Product: The reference tablet formulation of lumacaftor, 200 mg tablet (b) (4) Ivacaftor 150 mg tablet and 100 mg tablet. The coformulation was 200-mg VX-809/125-mg VX-770 CG.

- **Results**

PK results
Coformulation of lumacaftor and ivacaftor (200-mg VX-809/125-mg VX-770 CG tablet) had similar lumacaftor exposures (AUC0-∞ and Cmax GLSM ratios and 90% CIs of 1.00 [0.96, 1.04] and 0.93 [0.86, 1.00], respectively) as codosing with separate tablets when dosed at 400 mg of VX-809 and 250 mg of VX-770. Coformulation of lumacaftor and ivacaftor had similar ivacaftor AUC0-∞ (GLSM ratio and 90% CI of 1.14 [1.06, 1.23]), but 1.2-fold higher ivacaftor Cmax (GLSM ratio and 90% CI of 1.20 [1.09, 1.33]) as codosing with separate tablets when dosed at 400 mg of VX-809 and 250 mg of VX-770.

Table 106. Summary of Relative Bioavailability of Lumacaftor Between Coformulation Versus Co-Dose

Analyte	Parameters	N	Dose (mg)	Co-Dose GLSM	Coformulation GLSM	GLSM Ratio	90% CIs (Lower, Upper)
LUM	$AUC_{0-\infty}$ (µg·h/mL)	31	400	522	522	1.00	0.96, 1.04
	C_{max} (µg/mL)	31	400	22.3	20.6	0.93	0.86, 1.00
IVA	$AUC_{0-\infty}$ (µg·h/mL)	31	250	12.9	14.7	1.14	1.06, 1.23
	C_{max} (µg/mL)	31	250	1.05	1.26	1.20	1.09, 1.33

Source: Appendix 16.2.5.1.7
$AUC_{0-\infty}$: area under the concentration versus time curve from the time of dosing extrapolated to infinity; C_{max}: maximum observed concentration; CIs: confidence interval; GLSM: geometric least squares mean (Co-Form/Co-Dose); N: number of subjects.
Notes: Coformulation was dosed as 2 tablets of the 200-mg VX-809/125-mg VX-770 CG coformulation. For Co-Dose, ivacaftor was dosed as one 100-mg tablet and one 150-mg tablet.

(Source – Table 11-6, 11-7, Study 809-007 report)

- **Conclusions**

Overall, both the lumacaftor and ivacaftor exposures of the 200/125 FDC tablet were comparable to administration of lumacaftor and ivacaftor in combination as separate tablets.

4.3 Filing Memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**206038**	**Brand Name**	**Orkambi**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Lumacaftor/ivacaftor**
Medical Division	**Pulmonary, Allergy, and Rheumatology Products**	**Drug Class**	**Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) (b) (4) potentiator**
OCP Reviewer	**Jianmeng Chen**	**Indication(s)**	**CF patients with F508del homozygous mutations, 12 years and above**
OCP Team Leader	**Brar Satjit**	**Dosage Form**	**Tablet (200/125 mg)**
Pharmacometrics Reviewer	**Anshu Marathe**	**Dosing Regimen**	**400/250 BID**
Pharmacometrics Team Leader	**Liang Zhao**		
Date of Submission	**11/5/2014**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**4/7/2015**	**Sponsor**	**Vertex**
PDUFA Due Date	**7/5/2015**	**Priority Classification**	**P**

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**	**17**		
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		VX08-809-004
Isozyme characterization:	**X**	**5**		Report D072, D071, H060, D083, B242
Blood/plasma ratio:				
Plasma protein binding:	**X**	**4**		Report D152, G085, DM-021, DM-040,
Transporter specificity:	**X**	**2**		DM041, DM020
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**5**		Study 809-001, 003, 004, 007, 012
multiple dose:	**X**	**1+5**		Study 809-001, 005, 006, 008, 009, 010
Patients-				
single dose:	**X**	**1**		VX07-809-002
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	**X**			
Drug-drug interaction studies -				

In-vivo effects on primary drug:	**X**	**1**		VX12-809-009
In-vivo effects of primary drug:	**X**	**2**		Vx08-809-005, VX10-809-006
In-vitro:	**X**	**15**		Report K027, DM-019, J174, K020, K028, DM-018, G140, DM-028, k112, K111, DM-020, DM-039, DM-038, DM-041, CBDM304464,
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**X**	**1**		VX13-809-011 (6-11 yrs)
geriatrics:				
renal impairment:				
hepatic impairment:	**X**	**1**		VX13-809-010
PD -				
Phase 2:	**X**	**3**		Study 809-101, 102; study 770-104
Phase 3:	**X**	**2**		Study 809-103, 104 (No sweat chloride)
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**3**		Study 809-101, 102; study 770-104
Phase 3 clinical trial:	**X**	**2**		Study 103, 104 (No sweat chloride)
Population Analyses -				
Data rich:				
Data sparse:	**X**	**4**		Report J178, K050, K261, K272
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**		VX12-809-007
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**3**		VX08-809-003, VX13-809-012, VX07-809-002
Bio-waiver request based on BCS				
BCS class	**X**	**1**		DM020
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	**X**			Mutations in CFTR was characterized
QT studies	**X**	**1**		VX12-809-008
Chronopharmacokinetics				
Pediatric development plan	**NA**			Orphan status
Literature References				
Total Number of Studies		**17**		17 clinical studies (number of studies in black), and also *in vitro* studies and analytical report (number of studies in blue); duplicated study numbers shown in red

---

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
05/28/2015

ANSHU MARATHE
05/28/2015

YANING WANG
05/28/2015

SURESH DODDAPANENI
05/28/2015

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**206038**	**Brand Name**	**Orkambi**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Lumacaftor/ivacaftor**
Medical Division	**Pulmonary, Allergy, and Rheumatology Products**	**Drug Class**	**Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) (b) (4) potentiator**
OCP Reviewer	**Jianmeng Chen**	**Indication(s)**	**CF patients with F508del homozygous mutations, 12 years and above**
OCP Team Leader	**Satjit Brar**	**Dosage Form**	**Tablet (200/125 mg)**
Pharmacometrics Reviewer	**Anshu Marathe**	**Dosing Regimen**	**400/250 BID**
Pharmacometrics Team Leader	**Liang Zhao**		
Date of Submission	**11/5/2014**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**4/7/2015**	**Sponsor**	**Vertex**
PDUFA Due Date	**7/5/2015**	**Priority Classification**	**P**

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**	**17**		
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		VX08-809-004
Isozyme characterization:	**X**	**5**		Report D072, D071, H060, D083, B242
Blood/plasma ratio:				
Plasma protein binding:	**X**	**4**		Report D152, G085, DM-021, DM-040,
Transporter specificity:	**X**	**2**		DM041, DM020
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**5**		Study 809-001, 003, 004, 007, 012
multiple dose:	**X**	**1+5**		Study 809-001, 005, 006, 008, 009, 010
Patients-				
single dose:	**X**	**1**		VX07-809-002
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	**X**			
Drug-drug interaction studies -				

In-vivo effects on primary drug:	**X**	**1**		VX12-809-009
In-vivo effects of primary drug:	**X**	**2**		Vx08-809-005, VX10-809-006
In-vitro:	**X**	**15**		Report K027, DM-019, J174, K020, K028, DM-018, G140, DM-028, k112, K111, DM-020, DM-039, DM-038, DM-041, CBDM304464,
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**X**	**1**		VX13-809-011 (6-11 yrs)
geriatrics:				
renal impairment:				
hepatic impairment:	**X**	**1**		VX13-809-010
PD -				
Phase 2:	**X**	**3**		Study 809-101, 102; study 770-104
Phase 3:	**X**	**2**		Study 809-103, 104 (No sweat chloride)
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**3**		Study 809-101, 102; study 770-104
Phase 3 clinical trial:	**X**	**2**		Study 103, 104 (No sweat chloride)
Population Analyses -				
Data rich:				
Data sparse:	**X**	**4**		Report J178, K050, K261, K272
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**		VX12-809-007
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**3**		VX08-809-003, VX13-809-012, VX07-809-002
Bio-waiver request based on BCS				
BCS class	**X**	**1**		DM020
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	**X**			Mutations in CFTR was characterized
QT studies	**X**	**1**		VX12-809-008
Chronopharmacokinetics				
Pediatric development plan	**NA**			Orphan status
Literature References				
Total Number of Studies		**17**		17 clinical studies (number of studies in black), and also in vitro studies and analytical report (number of studies in blue); duplicated study numbers shown in red

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			No E-R analysis submitted for ivacaftor
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	The pediatric studies (12-17yr) were done w/o an WR
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	The pediatric studies were done w/o an WR
17	Is there adequate information on the pharmacokinetics and	X			

	exposure-response in the clinical pharmacology section of the label?				
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____Yes__

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- The labeling language for Section 7 (Drug Interactions) should reflect the concomitant medications used in the phase 3 trials. You should submit more specific language, addressing the recommendations for common CF concomitant medicines in Section 7 in the label.
- In addition, you should include recommendations for managing concomitant administration of the following drug classes in Section 7 of the label:

- *Other Antacids/H2 blockers*
- *Ibuprofen or other anti-inflammatory drugs*
- *Oral hypoglycemics*
- *Anti-depressants*

Submission in brief:

Indication and mechanism of action
Vertex has submitted NDA 206038 seeking the marketing approval for lumacaftor/ivacaftor (ORKAMBI), to be used as "*a cystic fibrosis transmembrane conductance regulator (CFTR)* (b) (4) *and potentiator combination indicated for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene."* ORKAMBI should not be used in patients other than those homozygous for the F508del mutation.

Lumacaftor (also known as VX-809) is a CFTR (b) (4) that acts by facilitating the cellular processing and trafficking of F508del-CFTR, thereby increasing the amount of functional CFTR protein at the cell surface. Ivacaftor (KALYDECO, also known as VX-770) is a selective potentiator of CFTR and has been approved "for the treatment of cystic fibrosis in patients age 6 years and older who have a G551D mutation in the CFTR gene" in the United States on January 31, 2012 under NDA203188. In February 2013, it was approved for use in eight additional mutations (G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R).

Lumacaftor/ivacaftor (hereafter referred to as LUM/IVA) is a tablet formulation of a fixed dose combination (FDC) of LUM (CFTR [redacted] (b) (4) and IVA (CFTR potentiator). The proposed dosing regimen is LUM 400 mg every 12 hours (q12h)/IVA 250 mg q12h, for a total daily dose of 800 mg of LUM and 500 mg of IVA taken with food. The proposed formulation is a 200-mg LUM/125-mg IVA FDC tablet for oral administration, 2 tablets q12h.

Table 1. Summary of Regulatory history relevant to clinical pharmacology

PNDA (Aug 2014)	• Agreed on general clinical pharm studies adequate to support NDA filing • General advice on pop PK and PK/PD analysis
EOP1/2 (Oct 2012)	• Agreed that 12-17 yr old can be included in phase III studies with the same dose as adults. • Agreed on the DDI plan • Agreed on the special population assessment plan, that a moderate hepatic impairment study is reasonable, and a renal impairment study is not necessary • Discussed about dose/supra-dose selection in QT study
Communication (June 2013)	• Agreed on the DDI plan, additional comment to sponsor: "CF patients are usually on many concomitant medicines. Address how these common concomitant medicines should be managed when used with lumacaftor/ivacaftor in the NDA submission"

Summary of information submitted

NDA 206038 consists of 17 clinical and clinical pharmacology studies, including 10 clinical pharmacology studies in healthy subjects, 4 clinical (dose ranging) and clinical pharmacology studies in CF subjects (Table 2), and 3 clinical studies (study 809-103, 104 and study 770-104) to demonstrate the efficacy and safety of LUM/IVA.

Table 2. List of Clinical Pharmacology Studies

Study	Study Description
Studies in Healthy Subjects	
VX07-809-001	Single-dose and multiple-dose escalation study of lumacaftor
VX08-809-003	Bioavailability and food effect of a capsule formulation of lumacaftor relative to a suspension formulation of lumacaftor
VX08-809-004	Mass balance study to investigate the absorption, metabolism, and excretion of lumacaftor
VX08-809-005	DDI study of lumacaftor and ivacaftor
VX10-809-006	DDI study of lumacaftor and ivacaftor
VX12-809-007	Relative bioavailability of a High Drug Load lumacaftor formulation compared to a reference lumacaftor formulation (Part A); Relative bioavailability of lumacaftor and ivacaftor formulated as a fixed-dose combination tablet compared to lumacaftor and ivacaftor formulated as separate tablets (Part B)
VX12-809-008	Safety, tolerability, and PK following multiple ascending doses of lumacaftor (Part A); Electrocardiogram study to evaluate the effect of lumacaftor in combination with ivacaftor on the QT/QTc interval (Part B)
VX12-809-009	DDI study of the effect of ciprofloxacin, itraconazole, and rifampin on the PK of lumacaftor in combination with ivacaftor in healthy adult subjects
VX13-809-010	PK and safety of multiple doses of lumacaftor in combination with ivacaftor in subjects with moderate hepatic impairment and in matched healthy subjects
VX13-809-012	Effect of food on the relative bioavailability of 2 fixed-dose combinations of lumacaftor and ivacaftor tablet formulations
Studies in Subjects with CF[a,b]	
VX07-809-002	PK study of lumacaftor and effect of food in pancreatic-insufficient subjects
VX13-809-011 (Part A)	PK, safety, and tolerability of lumacaftor in combination with ivacaftor in subjects 6 through 11 years of age
VX08-809-101	Multiple dose study to evaluate safety, PK, and PD of lumacaftor
VX09-809-102	Multiple-dose study to evaluate the safety, tolerability, efficacy, PK, and PD of lumacaftor monotherapy, and lumacaftor and ivacaftor combination therapy

a Studies included subjects with CF who are homozygous (Studies 011, 101, and 102) and heterozygous (Study 102) for the *F508del-CFTR* mutation.
b As part of the secondary objectives, studies VX12-809-103 and VX12-809-104 also included PK evaluation in subjects with CF who are homozygous for the *F508del-CFTR* mutation.

The clinical pharmacology information for LUM was mainly derived from Phase 1 studies as well as in vitro studies evaluating permeability, plasma protein binding, role of transporters, and potential for CYP 450 metabolic enzymes inhibition and induction. Population- based modeling analyses including population pharmacokinetics analysis were performed to assess the effect of covariates on LUM/IVA exposure and to understand the time course of effect and toxicities and their association with dose or exposure.

The clinical pharmacology information for ivacaftor has been submitted and reviewed under NDA203188 by Dr. Lokesh Jain (DARRTs date 1/18/2012).

Contribution of LUM and IVA to combination

-PK

LUM substantially reduced the exposure of IVA (by approximately 80%) with the steady-state induction effect achieved following the proposed dose (Table 3, study 005 and 006). IVA slightly reduced the exposure of LUM (by approximately 11%, data not shown). Therefore, the synergistic effect of LUM and IVA is not due to increased exposure of the two drugs.

Table 3. Summary of PK Parameters for Ivacaftor in the Presence of Lumacaftor

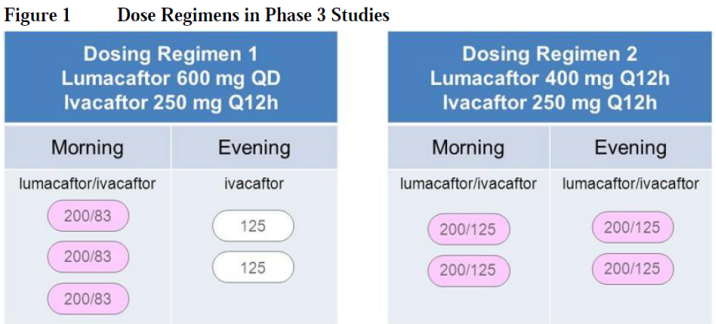
	Dose and Schedule			Effect on	GLSMR (90% CI) of IVA PK With/Without Coadministered Drug	
Drug	**Drug**	**IVA**	**N**	**IVA PK[a]**	**C_{max}**	**AUC_{0-12h}**
IVA in combination with LUM						
LUM[b]	LUM 200 mg q24h for 14 days; oral	IVA 150 mg q12h for 14 days	16	↓	0.228 (0.176, 0.296)	0.180 (0.139, 0.233)
LUM[c]	LUM 400 mg qd for 14 days; oral	IVA 150 mg q12h for 14 days	13	↓	0.38 (0.28, 0.51)	0.25 (0.20, 0.31)
	LUM 200 mg qd for 14 days; oral	IVA 250 mg q12h for 14 days	16	↓	0.26 (0.20, 0.34)	0.22 (0.17, 0.28)

(Source data: Table 31, summary of clinical pharmacology, study 005 and 006)

-PD

The two phase III studies (study 103 and 104) did not include monotherapy arms of LUM or IVA (Figure 1). Efficacy and safety of LUM monotherapy (Studies 101 and 102) and IVA monotherapy (Study 770-104) were evaluated in separate studies to support the contribution of LUM and IVA. The lack of efficacy of LUM monotherapy was demonstrated in a phase II study 102 (Figure 2), supporting the contribution of IVA in the combination. The treatment difference for IVA monotherapy (150 mg BID) compared to placebo was 1.72%, (95% CI: -0.63, 4.08, p=0.15), slightly lower than the effect size of 2.8% with combination therapy (LUM400mg/IVA250mg BID, pooled studies).

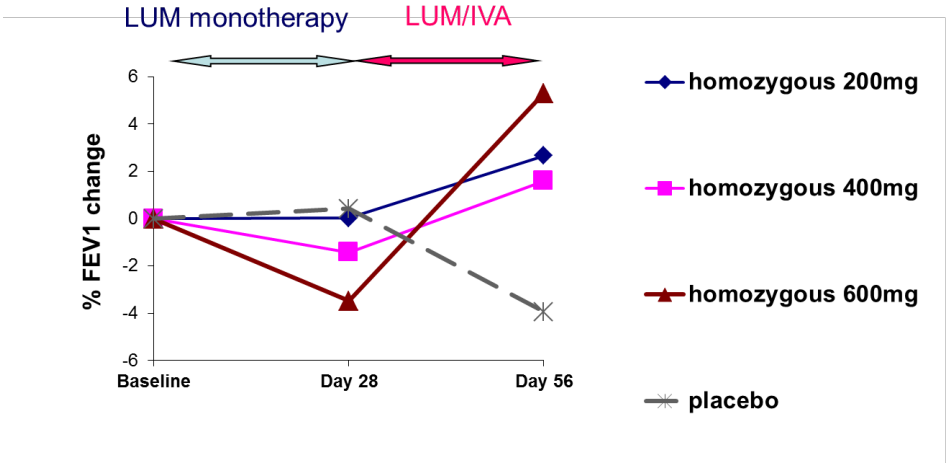
Figure 1: Rationale for 400/250 bid dose regimen selection



***-Lumacaftor*:** LUM 600 mg qd/IVA 250 mg q12h regimen was assessed in the phase II study 102, and was carried forward to phase 3 studies due to significant efficacy. In Study 102, all treatment groups either remained stable or demonstrated a dose dependent reduction in FEV1 during the 28-day period of LUM monotherapy (qd dosing, Figure 2). In contrast, during the 28-day period of combination therapy, an increase in FEV1 was observed in all active treatment cohorts, with the largest increase in the LUM 600 mg qd/IVA 250 mg q12h cohort.

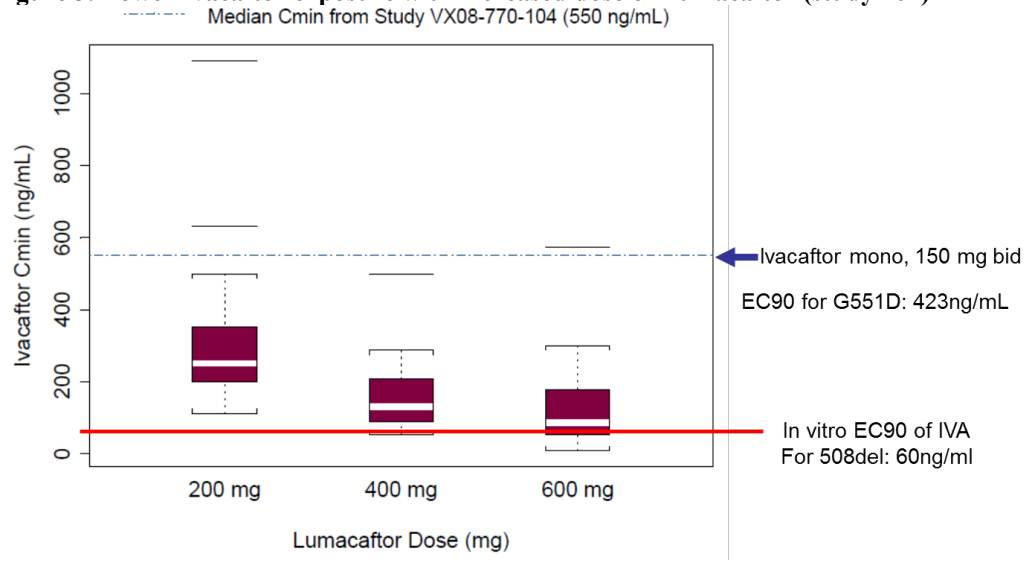
LUM 400mg/IVA 250 mg q12h regimen was also studied in phase 3, given the simplicity of the dosing regimen (Figure 1) and the potentially advantageous PK profile (smaller peak to trough concentration ratio with the BID regimen) of LUM.

Figure 2. %FEV1 change from baseline, study 102



-Ivacaftor: Based on the observed reduction in ivacaftor exposure when LUM was administered in combination, the dosage of ivacaftor was increased to 250 mg q12h from the approved ivacaftor dosage of 150 mg q12h when administered alone. However, IVA exposure in the LUM/IVA combination therapy is still much lower compared to that of the ivacaftor 150 mg q12h monotherapy (Figure 3). The sponsor suggested that IVA potency is 7-fold higher in F508del-CFTR (EC90 at 60ng/ml) compared to G551D-CFTR (EC90 at 423 ng/ml) in the in vitro studies, and therefore the IVA 250 mg q12h dose was sufficient for the patients with F508del.

Figure 3. Lower Ivacaftor exposure with increased dose of Lumacaftor (study 102)



-Efficacy in Phase 3 trials:

Studies 103 and 104 were Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies that evaluated the efficacy and safety of LUM/IVA combination therapy for

24 weeks in subjects 12 years and older with CF who are homozygous for the F508del-CFTR mutation. These studies evaluated 2 doses of LUM in combination with IVA (Figure 1), in comparison to placebo. Study 105 was a long-term, rollover study to assess the persistence of efficacy.

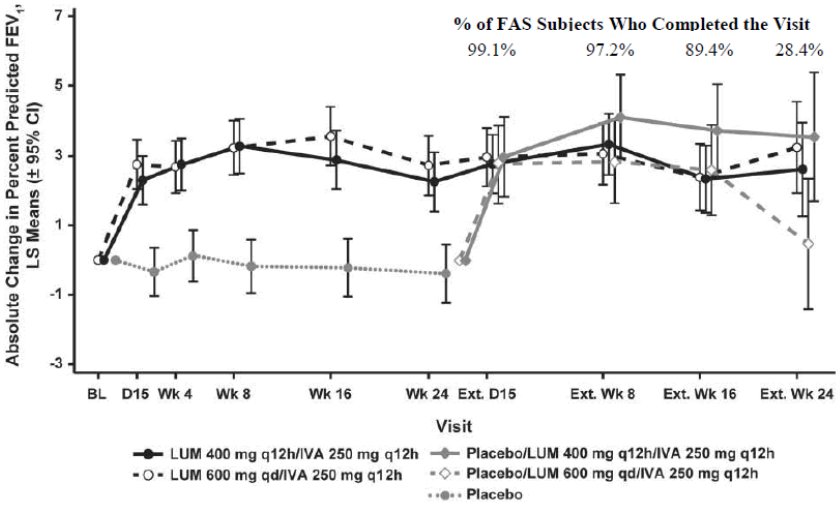


Figure 4. Absolute Change From Baseline in Percent Predicted FEV1(first 24 weeks, pooled data of study 103 and 104; Ext time, data from extension study 105)

Phase III studies indicated that both dosing regimens are superior to the placebo in the primary endpoint (Figure 4) and other key secondary endpoints (e.g. exacerbation), and there was no clear differentiation between the 2 combination therapy regimens. Therefore, the sponsor seeks approval for LUM/IVA 400/250 mg BID due to simplicity of the dosing regimen.

Effect of intrinsic/extrinsic factors on dose

As per sponsor's proposal, LUM/IVA is recommended to be administered with food. The sponsor-proposed dose adjustments based on the intrinsic (Table 4 and 5) and extrinsic factors (Table 6) were summarized in Table 4-6.

For hepatic impairment, subjects with moderately impaired hepatic function (Child-Pugh B) had higher exposures (AUCτ by approximately 50% and Cmax by approximately 30%) and similar protein binding compared with healthy subjects. Therefore, the sponsor proposed to reduce dose by 25% for patients with moderate hepatic impairment. The sponsor did not conduct a dedicated PK study for patients with mild or severe hepatic impairment, and the dose recommendation for these patients were based on the assumption of higher LUM/IVA exposure in the severe hepatic impairment patients. For renal impairment, no dose adjustments are recommended for mild or moderate cases, and caution is recommended in patients with severe renal impairment (Table5).

Table 4. Intrinsic Factors

Factor	Impact		Dosing recommendation
	lumacaftor	ivacaftor	
Gender	↔	↔	
Weight	↑ in lower weight	↑ in lower weight	Not mentioned in the label
Race	NA	NA	Not mentioned in the label
Age	Slightly higher with increasing age	↔	Not mentioned in the label
Healthy vs CF	1.81 fold higher in healthy	1.53 fold higher in healthy	mentioned in the label

↑- Increase, ↔ - no change

Table 5. Special population

Special population	Effect on PK	AUC_{inf}	C_{max}	Dosing recommendation
Renal impairment	NA	NA	NA	Caution in severe and end-stage renal impairment
Mild hepatic impairment	Lumacaftor	NA	NA	No dose adjustment
	Ivacaftor	NA	NA	
Moderate hepatic impairment	↑ Lumacaftor	1.5	1.3	A dose reduction to 2 tablets in the morning and 1 tablet in the evening (LUM 600 mg/IVA 375 mg total daily dose)
	↑ Ivacaftor	1.6	1.3	
Severe hepatic impairment	Lumacaftor	NA	NA	Max dose 200/125 mg BID
	Ivacaftor	NA	NA	

↑- Increase, ↔ - no change

Table 6. Extrinsic Factors

Co-administered drug	Effect on PK	AUC_{inf}	C_{max}	Dosing recommendation
Strong CYP3A inhibitor: itraconazole	↔ Lumacaftor	0.97	0.99	CYP3A4 inhibitor add to LUM/IVA, no dose adjustment; initiate LUM/IVA on background of strong CYP3A inhibitor, 200/125 qd x 1w.
	↑ Ivacaftor	4.30	3.64	
CYP3A inducer: Rifampin	↔ Lumacaftor	0.87	0.96	Co-administration not recommended
	↓ Ivacaftor	0.43	0.50	
Moderate CYP3A inhibitor: Ciprofloxacin	↔ Lumacaftor	0.86	0.88	No dose adjustment
	↔ Ivacaftor	1.29	1.29	

↑- Increase, ↔ - no change

Summary of drug-interaction studies

-Effect of other drugs on LUM/IVA

Effect of co-administration of itraconazole, rifampicin, and ciprofloxacin on LUM/IVA exposure (AUC) and C_{max} was evaluated (Table 6).

-Effect of LUM/IVA on other drugs

Lumacaftor is a strong inducer of CYP3A. In vitro studies suggest that LUM has the potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19. Therefore, concomitant use of LUM/IVA may alter exposure of many medicines commonly used in CF patients. The sponsor listed recommendation of common co-meds in Section 7 of the label, including hormonal contraceptives; antibiotics; antifungals; glucocorticoids, and proton pump inhibitors. However, some recommendations are quite general, such as (b) (4) .

Reviewer's comment: Most medications listed in section 7 were also used in CF patients in the phase III studies (study 103 and 104). Therefore, we suggested that the label should be more specific in the recommendations in managing concomitant medications based on the phase III experience, such as (b) (4) *". Also, the recommendations should include other commonly used medications in CF patients, such as Ibuprofen, oral hypoglycemic, anti-depressant, etc.*

Effect on QT interval

Per sponsor's report, LUM and IVA combination therapy does not prolong the QTc interval at the therapeutic (LUM 600 mg qd/IVA 250 mg q12h) and supra-therapeutic (LUM 1000 mg qd/IVA 450 q12h) dose levels tested in a thorough QT study (study 008). The upper limit of the 2-sided 90% CI for the LS mean difference from placebo for the time-matched, baseline-adjusted QTcF interval for both the therapeutic dose regimen and the supra-therapeutic dose regimen did not exceed 10 msec.

Pediatrics development plan

LUM/IVA has been granted Orphan Drug Status, and there is no Pediatric Study Plan (PSP) included in this submission; per 21 CFR 314.55(d), Orphan Drugs are exempt from the requirements to assess pediatric use under PREA.

Summary of PK

The PK characteristics of LUM/IVA are summarized in Table 7. The median (range) time of the maximum concentration (Tmax) of LUM is approximately 4.0 hours (2.0; 9.0) in the fed state. LUM is approximately 99% bound to plasma proteins, primarily to albumin. In vitro and in vivo data indicate that LUM is mainly metabolized via oxidation by CYP3A and glucuronidation. LUM is not extensively metabolized in humans, with the majority of LUM excreted unchanged in the feces. The mean plasma LUM terminal phase half-life (t1/2) was approximately 26 hours across the tested dose range. In subjects with CF, LUM Cmax and AUC increased approximately proportionally with dose, over a range of doses from LUM 25 mg qd to 400 mg q12h. Steady-state plasma concentrations of LUM were reached after 7 days of treatment.

Following multiple oral dose administration of IVA in combination with LUM, the exposure of IVA generally increased with doses from 150 mg q12h to 250 mg q12h. The median (range) tmax of IVA is approximately 4.0 hours (2.0; 6.0) in the fed state. The human plasma protein binding of IVA was greater than 99%, primarily to alpha-1-acid glycoprotein and albumin. IVA is extensively metabolized in humans. In vitro and in vivo data indicate that IVA is primarily metabolized by CYP3A. For IVA and its metabolites, elimination in the feces as metabolites was the predominant route of elimination, with minimal renal excretion of parent or metabolites.

Table 7. Summary of PK characteristics for lumacaftor and ivacaftor

	Lumacaftor	Ivacaftor
Food effect	minimal	Administer with fat containing food
Tmax	4 – 6 hrs	4 hrs
Protein binding	99.97%	99%
Metabolism	Minor, CYP 3A4	Major pathway, CYP3A4
DDI	CYP 3A4 inducer	AUC↓ 75% with Lumacaftor
Plasma	Mainly parent	Mainly metabolite
Elimination	Renal 8.6%, Feces 80% Mostly parent	Renal 6.6% Feces 87% Mostly metabolite
T1/2	~26 hrs	12 – 24 hrs
Linear PK	25 – 800 mg	25 – 150 mg

Summary of population based modeling analysis

Population PK analyses for LUM and IVA were conducted on pooled data from Phase 1, 2, and 3 studies (Studies 005, 006, 011, 101, 102, 103, and 104). Exposure-response analysis was conducted for lumacaftor for efficacy endpoints (i.e., sweat chloride, PPFEV1, and BMI) and safety endpoints (i.e., ALT/AST). The sponsor did not submit E-R analysis for ivacaftor. Also, sweat chloride information is not collected in phase III studies.

Mid-Cycle Deliverables

Following are the Mid-Cycle Deliverables;

- Any approvability issues
- Dose Selection
- Preliminary Assessment of Exposure-Response Evaluation for Efficacy
- Drug-drug Interaction and Extrinsic/Intrinsic Factors
- Labeling

Comments to Sponsor

- The labeling language for Section 7 (Drug Interactions) should reflect the concomitant medications used in the phase 3 trials. You should submit more specific language, addressing the recommendations for common CF concomitant medicines in Section 7 in the label.

- In addition, you should include recommendations for managing concomitant administration of the following drug classes in Section 7 of the label:
    - Other Antacids/H2 blockers
    - Ibuprofen or other anti-inflammatory drugs
    - Oral hypoglycemics
    - Anti-depressants

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JIANMENG CHEN
01/02/2015

SATJIT S BRAR
01/02/2015