CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203188Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 203-188 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D.	
Division:	DPARDP		
Applicant:	Vertex Pharmaceuticals Inc.	**Biopharmaceutics Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	--		
Generic Name:	Ivacaftor (VX-770) Film-Coated IR Tablets	**Date Assigned:**	Rolling NDA- Aug 9, 2011
Indication:	Cystic Fibrosis	**Date of Review:**	Jan 16, 2012
Formulation/strength	Immediate Release Tablet/150 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
Rolling NDA Jul 21, 2011 Original NDA Oct 18, 2011 Dec 22, 2011, Jan 09, 2012, Jan 16, 2012	July 27, 2011 Oct 18, 2011 Jan 09, 2012	Aug 9, 2011	Jan 27, 2012

Type of Submission:	Rolling NDA
Type of Consult:	• Dissolution method and acceptance criterion • Role of dissolution on QbD

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

Ivacaftor is a selective potentiator of the CFTR protein that is being proposed for the treatment of cystic fibrosis in patients age 6 years and older who have a G551D mutation in the CFTR gene. It was granted Fast Track status (IND 74,633) and Orphan Drug Designation. Ivacaftor drug product is an immediate release film-coated tablet for oral administration. Each tablet contains 150 mg of ivacaftor drug substance.

(b) (5) Ivacaftor is practically insoluble in water (<0.05 µg/mL in water) (b) (5)

This review focuses on the evaluation of: **1)** the acceptability of the dissolution method and acceptance criterion; **2)** the role of dissolution as a methodology that ensures control of physical form (b) (4) of ivacaftor tablets; and **3)** the role of dissolution on the construction of the design space for ivacaftor film-coated tablets.

1) Dissolution Method and Acceptance Criterion:

The following dissolution method and acceptance criterion for ivacaftor IR tablets, 150 mg were recommended by the FDA and accepted by the Applicant on Jan 13, 2012.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II	65 rpm	900mL 3-prong sinker	37°C	50 mM sodium Phosphate buffered 0.7% (w/v) SLS	Q= (b) (4) % at 15 min

The recommended dissolution acceptance criterion was based on the mean dissolution profiles of clinical and stability batches and on the ability of the specification to reject batches which dissolution profiles do not meet the f2 statistical resting (f2> 50) when compared to the clinical batches.

b) Role of Dissolution as a Methodology that Ensures Control of Physical Form (b) (4) of Ivacaftor Tablets

(b) (4)

(b) (4) (b) (4) Therefore, the following comments were sent to the Applicant on Jan 12, 2012;

1. To facilitate the implementation of our recommended dissolution specification, the Agency recommends the following dissolution specification and time point (b) (4) Mean of 6 tablets (b) (4) in 15 minutes
   a. Alternatively, your proposed specification of mean of (b) (4) in 20 minutes (n=6) (b) (4)

On a teleconference that took place on Jan 13, 2012, the Applicant agreed to retain the originally proposed dissolution (b) (4) at 20 minutes.

(b) (4)

However, based on the exposure-response analysis done by the pharmacometrics reviewer (refer to Dr. Atul Bhatarram's review) and on a phone conversation with Dr. Durmowicz, the flat exposure-response curve indicates that (b) (4) In addition, according to the Applicant, variability in ivacaftor exposures in the Phase 3 studies was 39-41% CV for AUC and 62-78% CV for Cmin; however, efficacy appeared to be consistent over time. Therefore, small changes in ivacaftor bioavailability are not expected to result in substantial effects on efficacy at the 150 mg q12h dose.

c) Role of Dissolution on the Construction of the Design Space

Dissolution was classified as a CQA and used as a tool to guide the construction of the design space. During development of the ivacaftor drug product, (b) (4)

(b) (4)

In general, this reviewer is of the opinion that the compression model lack robustness for the following reasons;

1. The model was constructed using a dissolution specification (b) (4)
    a. Under these assumptions, the model predicts acceptable dissolution performance for a batch (A4020-146; hardness (b) (4) that fails f2 testing).
2. The amount of data used in the construction and validation of the model are limited.
3. The model did not include data outside an acceptable dissolution criterion; therefore, the power of the model in predicting dissolution values outside the acceptable range is questionable.
4. The relatively low R squared values indicate that about 30% of the variability is not described by the model, suggesting that there may be other parameters that contribute to the variability of dissolution.

Therefore, the following comments were conveyed to the Applicant on Jan 12, 2012.

1. Your proposed design space for tablet hardness is not acceptable because it was determined based on a model that considered (b) (4) dissolution acceptance criterion.
    a. Under these assumptions, the model predicts acceptable dissolution performance for a batch (A4020-146) that fails f2 testing (b) (4)
    b. Therefore, determine if the PAR specifications for tablet hardness need revision considering a dissolution acceptance criterion Q (b) (4) at 15 min.

2. There were insufficient data (e.g. dissolution profiles comparison with f_2 statistical testing, in vitro in vivo correlation (IVIVC) models, or in vivo bioequivalence studies) to determine whether batches manufactured throughout the drug product design space would result in products that are bioequivalent. Therefore, we recommend performing dissolution profile comparisons with f2 testing for any movements outside the NOR and within your proposed design space.

On a teleconference that took place on Jan 13, 2012, the Applicant proposed to revise their proposed DS for hardness based on meeting f2 testing calculated between the clinical batches and batches used in the (b) (4). Based on these calculations the following revised PAR upper bound for hardness is being proposed:

PAR upper bound: (b) (4)

This upper bound is acceptable from the biopharmaceutics perspective. The Applicant did not address the lower bound. Data provided show that f2 testing is acceptable for a batch with low hardness (b) (4) and low BD (b) (4) however, there is no data demonstrating that *f2* passes (b) (4) (b) (4) Given that the lack of interaction between hardness and BD is questionable based on this reviewer's assessment of the model, the following comments should be conveyed to the Applicant;

The data to determine whether batches manufactured throughout the drug product design space would result in products that are bioequivalent still are insufficient. The f2 comparisons provided on Jan 13, 2012, did not consider all the corners of the proposed DS for harness and did not address the proposed DS for other key variables. Therefore, we still are recommending performing dissolution profile comparisons with f2 testing for any movements outside the NOR and within your proposed design space.

RECOMMENDATION:

The ONDQA-Biopharmaceutics team has reviewed NDA 203-188 for Ivacaftor IR tablets, 150 mg. We found NDA 203-188 acceptable from the Biopharmaceutics perspective. The following dissolution method and dissolution acceptance criterion have been agreed upon with the Applicant on a teleconference dated Jan 13, 2012,

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II	65 rpm	900 mL 3-prong sinker	37°C	50 mM sodium Phosphate buffered 0.7% (w/v) SLS	Q (b) (4) at 15 min

The recommended dissolution acceptance criterion was based on the mean dissolution profiles of clinical and stability batches and on the ability of the specification to reject batches which dissolution profiles do not meet the f2 statistical resting (f2> 50) when compared to the clinical batches.

In addition, the Applicant agreed to retain their originally proposed dissolution (b) (4) at 20 minutes.

The following comment should be conveyed to the Applicant:

- The provided information/data (b) (4) still is insufficient to determine whether batches manufactured throughout the drug product design space (DS) would result in products that are bioequivalent. The *f2* comparisons provided on Jan 13, 2012 did not consider all possible combinations within the proposed DS (b) (4) Therefore, we recommend performing dissolution profile comparisons with *f2* testing for any movements outside the NOR and within your proposed design space, to be handled within your internal quality control system.

Comments to the CMC ONDQA team:

- Dissolution data from batches manufactured at the extremes of the DS for hardness and BD indicate (b) (4) dissolution acceptance criterion is considered (i.e. Q (b) (4) in 15 min). Therefore, we recommend that a range of specification for bulk density be recommended to the Applicant.
- The proposed PAR upper bound for hardness (b) (4) is acceptable from biopharmaceutics perspective. The Applicant stated that the NOR for hardness will remain at (b) (4) since it was derived based on the dissolution (b) (4) at 20 minutes. Since the Applicant demonstrated that batches manufactured within the PAR for hardness meet f2 testing, the proposed upper bound for NOR is acceptable (b) (4) However, given the lack of robustness of the dissolution model, the lower bound of PAR for hardness should be set based on those batches that meet f2 testing when compared to the clinical batches rather that relying on model predictions. In addition, the NOR should be set based on clinical batches with the lowest hardness values evaluated.
- The dissolution data supporting the proposed range coating weight gain from (b) (4) for NOR and (b) (4) for PAR was not included in the submission and therefore, could not be qualified by this reviewer. However, any uncertainty/risk about this proposed ranges may be addressed given that the Applicant is being recommended to calculate f2 testing for any movements outside the NOR and within the proposed design space in the quality control system.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Lead
Office of New Drug Quality Assessment

INTRODUCTION

Ivacaftor is a selective potentiator of the CFTR protein that is being proposed for the treatment of cystic fibrosis in patients age 6 years and older who have a G551D mutation in the CFTR gene. It was granted Fast Track status (IND 74,633) and Orphan Drug Designation. Ivacaftor drug product is an immediate-release film-coated tablet for oral administration. Each tablet contains 150 mg of ivacaftor drug substance.

Drug Substance

Ivacaftor drug substance is a [redacted] (b) (4) The chemical structure of Ivacaftor is shown in Figure 1.

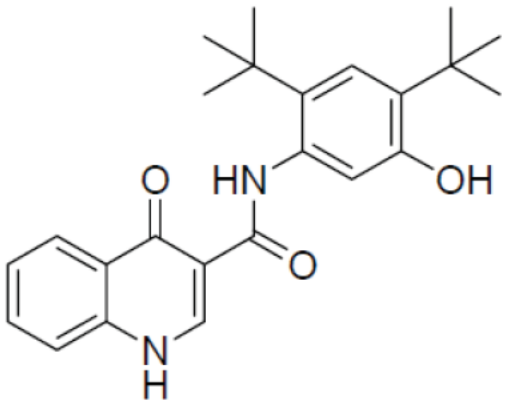

Figure 1. Chemical Structure of Ivacaftor.

[redacted] (b) (4) ivacaftor drug substance has very low aqueous solubility (<0.05 mcg/mL) [redacted] (b) (4)

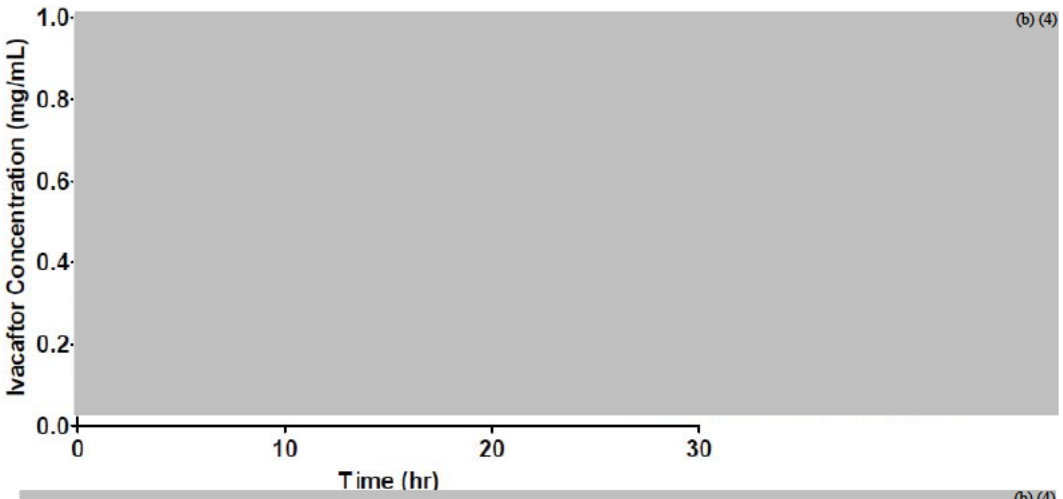

Figure 2. (b) (4)

Drug Product

Ivacaftor drug product is an immediate-release tablet for oral administration. It is a light blue film-coated tablet, printed in black ink with "V 150" on one face. Each tablet contains 150 mg of ivacaftor drug substance, and has a total target weight of 567 mg. The components and composition of ivacaftor are summarized in Table 1.

Table 1. Composition of Ivacaftor Tablet, 150 mg

Component	Quality Reference	Component Function	Amount per Tablet (mg)	Content (% w/w)
Core Tablet:				
Ivacaftor (b) (4) (b) (4)	(b) (4)	Drug Product (b) (4)	(b) (4)	(b) (4)
Microcrystalline cellulose[a]	USP/NF			
Lactose monohydrate	USP/NF			
Croscarmellose sodium	USP/NF			
Sodium lauryl sulfate (SLS)	USP/NF			
Colloidal silicon dioxide	USP/NF			
Magnesium stearate	USP/NF			
Total core weight		--	550	--
Film Coat:				
(b) (4)	DMF No. (b) (4)	(b) (4)	(b) (4)	
Carnauba wax (b) (4)	USP/NF USP			
Printing Ink:				
(b) (4)	DMF No (b) (4)	(b) (4)	(b) (4)	
Total Tablet Weight:		--	**567**	(b) (4)

a The (b) (4) contains 150 mg of drug substance. (b) (4)

Formulation Development of Film-Coated Tablet, 150 mg

The formulations used throughout the clinical development of the proposed product are summarized in Table 2. Figure 3 shows the main BE studies conducted to bridge the phase and 3 clinical trials.

Table 2. Formulations of Ivacaftor Used in Clinical and Primary Stability Studies

Vertex Clinical Study Number	Abbreviated Formulation Description	Composition
VX05-770-001	(b) (4)	(b) (4)
VX06-770-002		
VX06-770-003		
VX06-770-101 VX09-809-005		
VX08-770-005		
VX08-770-006		
VX08-770-007		
VX08-770-102	Film-Coated Tablet, 150 mg	Film-coated 150 mg tablet (b) (4) (b) (4)
	Intended Commercial Formulation, 150 mg	Film-coated, waxed 150 mg tablet (b) (4) (b) (4)
VX08-770-103	Film-Coated Tablet, 100 mg	Film-coated 100 mg tablet (b) (4) (b) (4)
	Intended Commercial Formulation, 150 mg t	Film-coated, waxed 150 mg tablet (b) (4) (b) (4)
VX08-770-104 VX08-770-105 VX10-770-106 VX10-770-107 VX09-770-008 VX09-770-009 VX09-770-010 VX09-770-011 VX10-770-012 VX10-770-013	Intended Commercial Formulation, 150 mg	Film-coated, waxed 150 mg tablet (b) (4) (b) (4)

1

Figure 3. Schematic Overview on the Ivacaftor Oral Formulation Development

The final composition of the proposed commercial tablets is summarized in Table 1. Three lots of tablets of this formulation were manufactured and used as primary stability lots. These lots, as well as additional resupply lots, were used in pivotal clinical studies VX08-770-102, VX08-770-103, and VX08-770-104, as well as other clinical studies.

The manufacture of ivacaftor drug product is summarized in the diagram below. (b) (4)

DISSOLUTION METHOD

The dissolution method that is being proposed as a quality control tool for Ivacaftor film-coated IR tablets, 150 mg is summarized below:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium
II	65 rpm	900mL 3-prong sinker	37°C	(b) (4)

DISSOLUTION METHOD DEVELOPMENT

Dissolution Medium Selection

The aqueous solubility of (b) (4) ivacaftor is very low (< 0.05 mg/mL (b) (4)

(b) (4)

Figure 4. (b) (4)

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/s/

SANDRA SUAREZ
01/18/2012

ANGELICA DORANTES
01/18/2012

CLINICAL PHARMACOLOGY REVIEW

NDA/Supporting document no.	203188
Submission Date	10/18/2011
Brand Name	Kalydeco
Generic Name	Ivacaftor (VX770)
Clinical Pharmacology Reviewer	Lokesh Jain, Ph.D.
Pharmacometrics Reviewer	Atul Bhattaram, Ph.D.
Pharmacogenomics Reviewer	Hobart Rogers, Pharm.D., Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Pharmacogenomics Team Leader	Michael Pacanowski, Pharm.D., M.P.H.
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 Pharmaceuticals
Submission Type; Code	505(b)(1); priority review; orphan drug
Formulation; Strength(s)	Tablet ; 150 mg
Indication	For the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the *CFTR* gene
Dosage Regimen	for adults and pediatric patients age 6 years and older: 150 mg taken orally every 12 hours (300 mg total daily dose) with fat-containing food

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1. Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology finds NDA 203188 acceptable

1.2 Phase IV Commitments

In vitro studies indicate that ivacaftor has potential to inhibit P-gp. Evaluate the potential for in vivo drug-drug interaction of ivacaftor with a sensitive P-gp substrate.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Vertex pharmaceuticals, Inc. has submitted NDA 203188 seeking marketing approval for ivacaftor (VX-770). If approved this will be the first in class product in the category of cystic fibrosis transmembrane conductance regulator (CFTR) potentiator.

Ivacaftor is intended for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* mutation in the CFTR gene. It is not effective in CF patients homozygous for the *F508* mutation in the CFTR gene, which is the predominant genotype in CF patients.

In support of this NDA, sponsor conducted 23 clinical/clinical pharmacology studies (17 completed, 6 ongoing) including 15 Phase 1 studies, 4 Phase 2 studies, and 3 Phase 3 studies, including single- and multiple-dose PK, special population, food effect, QT, dose-finding, and safety and efficacy studies.

Dose-Response

- A trend of increase in response with increasing dose was observed for ivacaftor doses ranging from 25 mg every 12 hours (q12h or bid) to 250 mg q12h for forced expiratory volume in 1 second (FEV_1), nasal potential difference (NPD), and sweat chloride efficacy endpoints in CF patients with G551D mutation in at least 1 CFTR allele (see section 2.4.1).
- Among tested dose levels, numerically, maximum mean increase in FEV_1 and maximum mean reduction in sweat chloride were achieved with dose 150 mg q12h or higher. For 150 mg q12h dose, these endpoints were significantly different from baseline and placebo (baseline adjusted) for day 14 or day ≥ 14 analysis.

Exposure-Response

- Relationship of FEV_1 and sweat chloride with ivacaftor exposure was defined with a direct E_{max} model.
- Ivacaftor dose of 150 mg q12h was selected based on simulations showing that this dose would provide a median trough concentration ($C_{min,ss}$) of at least equal to the

predicted EC_{90} value for FEV_1 endpoint and EC_{84} value for sweat chloride endpoint (i.e., approximately 250 ng/mL). This dose was anticipated to result in a reasonable optimization of the effects on both the clinical endpoints: FEV_1 and the activity of CFTR as measured by sweat chloride.

Pharmacokinetics

- Increase in ivacaftor $AUC_{0-\infty}$ was dose-proportional for doses ranging from 25-800 mg, but increase in C_{max} was not dose proportional
- T_{max} was reached by approximately 4 hours in the fed state
- Coadministration with food significantly increased the bioavailability of ivacaftor (e.g., for the to-be-marketed formulation, 2.98 fold increase in $AUC_{0-\infty}$ and 3.89 fold increase in C_{max}); therefore, it is recommended to be taken with food
- The terminal elimination half-life of ivacaftor was approximately 12-14 hours after single- or multiple-dose
- Following multiple-dose administration of 150 mg q12h, steady-state was reached by day 5 with median accumulation ratio of 2.2 to 2.9 across studies
- Ivacaftor was more than 98% plasma protein bound, primarily to alpha 1-acid glycoprotein and human serum albumin
- Ivacaftor was extensively distributed in tissues with volume of distribution (Vz/F) of 203 L and 220 L in subjects with CF and healthy subjects, respectively
- Ivacaftor was extensively metabolized, primarily by CYP3A enzymes. Metabolism primarily involved oxidation of ivacaftor to M1 (hydroxymethyl-ivacaftor) and M6 (ivacaftor carboxylate), with a minor contribution by glucuronidation and sulfation.
- Metabolite M1 had approximately $1/6^{th}$ of the potency of ivacaftor and M6 had approximately $1/50^{th}$ of the potency of ivacaftor with respect to potentiating the CFTR-mediated chloride transport
- The metabolite to parent ratio (i.e., $AUC_{0-tlast}$ for metabolite/$AUC_{0-tlast}$ for ivacaftor) for M1 and M6 at steady-state were 4.89 and 1.73, respectively
- Ivacaftor was mostly eliminated through feces (primarily in form of metabolites) with minor elimination through renal route (approximately 6.6%)
- PK was similar between healthy volunteers and patients with CF
- Similar exposure were observed for a dose of 150 mg q12h in subjects with the G551D mutation on at least 1 CFTR allele or subjects homozygous for the F508del-*CFTR* mutation who are at least 12 years old

Special Population

- No dose adjustments are recommended based on weight, age, and gender
- A reduction in dose to 150 mg once daily is recommended for subjects with moderate hepatic impairment (Child-Pugh Class B). These subjects had an approximately 2-fold higher systemic exposure ($AUC_{0-\infty}$) than matched healthy subjects
- The impact of mild hepatic impairment (Child-Pugh Class A) on pharmacokinetics of ivacaftor has not been studied, but the increase in ivacaftor $AUC_{0-\infty}$ is expected to be less than two-fold. Therefore, no dose adjustment is necessary for patients with mild hepatic impairment.
- Impact of severe hepatic impairment (Child-Pugh Class C) on pharmacokinetics of

ivacaftor has not been studied; therefore, ivacaftor is not recommended in these patients as exposure is expected to be higher and the magnitude of increase is unknown

- Impact of mild, moderate, and severe renal impairment or end stage renal disease on ivacaftor exposure has also not been studied. No dose adjustments are recommended for mild and moderate renal impairment patients because of negligible elimination of ivacaftor and its metabolites in urine. However, caution is recommended while administering ivacaftor to patients with severe renal impairment or end stage renal disease because renal impairment may also affect some pathways of hepatic and gut drug metabolism and transport

Drug-Drug Interaction (DDI)

Effect of coadministered drugs on ivacaftor exposure

In vitro studies showed that ivacaftor and metabolite M1 were substrates of CYP3A enzymes (i.e., CYP3A4 and CYP3A5). Ivacaftor dosing recommendations for coadministration with CYP3A inhibitors or inducers are as below:

- Ivacaftor coadministration with strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin) has potential to increase the exposure (AUC) by approximately 8-fold. Therefore, a reduction in the ivacaftor dose to 150 mg twice-a-week is recommended when coadministered.
- Coadministration with moderate CYP3A inhibitors (e.g., fluconazole) has potential to increase ivacaftor exposure by approximately 3-fold; therefore, a reduction in ivacaftor dose to 150 mg once daily is recommended
- Ivacaftor coadministration with strong CYP3A inducers (e.g., rifampin, rifabutin) is not recommended because of potential for substantial decreases in exposure (by approximately 9 fold) which may diminish therapeutic effectiveness and appropriate dose adjustment is not feasible
- No dose adjustment recommended for coadministration with oral contraceptives

Effect of ivacaftor on exposure of coadministered drugs

In vitro studies showed that ivacaftor is a weak inhibitor of CYP3A and a potential inhibitor of P-gp at therapeutic concentrations, and may also inhibit CYP2C8 and CYP2C9. Metabolite M1, but not M6, also has potential to inhibit CYP3A and P-gp. Ivacaftor, M1, and M6 were not inducers of CYP isozymes. Dosing recommendations for coadministered drugs following administration with ivacaftor are as below:

- Concomitant use with ivacaftor increased the exposure of midazolam, a sensitive CYP3A substrate, by 1.54 fold. Therefore, caution is warranted and monitoring for benzodiazepine-related side effects is recommended when using midazolam, triazolam, diazepam, and alprazolam with ivacaftor
- Concomitant use may increase the concentrations of CYP3A and/or P-gp substrates with narrow therapeutic index such as digoxin, cyclosporine, and tacrolimus. Appropriate monitoring is recommended when using these drugs with ivacaftor
- Concomitant use may increase the concentrations of CYP2C9 substrate warfarin.

Since, warfarin is a narrow therapeutic index drug, adequate monitoring of international normalization ratio (INR) is recommended

- No dose adjustment recommended for rosiglitazone, a CYP2C8 substrate, and oral contraceptives, which are weak CYP3A substrates

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

In vitro studies

1. Nonclinical reports E156 and E111 - Assessment of pharmacological activity of metabolites
2. Report VX-770-DMPKDM-041 – Assessment of P-gp substrate potential for ivacaftor, M1, and M6
3. Reports B230, H191, B242, VX-770-DMPK-DM-039, and VX-770-DMPK-DM-038 – characterization of metabolic profile and enzyme inhibitory and induction potential for ivacaftor and key metabolites
4. Report VX-770-DMPK-DM-040 – *in vitro* assessment of plasma protein binding

Clinical studies

Single- and Multiple-Dose PK studies

1. Study* 001 – single- and multiple-dose PK in healthy subjects and subjects with CF (with genotype G551D-*CFTR* on at least 1 allele), age 19 to 51 years
2. Study 003 – mass balance ADME study in healthy subjects
3. Study 008 – multiple-dose PK and QT study in healthy subjects
4. Study 013 – assessment of impact of hepatic impairment
5. Study 004 – to test palatability

Drug-Drug interaction (DDI) studies

6. Study 005 – DDI with oral contraceptives
7. Study 006 – DDI with ketoconazole
8. Study 009 – DDI with rifampin
9. Study 010 – DDI with midazolam, rosiglitazone, and fluconazole
10. Study 011 – DDI with desipramine

Biopharmaceutics studies

11. Study 002 – single-dose relative bioavailability and food-effect cross over study
12. Study 007 – single-dose relative bioavailability and food-effect cross over study
13. Study 012 - single-dose relative bioavailability and food-effect cross over study

* All study numbers are abbreviated to last 3 numbers. For example study 001 refers to VX-08-770-001.

Efficacy and Safety studies

14. Study 101 – Phase 2a, PK, PD, safety, and efficacy study in CF patients with G551D mutation in at least 1 CFTR allele, age 18 years and above
15. Study 102 – Phase 3 efficacy and safety study to evaluate ivacaftor in CF patients with G551D mutation in at least 1 CFTR allele, age 12 years and above (sparse PK)
16. Study 103 – Part A, evaluation of single-dose PK in CF subjects with G551D-*CFTR* genotype for age group 6 to 11 Years. Part B, Evaluation of safety and efficacy in CF subjects with G551D-*CFTR* genotype for 24 weeks for age group 6 to 11 years.
17. Study 104 – Part A, Phase 2 efficacy and safety in CF subjects who are homozygous for F508del-*CFTR* mutation, sparse PK, age 12 years and above. Part B, Long term safety in CF subjects who are homozygous for F508del-*CFTR* mutation

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?

Ivacaftor is a small molecule drug (Figure 1). Physical and chemical properties of ivacaftor are displayed in Table 1

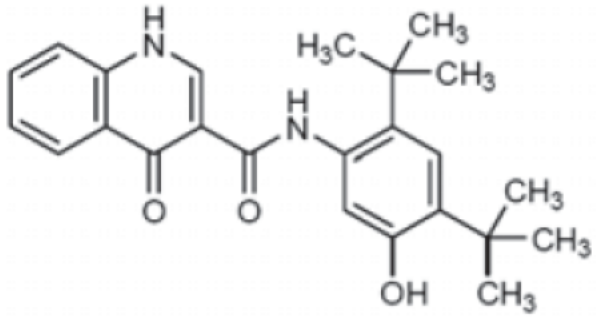


Figure 1: Ivacaftor chemical structure

Table 1: Ivacaftor physical-chemical properties

Molecular Formula	$C_{24}H_{28}N_2O_3$
Molecular Weight	392.49 g/mol
Physical State	Powder
Dissociation Constants	(b) (4)
Partition Coefficients	(b) (4)
Solubility	• Water: practically insoluble (<0.05 µg/mL) (b) (4) • (b) (4))

Drug Product

Ivacaftor is available as a light blue, capsule-shaped, film-coated tablet for oral administration containing 150 mg of drug. Each tablet contains the inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate

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

Ivacaftor is a CFTR modulator, a new class of drugs, which acts by restoring the defective function of the CFTR protein, i.e., targets the underlying defect in patients with CF. Ivacaftor acts on the CFTR protein to increase the channel open probability (or gating) to enhance chloride transport. Its action on CFTR is reported to be highly selective with lack of interaction with, or modulation of activity of, a broad panel of receptors and enzymes, *in vitro*. In vitro effects of ivacaftor on ten known CFTR gating mutations is summarized in Table 2, which demonstrates more than 10 fold increase in chloride transport over baseline across all mutations.

The proposed indication for ivacaftor is for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the *CFTR* gene.

It is not effective in CF patients homozygous for the *F508-del* mutation in the CFTR.

Table 2: In vitro effects of ivacaftor on CFTR gating mutations

	CFTR-mediated Chloride Transport				
	Baseline (% normal)		With Ivacaftor (% normal)		Fold Increase
Mutation	Mean	SEM	Mean	SEM	Over Baseline
G551D	1.0	0.5	55.3	6.3	55.3
G178R	2.9	0.5	87.2	8.2	30.1
S549N	1.6	0.4	95.7	6.5	59.8
S549R	0.02	0.0	21.0	6.1	1050.0
G551S	9.7	0.7	157.6	8.2	16.2
G970R	1.6	0.6	48.8	9.8	30.5
G1244E	0.3	0.1	38.9	2.2	129.7
S1251N	3.9	0.7	98.2	8.6	25.2
S1255P	0.8	0.3	58.5	12.9	73.1
G1349D	1.7	0.5	79.3	4.1	46.7

Source: Module 2.4/Table 4
CFTR: cystic fibrosis transmembrane conductance regulator; SEM: standard error of the mean

2.2.3 What are the proposed dosages and routes of administration?

Proposed dose for ivacaftor tablet is 150 mg q12h, which is to be administered orally with fat-containing food.

2.2.4 What drugs (substances, products) indicated for the same indication

are approved in the US?

The currently approved treatments do not treat the underlying defect in CFTR protein, but 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 3.

Table 3: Approved therapies indicated for cystic fibrosis

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?

Ivacaftor clinical pharmacology and clinical development program consisted of the following studies. (N=number of studies):

I. Phase 1 (Healthy Volunteers and Subjects with CF)
   a. Pharmacokinetics (N=2): Single dose and dose proportionality, and mass balance
   b. Specific population (N=1): hepatic impairment
   c. Biopharmaceutics (N=4): Food effect and relative bioavailability
   d. Drug-drug interaction studies (N=5): with ketoconazole, fluconazole, rifampin, midazolam, desipramine, rosiglitazone, and oral contraceptive
   e. QT study (N=1)

II. Phase 2 (N=2)
   a. Dose ranging study and assessment of pharmacodynamics (studies VX08-770-101 and VX08-770-104)

III. Phase 3 (N=2)
   a. Pivotal double-blind, placebo controlled, parallel group studies in CF subjects with G551D mutation in CFTR protein (studies VX08-770-102 and VX08-770-103)

Population pharmacokinetic analysis – was performed using data from Phase 2 and Phase 3 studies (-101, -104, -102, -103)

Exposure-response analysis was performed for FEV_1 and sweat chloride using data from Phase 2 and Phase 3 studies (-101, -104, -102, -103)

Sponsor reported efficacy results are shown in Figure 2 and Figure 3, which show a

significant treatment effect for endpoints FEV_1 and sweat chloride in studies 102 and 103. For final assessment of efficacy and safety findings of ivacaftor from these studies, please refer to the clinical review by Dr. Kimberly Witzmann.

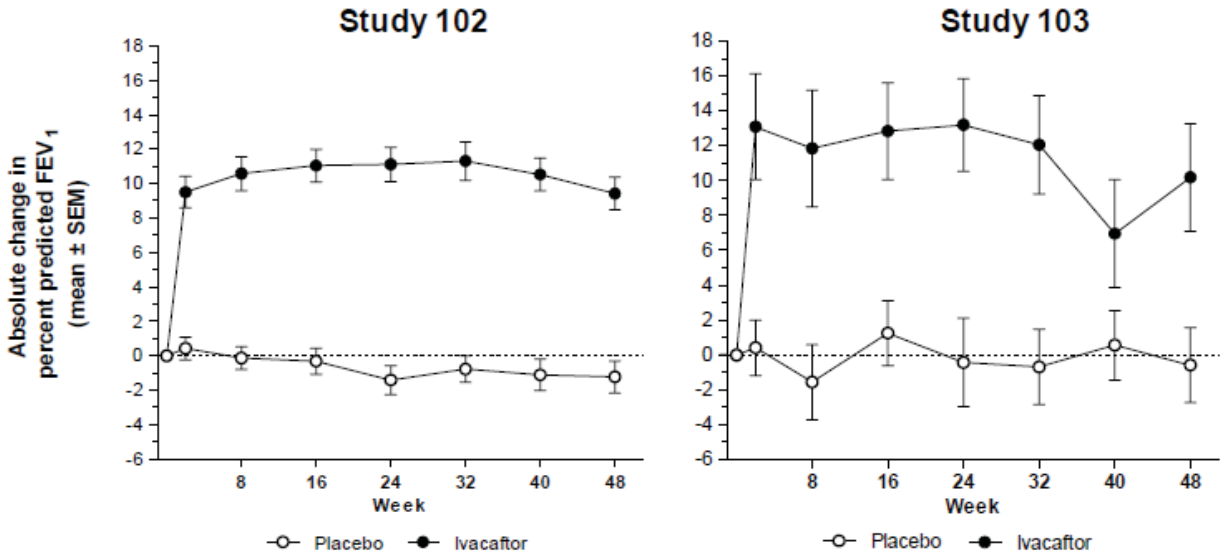


Figure 2: Change in FEV_1 from baseline through week 48 in Phase 3 studies 102 and 103

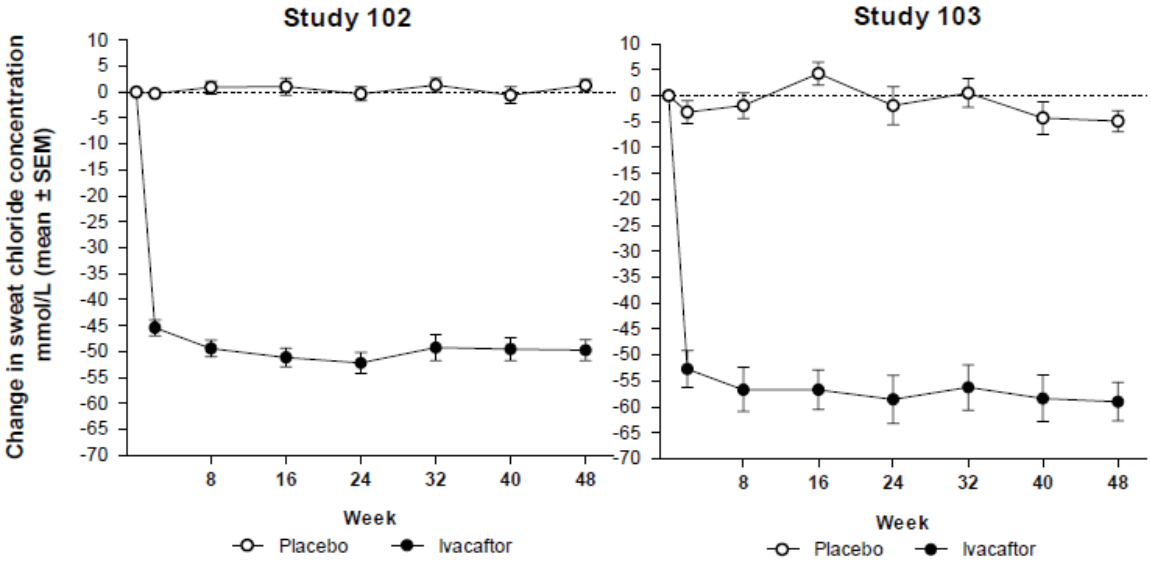


Figure 3: Change in sweat chloride concentration from baseline through week 48 in Phase 3 studies 102 and 103

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

The response endpoints measured are: FEV_1, NPD, and sweat chloride levels.

FEV_1 is a commonly used endpoint to measure the lung function and it reflects the extent of airway obstruction. It is a clinically accepted measure of disease progression in CF, because the primary cause of morbidity and mortality in CF patients is the CF lung disease. In the lungs, the dysfunction in the CFTR protein leads to obstruction of airways with thick mucus, establishment of chronic bacterial infection, and damaging inflammatory responses that are all thought to play a role in causing irreversible structural changes. Patients with CF typically experience a progressive loss of lung function ultimately resulting in respiratory failure and death.

NPD test measures the abnormalities in ion transport in the respiratory epithelium resulting from a defective CFTR protein, by measuring the salt (sodium and chloride) transport in and out of the cells in the nose (i.e., potential difference in nasal mucosa) in response to different salt solutions. A decrease in NPD is indicative of increased CFTR function.

Measurement of amount of chloride in sweat also informs about the function of chloride transport channels. A decrease in sweat chloride concentration is indicative of increased CFTR function. It is the most commonly used diagnostic tool for CF. A sweat chloride concentration of at least 60 mmol/L is considered indicative of CF, whereas a sweat chloride concentration less than 40 mmol/L is considered normal.

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?

Ivacaftor and two major metabolites (M1 and M6) were appropriately measured. Please refer to section 2.9 for more details.

2.4 Exposure-Response

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

Dose-response relationship for ivacaftor

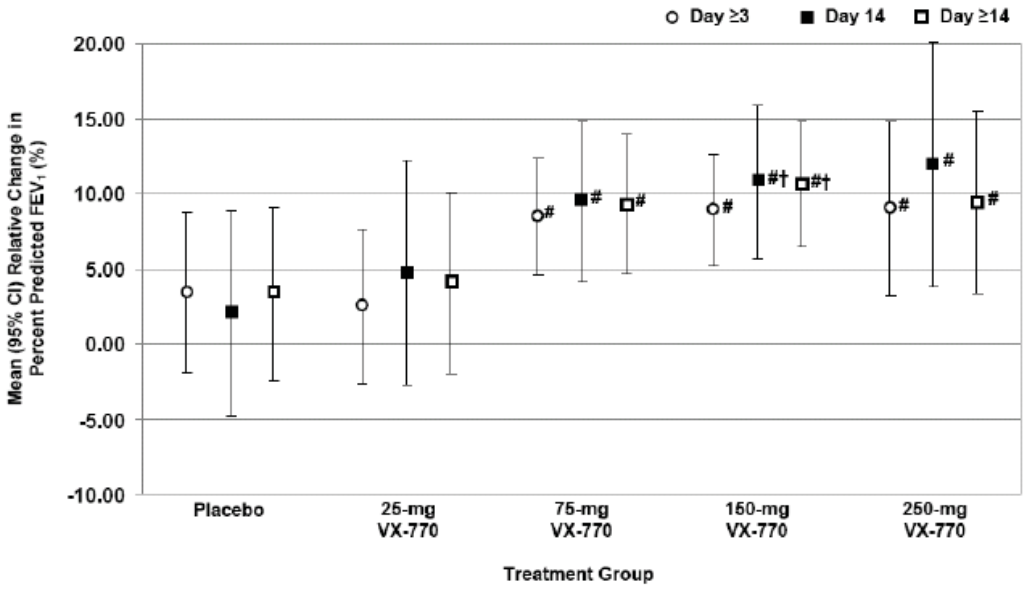
In a double-blind, placebo-controlled, crossover study (#101), in subjects with CF aged 18 years or older with genotype G551D-*CFTR* on at least 1 allele, effect of multiple doses of ivacaftor, ranging from 25 mg q12h to 250 mg q12h, on pharmacodynamic endpoints FEV1, NPD, and sweat chloride was tested. Analysis was based on the linear mixed-effect modeling, using baseline, period, and dose group as fixed effects, subject as a random effect, and change from baseline as the dependent variable.

For FEV1, a linear trend of increasing response with increasing ivacaftor dose was observed (Figure 4). Statistically significant within-group mean change from baseline in FEV1 (absolute volume, percent predicted, and relative change in percent predicted) was observed in the 75-, 150-, and 250-mg ivacaftor groups in the Day ≥3, Day 14, and Day

≥14 analyses. The treatment differences between the 150-mg ivacaftor group versus the placebo group were statistically significant for the Day 14 and Day ≥14 analyses.

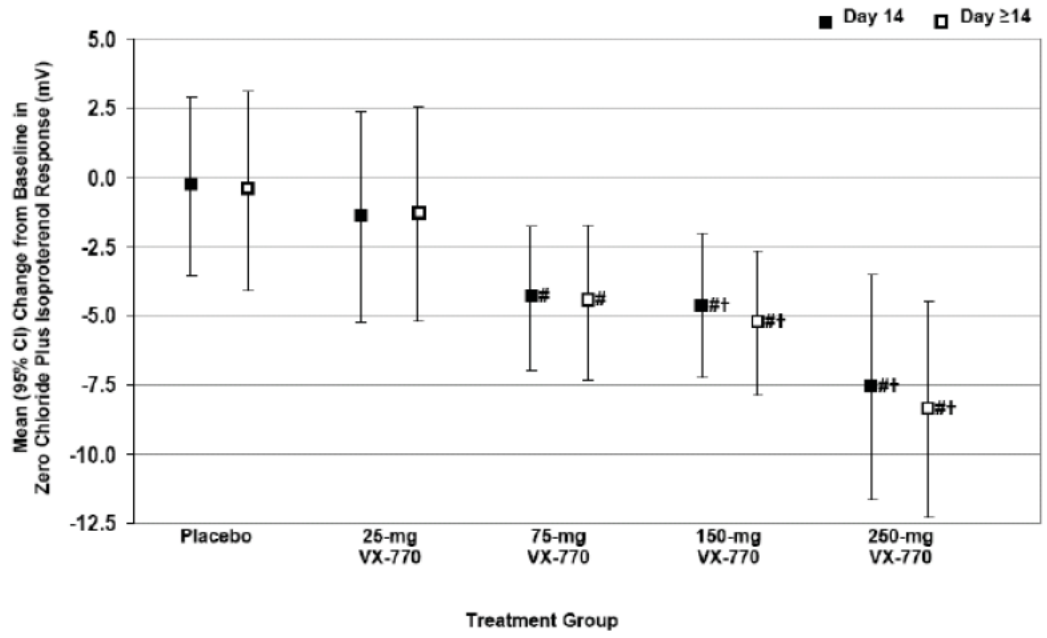
A linear trend was also observed for NPD response with increasing dose (Figure 5). Statistically significant mean change from baseline in NPD (zero chloride plus isoproterenol) response was observed in the 75-, 150-, and 250-mg ivacaftor groups in the Day 14 and Day ≥14 analyses. The treatment differences between the 150- and 250-mg ivacaftor groups versus the placebo group were also statistically significant in the Day 14 and Day ≥14 analyses.

Similar to FEV1 and NPD, a linear trend was also observed for decrease in sweat chloride with increasing dose (Figure 6). Statistically significant mean change from baseline in maximum sweat chloride was observed in all ivacaftor groups (25-, 75-, 150-, and 250-mg groups) in the Day ≥3, Day 14, and Day ≥14 analyses. The treatment differences between all ivacaftor groups versus the placebo group were also statistically significant in the Day ≥3, Day 14, and Day ≥14 analyses.



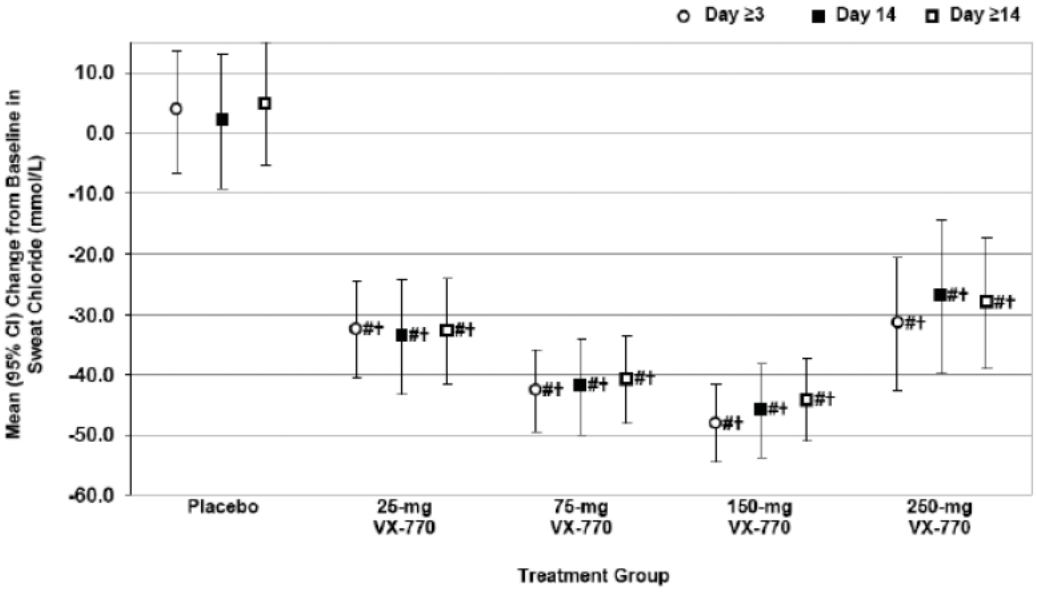
 # p<0.05 least squares mean change from baseline
+ p<0.05 for treatment difference between change from baseline for ivacaftor group versus placebo

Figure 4: Mean (95% CI) relative change from baseline in percent predicted FEV1 for day ≥3, day 14, and day ≥14, full analysis data set



 # p<0.05 least squares mean change from baseline
+ p<0.05 for treatment difference between change from baseline for ivacaftor group versus placebo

Figure 5: Mean (95% CI) change from baseline of NPD (Zero Chloride plus Isoproterenol Response) for day 14 and day ≥14, full analysis set



 # p<0.05 least squares mean change from baseline
+ p<0.05 for treatment difference between change from baseline for ivacaftor group versus placebo

Figure 6: Mean (95% CI) change from baseline in sweat chloride for day ≥3, day 14, and day ≥14, full analysis set

Exposure-response relationship for ivacaftor

An exposure-response relationship was developed for data from study # 101 using non-linear mixed effect modeling to support the selection of dose(s) for Phase 3 efficacy and safety studies. A direct E_{max} model with baseline effect described the relationship between ivacaftor trough plasma concentrations ($C_{min,ss}$) and FEV_1 (L) or sweat chloride (mmol/L). Parameter estimates from the final model for population pharmacodynamic (PD) model for FEV_1 and sweat chloride are shown in Table 4 and Table 5, respectively.

Simulated exposure-response curves for FEV1 and sweat chloride based on these estimated PD parameters from Study 101 are shown in Figure 7. The predicted EC_{90} for FEV1 based on Figure 7 was 250 ng/mL, which was also the predicted EC_{84} for sweat chloride. Based on this relationship, to achieve 90% of predicted maximum efficacy for FEV_1 a dose with a median ivacaftor $C_{min,ss}$ of at least the 250 ng/mL would need to be selected. It was expected that the selected dose would result in a reasonable optimization of the effects on both the clinical endpoint FEV1 and the activity of CFTR as measured by sweat chloride.

Table 4: Parameter estimates from the FEV_1 final Population PD model

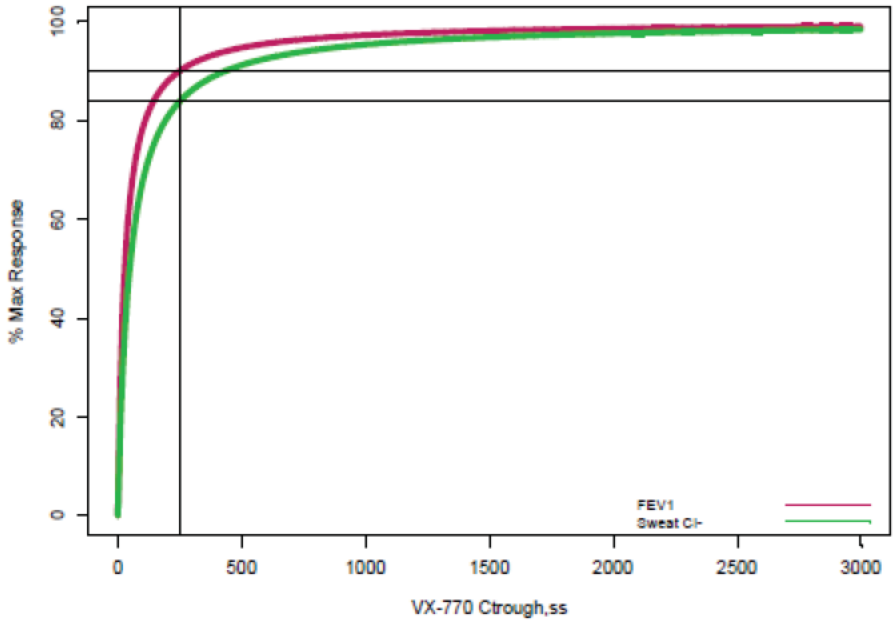
Parameter	Point Estimate	%RSE	95% CI	Interindividual Variation
S_0	3.33 (L)	2.96	(3.13, 3.53)	27.4 (CV%)
E_{max} *G551D*	0.322 (L)	13.0	(0.234, 0.403)	59.9 (CV%)
E_{max} *F508del-CFTR*	0.026 (L)	62.7	(-0.0122, 0.0527)	
EC_{50}	47.0 (ng/mL)	40.4	(5.03, 96.1)	
SLOPE	-0.110 (L/year)	145	(-0.0317, 5.17)	0.132 (SD)
K_{E0}	0.119 (h^{-1})	54.4	(0.00273, 0.121)	

FEV_1 model equation: **Effect = (E0 + Slope*Time/8760) + E_{max}*F/(EC_{50} + F)**
Abbreviations: %RSE, percent relative standard error of the parameter estimate; S_0, baseline FEV_1; SLOPE, slope of FEV_1 time course to describe natural disease progression; K_{E0}, effect compartment equilibration constant

Table 5: Parameter estimates from the sweat chloride final Population PD model

Parameter	Point Estimate	%RSE	95% CI	Interindividual Variability
S_0	103 (mM)	0.851	(100, 104)	7.79 (CV%)
E_{max} *G551D*	-50.6 (mM)	4.37	(-52.9, -42.2)	23.2 (CV%)
E_{max} *F508del*	-3.05 (mM)	37.7	(-6.12, 0.312)	
EC_{50}	100 (ng/mL)	11.0	(85.1, 112)	
K_{E0}	0.0230 (h^{-1})	22.6	(0.0177, 0.0434)	

Sweat model equation: **Effect = E0 + E_{max}*F/(EC_{50} + F)**
Abbreviations: %RSE, percent relative standard error of the parameter estimate; S_0, baseline sweat chloride concentration; K_{E0}, effect compartment equilibrium constant



Abbreviations:
$C_{trough,ss}$, predose plasma concentration at steady-state; Sweat Cl-, sweat chloride concentration
Note: The Y-axis is the % maximum response as change from baseline for FEV1 and sweat chloride. The 2 horizontal lines denote 90% and 84% maximum response level. The vertical line denotes a concentration of 250 ng/mL. The X-axis is labeled "VX-770 $C_{trough,ss}$," which is equivalent to "Ivacaftor $C_{min,ss}$"

Figure 7: Simulated Exposure-Response Curves for FEV1 (L) and Sweat Chloride (mmol/L) based on data from study 101

2.4.2 What are the characteristics of the exposure-response relationships for safety?

No specific dose-limiting safety concerns were identified for ivacaftor in early dose-escalation studies. Therefore, exposure-response analysis for safety was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

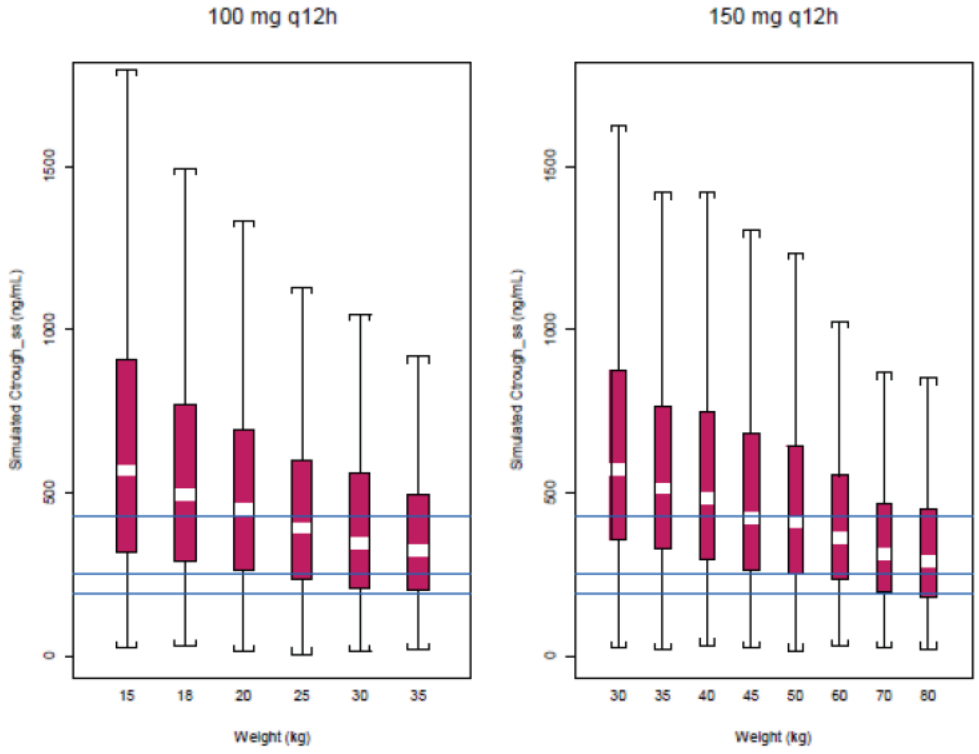
Ivacaftor does not have any significant impact on QTc interval. Please refer to the review by QT-IRT group for further details.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

The selection of the proposed dose and dosing regimen was based on the exposure-response analysis, which is shown in Figure 7. Selection of dose was based on the $C_{min,ss}$ as the target exposure matrix. The $C_{min,ss}$ were simulated for one thousand subjects based on PK data from the relative bioavailability study 007, to identify the ivacaftor dose with a median $C_{min,ss}$ of at least equal to the predicted EC_{90} for FEV_1 (i.e., 250 ng/mL, which also corresponded to the predicted EC_{84} for sweat chloride).

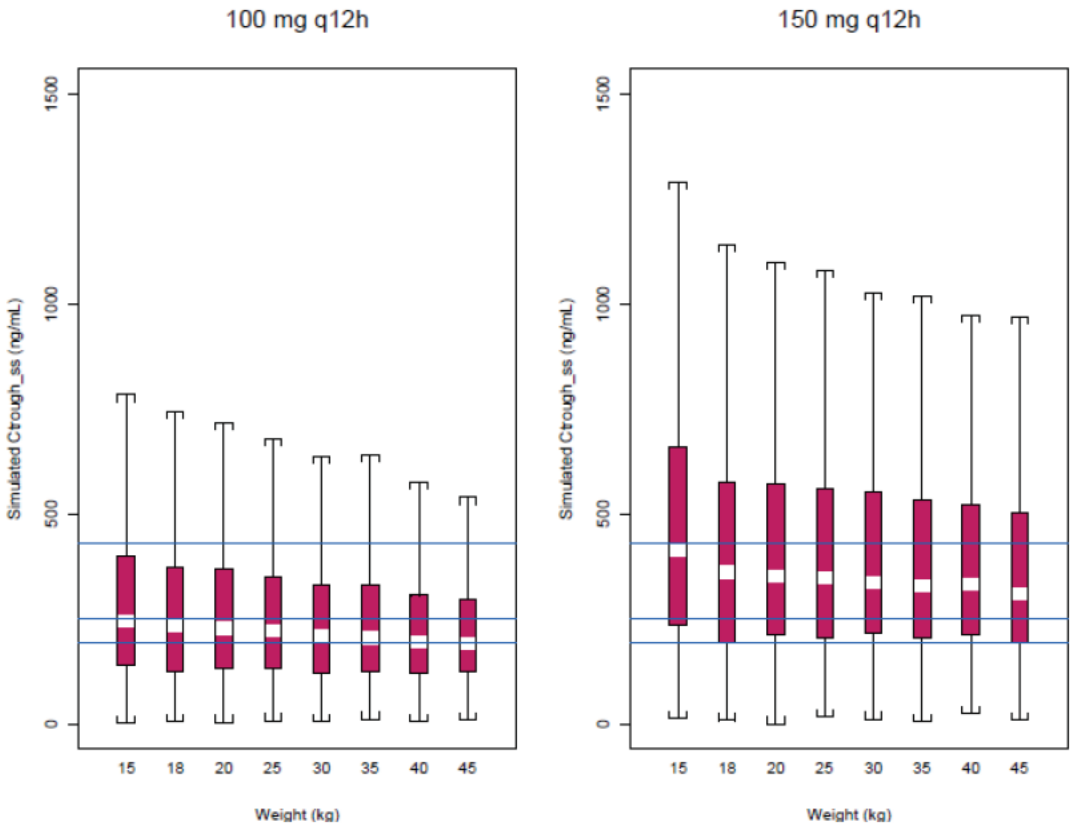
As shown in Figure 8, a dose regimen of 150 mg q12h provided the $C_{min,ss}$ of 250 ng/mL for the body weight ranging from 30 to 80 kg (approximating the weight range for subjects aged at least 12 years); which was then evaluated in the Phase 3 trial 102 enrolling subjects 12 years of age and above.

For the lower weight group ranging from 15 to 35 kg (approximate weight range for subjects age 6 to 11 years) simulations showed that a lower 100 mg q12h dose was needed to achieve the $C_{min,ss}$ of 250 ng/mL (Figure 8). These simulations were based on allometric scaling using coefficients of 0.75 for clearance and 1 for volume of distribution. Subsequent to these simulations, a single-dose PK study for 100 mg dose was conducted in subjects aged 6 to 11 years (lead-in PK study 103, Part A). Allometric scaling coefficients were recalculated using these actual PK data, which were 0.384 for clearance and 0.796 for volume of distribution. Using this updated model, a further one-thousand simulations were performed for $C_{min,ss}$, for two dose levels 100 mg q12h and 150 mg q12h for body weights ranging from 15 to 45 kg (approximate weight range for subjects age 6 to 11 years). Results based on updated model are shown in Figure 9, which revealed that even in 6 to 11 years age group, a dose regimen of 150 mg q12h would be needed to achieve a median $C_{min,ss}$ of at least 250 ng/mL. Therefore, an ivacaftor dose of 150 mg q12h was evaluated in Part B of the Study 103 in age groups 6 to 11 years.



Note: The 3 horizontal dotted lines are, from top to bottom, at 430 ng/mL (EC_{90} of sweat chloride), 250 ng/mL (the estimated EC_{90} of FEV_1 and EC_{84} of sweat chloride), and 192 ng/mL (estimated EC_{80} of sweat chloride), respectively. The Y-axis label "Simulated $C_{trough,ss}$" is equivalent to "Simulated $C_{min,ss}$"

Figure 8: Distribution of simulated ivacaftor $C_{min,ss}$ by body weight and dose



Note: The 3 horizontal lines are, from top to bottom, at 430 ng/mL (estimated EC_{90} of sweat chloride), 250 ng/mL (the estimated EC_{90} of FEV_1 and EC_{84} of sweat chloride), and 192 ng/mL (estimated EC_{80} of sweat chloride), respectively. Y-axis label "Simulated $C_{trough,ss}$" is equivalent to "Simulated $C_{min,ss}$"

Figure 9: Distribution of simulated ivacaftor $C_{min,ss}$ by body weight and dose

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?

Ivacaftor PK

Single dose PK of ivacaftor (healthy subjects)

PK for single dose ranging from 25 to 800 mg was characterized in study 001 following administration of an ivacaftor (b) (4) formulation. The plasma concentration-time profiles for these dose levels are shown in Figure 10. The median time to maximum concentration ranged from 1.6 to 4.1 hours. The median for maximum concentration (C_{max}) of ivacaftor increased up to doses of 375 mg, after which it appeared to plateau, possibly because of low solubility at higher doses. The slopes of the terminal phase on log scale are apparently similar across dose range of 25-800 mg, indicating linear

elimination kinetics. The ivacaftor PK parameters for these dose levels are listed in Table 6.

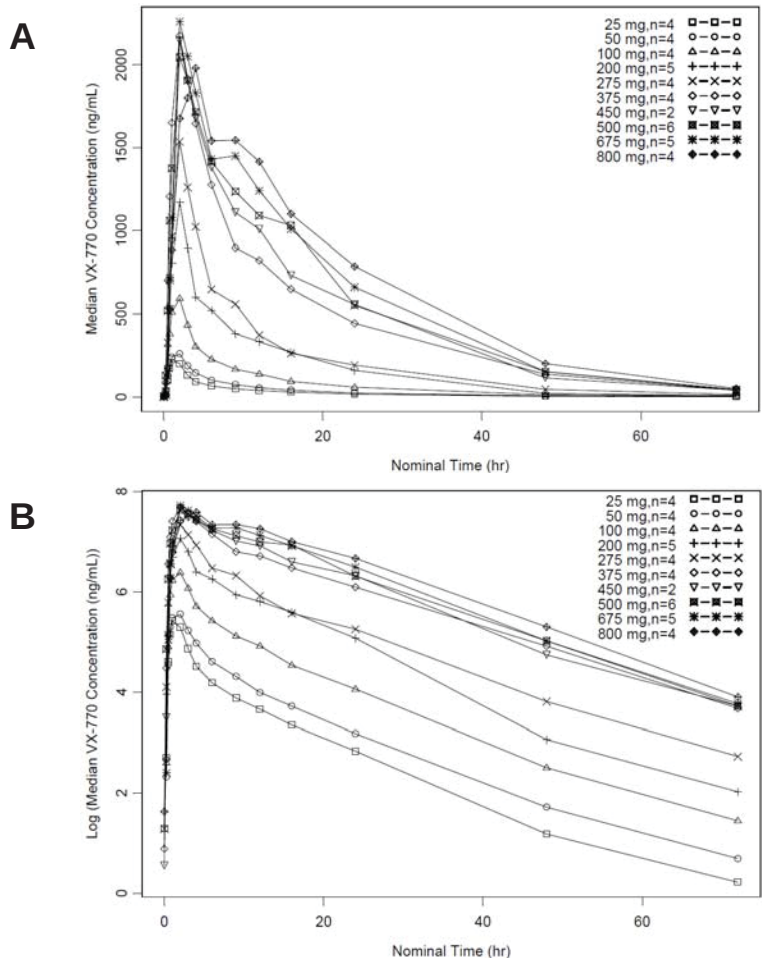


Figure 10: Median VX770 concentration (ng/mL) vs. nominal time (hour). (A) Normal scale and (B) Log-scale

Table 6: Summary of PK parameters (non-compartmental analysis) after oral administration of single dose in healthy subjects

Dose (mg)	N	T_{max} (hour) Median (range)	Mean (CV%)				
			C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng/mL.hr)	$t_{1/2}$ (hour)	CL/F (L/hour)	V/F (L)
25	4	1.6 (1.1-2.1)	214.8 (21.4)	1627 (15.5)	11.1 (17.4)	15.6 (15.4)	246.6 (15.9)
50	4	2.1 (1.1-2.1)	258 (15)	2344.6 (18.2)	12.1 (9.8)	21.9 (18.3)	381.8 (21.3)
100	4	2.1 (2.1-2.1)	611.3 (11.4)	5362.7 (18.1)	11.6 (13.7)	19.1 (16.2)	315.8 (13.2)
200	5	2.1 (2.1-9.1)	1234 (13.3)	12630.4 (20.6)	11.2 (11.6)	16.4 (20.5)	264.5 (23.4)
275	4	2.1 (2.1-2.1)	1675.5 (17.6)	19846.3 (50.7)	14.2 (27.4)	16 (36.8)	303.8 (18.5)
375	4	2.1 (2.1-3.1)	2262.5 (10.3)	31570 (25.4)	14.4 (14.3)	12.5 (27.9)	258.1 (25.3)
450	2	2.1 (2.1-2.1)	2145 (3)	33433.9 (11.6)	12.9 (0.2)	13.6 (11.6)	252.8 (11.4)
500	6	2.8 (2.1-4.1)	2273.3 (22)	46265.8 (56.9)	14.6 (27.6)	12.8 (35.1)	255.5 (33.9)
675	5	4.1 (2.1-12.1)	2310 (23.7)	56367.6 (85)	15.1 (37.1)	17 (47.3)	323.5 (33.2)
800	4	3.1 (2.1-9.1)	2335 (20.3)	43495.5 (21.8)	13.3 (26.1)	19.3 (27.8)	354.4 (16.9)

N = number of subjects, CV% = percent coefficient of variation

Multiple dose PK of ivacaftor (healthy volunteers)

Selected PK parameters following administration of multiple doses in healthy volunteers are summarized in Table 7. Across studies for doses ranging from 125 mg q12h to 250 mg q12h, steady-state was reached by days 3 to 5 and accumulation ratio ranged from 2.2 to 2.9. Given that ivacaftor was administered nearly every half-life, accumulation ratio was expected to be close to 2. The mean terminal half-life was approximately similar after a single-dose and at steady-state, i.e., 12-14 hours.

Table 7: Selected multiple-dose ivacaftor PK parameters in healthy subjects for 150 mg q12h dose level

Study Formulation	Ivacaftor Dosage	Type of Subjects (N)	Median (range) t_{max} (hr)	Arithmetic Mean (SD) $t_{1/2}$ (hr)	C_{max} (ng/mL)	AUC_{0-12} (ng.hr/mL)	C_{min} (ng/mL)
Study 809-005 (b) (4)	150 mg q12h, 14 days, fed	Healthy (17)	4.00 (1.00, 6.00)	14.08 (4.05)	1970 (1040)	17700 (11700)	1060 (820)
Study 005 (b) (4)	150 mg q12h, 28 days, fed	Healthy (22)	4.00 (4.00, 8.00)	NA	1433 (296)	12640 (3072)	691 (238)
Study 008 Part B Waxed, film-coated tablet	150 mg q12h, 5 days, fed	Healthy (69)	4.00 (2.00, 6.00)	NA	1390 (522)	11600 (4700)	636 (293)
Study 010 Waxed, film-coated tablet	150 mg q12h 10 days, fed	Healthy (21)	4.00 (3.00, 6.00)	14.7 (3.68)	1158 (485)	9544 (4603)	523 (303)
(b) (4)							

Single dose PK of ivacaftor (CF subjects)

Based on non-compartmental analysis, PK for single 275 mg dose of ivacaftor administered as (b) (4) in fed state (study 001) was similar between healthy subjects and subjects with CF (Table 8).

PK parameter estimates from 9 subjects with CF, aged 6 to 11 years, following administration of a single oral dose of a100-mg film-coated tablet of ivacaftor following a standard high-fat, high-calorie CF breakfast (Study 103, Part A), was consistent with PK parameters in adults (e.g., 150 mg dose in Study 009) after dose normalization (Table 8), except possibly a shorter half-life in CF subjects 6 to 11 years of age than healthy adults. However, these differences need to be investigated further because some of the terminal slopes in for 6 to 11 years CF patients were based on only 2 time points.

Table 8: Selected single-dose PK parameters from subjects with CF and healthy subjects

Study Formulation	Ivacaftor Dose	Type of Subjects (M/F)	Median (range) t_{max} (hr)	Arithmetic Mean (SD) C_{max} (ng/mL)	Arithmetic Mean (SD) $t_{1/2}$ (hr)	Arithmetic Mean (SD) $AUC_{0-\infty}$ (ng.hr/mL)
Study 001						
(b) (4)	275-mg, single dose, fed (Part C)	Healthy (8M)	2.6 (2.1; 3.1)	1788 (376)	13.3 (2.7)	25913 (9103)
	275-mg, single dose, fed (Part D)	CF (1M/3F)	2.1 (2.1; 3.1)	2370 (756)	11.7 (3.1)	25405 (9530)
Study 007						
(b) (4) Tablet	150-mg, single dose, fed	Healthy (16M)	6.0 (3.0, 6.1)	506 (111)	10.8 (1.1)	6649 (1853)
Study 009						
Waxed, Film-Coated Tablet	150-mg, single dose, fed	Healthy (20M)	4.0 (3.0, 6.0)	673 (245)	12.9 (2.62)	8814 (4363)
Study 012						
Waxed, Film-Coated Tablet	150-mg, single dose, fed	Healthy (18M)	4.00 (3.0; 6.0)	768 (233)	11.87 (2.70)	10600 (5260)
Study 103 (Part A)						
Film-Coated Tablet	100-mg, single dose, fed	CF (4M/5F)[a]	4.04 (1.93;11.9)	434 (118)	6.56 (1.40)[b]	4740 (1380)[b]

Multiple dose PK of ivacaftor (CF subjects)

Multiple dose sparse PK samples were collected from Phase 2 and Phase 3 studies. These data were included in population PK analysis, which predicted similar steady-state exposures (AUC and C_{min}) and apparent clearance (CL/F) between healthy subjects and subjects with CF. Please refer to Pharmacometrics review by Dr. Atul Bhattaram in Appendix 2 for more details on population PK analysis.

PK of metabolites

PK of metabolites M1 and M6 were characterized in most clinical studies except 001, 002, 003, 004, and 012. Selected PK results are summarized below.

Single dose PK for metabolite M1 (healthy subjects)

Based on relative BA study 007, t_{max} for metabolite M1 was reached in 3.5-4 hours in fasted state and approximately 5.75 hours in fed state. The C_{max} and $AUC_{0-\infty}$ for (b) (4) formulation (see section 2.8 for further information on formulation) were 1696 ng/mL and 19293 ng*hr/mL in the fasted state, which increased to 2534 ng/mL and 37237 ng*hr/mL in the fed state. Half-life was 21.2 hours and 15.7 hours in fasted and fed state, respectively. The exposure ratio (i.e., $AUC_{0-tlast}$ for M1/ $AUC_{0-tlast}$ for ivacaftor) for M1 was 7.26 and 5.67 in fasted and fed state, respectively.

Multiple dose PK for metabolite M1 (healthy subjects)

In DDI study 010, multiple dose PK was assessed in fed state. The t_{max} for metabolite M1 was 4 hours, with C_{max} and AUC_{τ} of approximately 5800 ng/mL and 48060 ng*hr/mL, respectively. Half-life was 19 hours with metabolite/parent ratio of about 4.89 at steady-state.

Single dose PK for metabolite M6 (healthy subjects)

Based on relative BA study 007, t_{max} for metabolite M6 was reached in 5.5-6 hours in fasted state and approximately 9 hours in fed state. The C_{max} and $AUC_{0-\infty}$ for (b) (4) formulation were 404.2 ng/mL and 7764 ng*hr/mL in the fasted state, which increased to 604.2 ng/mL and 12985 ng*hr/mL in the fed state. Half-life was 21.6 hours and 16.9 hours in fasted and fed state, respectively. The exposure ratio (i.e., $AUC_{0-tlast}$ for M6/ $AUC_{0-tlast}$ for ivacaftor) for M6 was 2.85 and 2.01 in fasted and fed state, respectively

Multiple dose PK for metabolite M6 (healthy subjects)

In DDI study 010, multiple dose PK was assessed in fed state. The t_{max} for metabolite M6 was 5 hours, with C_{max} and AUC_{τ} of approximately 1670 ng/mL and 15337 ng*hr/mL, respectively. Half-life was 18.9 hours with metabolite/parent ratio of about 1.73 at steady-state.

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?

Population PK analysis involved data from both healthy subjects and CF patients, which showed that patient status did not describe the variability in PK of ivacaftor. In the same analysis, for metabolite M1, CF subjects had a slightly higher CL/F than healthy subjects. The typical estimate (95% CI) of the reduction in M1 CL/F for healthy subjects was 0.843 (0.766, 0.920) when compared to CF subjects. This small difference is not likely to be clinically important.

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

Inter-subject variability (%CV) in ivacaftor single-dose PK (C_{max} and AUC) was approximately 15-21% for doses ranging from 25 to 200 mg (Table 6, based on data from (b) (4) formulation). The inter-subject variability on C_{max} and AUC for the final waxed, film coated formulation ranged from 30-43% and 45-50%, respectively. The variability in PK after multiple-dose ranged from 27-50% (based on data shown in Table 7).

2.5.4 What are the characteristics of drug absorption?

The absolute bioavailability of ivacaftor in humans has not been determined because it is very insoluble (<0.001 mg/mL in water) and no intravenous formulation was available.

Administration with food increases the bioavailability approximately by 2- to 4-fold (see section 2.8.3), therefore ivacaftor should be administered with food. The median time to reach maximum plasma concentration (t_{max}) is approximately 4.0 hours in the fed state. In vitro studies showed that ivacaftor is not a substrate, but may be an inhibitor of P-gp transporter.

2.5.5 What are the characteristics of drug distribution?

Ivacaftor, and its metabolites, M1 and M6, were >98% bound to proteins in human plasma at all tested concentrations, in vitro. Human serum albumin (HAS) was the main plasma component involved in the binding of ivacaftor and its metabolites in human plasma. Binding of ivacaftor to alpha1-acid glycoprotein (AAG; >99%) and human gamma globulin (HGG; >97%) was also high at all AAG and HGG concentrations tested, whereas both M1 and M6 showed moderate to low concentration-dependent binding to these proteins. In an in vitro study, presence of ivacaftor, M1, or M6 did not affect the protein binding of warfarin, which was high, ~99%, and remain unaltered; vice versa, protein binding percentages of ivacaftor, M1, or M6 were not affected by presence of warfarin, indicating no plasma protein related DDI between ivacaftor and warfarin.

In mass balance study 003, radioactivity in plasma was higher than in blood suggesting that ivacaftor does not bind to human red blood cells.

Ivacaftor has a large Vz/F, suggesting extensive tissue distribution. Based on noncompartmental analysis, the mean (SD) Vz/F of ivacaftor after a single dose of 275 mg of ivacaftor as a solution formulation was 220 (61) L and after multiple-dose administration of ivacaftor 250 mg q12h was 206 (47) L, in healthy subjects in the fed state. A similar mean (SD) Vz/F of ivacaftor was obtained after a single dose of 275 mg of ivacaftor in the fed state in subjects with CF: 203 (82) L. These results were consistent with the whole body autoradiography studies of ^{14}C-ivacaftor conducted in rats, which showed distribution of radioactivity into several body tissues.

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

Mass balance study (003) showed hepatic metabolism as the major route of elimination with very little renal elimination.

In mass balance study mean total recovery was 94.6%, of which 87.8% (mean) was excreted in feces and 6.6% was excreted in urine. The amount of unchanged drug excreted in feces was only 2.52%, suggesting that most of the drug was excreted as metabolites.

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

Following oral administration to healthy human males, ^{14}C-ivacaftor was extensively metabolized, and gets converted into metabolites M1 and M6 (see section 2.5.8, Figure 11). Percent of sample radioactivity as parent or metabolite across sampling time, after administration of a single-dose of radiolabeled drug, is shown in Table 9. In plasma, ivacaftor, M1, and M6 were the main circulating radioactive components detected. Small amount of M5 was also detected in plasma at 6, 12, and 24 hours after dosing.

Table 9: Percent of sample radioactivity as ^{14}C-ivacaftor or metabolites of ^{14}C-ivacaftor in pooled plasma after administration of single 133 mg (100 μCi) oral dose of ^{14}C-ivacaftor to healthy male subjects

	Percent of Radioactivity Injected					
Proposed	Collection Time Point (Hours)					
Identification	0.75	2	6	12	24	48
M585A/B	ND	ND	4.67	6.40	6.88	ND
M6-VX-770	ND	7.01	38.6	32.0	29.4	ND
M1-VX-770	29.1	54.9	37.9	30.8	36.2	78.4
Unknown	ND	3.11	2.15	2.20	ND	ND
VX-770	69.3	30.6	11.7	15.9	13.3	ND
Total:	98.4	95.6	95.1	87.3	85.9	78.4

VX-770: ivacaftor; **M1-VX-770**: metabolite M1; **M6-VX-770**: metabolite M6

2.5.8 What are the characteristics of drug metabolism?

Following oral administration, ivacaftor was extensively metabolized and majority of drug was excreted from body via feces as metabolites. The proposed metabolic pathway of ivacaftor or VX-770 is shown in Figure 11. Metabolism primarily involved oxidation of ivacaftor to M1 (hydroxymethyl-ivacaftor) and M6 (ivacaftor carboxylate), with a minor contribution by glucuronidation and sulfation. M1 and M6 metabolites accounted for approximately 65% of total dose excreted, with 22% as M1 and 43% as M6. Metabolite M5 is formed by glucuronidation, M1 sulfate by sulfation, and M8 by oxidation. Metabolite M6 is further conjugated to glucuronic acid and decarboxylated to form metabolite M7 or undergoes ring closure to form furanone metabolite of ivacaftor, designated as M405. Metabolite M8 also further conjugated to glucuronic acid. Based on in vitro data, CYP3A4 and CYP3A5 are the predominant enzymes involved in metabolism of ivacaftor and M1. The primary Phase I metabolism occurred by oxidation, and the primary Phase II metabolism occurred by glucuronic conjugation of metabolites.

After 150 mg q12h of the commercial tablet formulation in the fed state, the mean exposure (AUC_τ metabolite/AUC_τ ivacaftor) ratio was approximately 6 for M1 and 2 for M6 (Study 008). M1 and M6 were also major metabolites of ivacaftor in children 6 to 11 years of age (Study 103 Part A), consistent with results in adult subjects from other studies.

In *in vitro* studies, ivacaftor metabolite M1 potentiated CFTR-mediated chloride transport in human bronchial epithelia (HBE), from a single donor with G551D-*CFTR* and F508del-*CFTR* gene mutations, with approximately 1/6th of the potency of ivacaftor; therefore, it was considered pharmacologically active. Ivacaftor metabolite M6

potentiated CFTR-mediated chloride transport in G551D/F508del-HBE with less than 1/50th of the potency of ivacaftor, and therefore is not considered pharmacologically active.

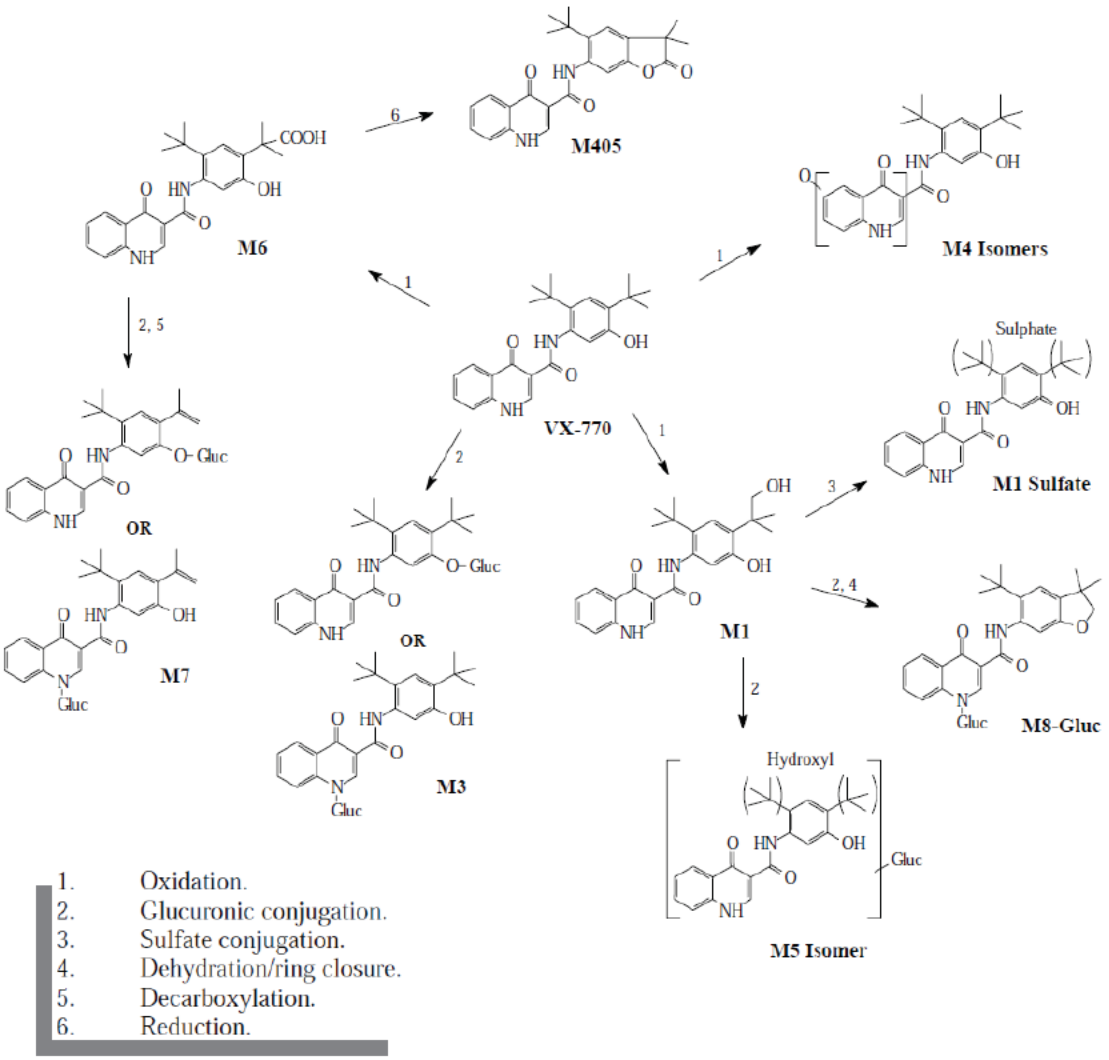


Figure 11: metabolic pathway of ^{14}C-ivafactor (or ^{14}C-VX-770) in healthy subjects

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

Preclinical studies with bile duct cannulated rats showed that excretion in bile accounted for approximately 31-32% of the total recovered dose in 168 hours (i.e., ~94%). In a mass balance study in humans, of the 94.6% recovered dose, 87.8% was excreted in feces (65% as metabolites M1 and M6) with minimal renal excretion, i.e., 6.6%. In humans, recovery of metabolites in feces after oral administration suggests biliary excretion of parent and metabolites.

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

For doses up to 200 mg, there were no secondary peaks observed in plasma concentration – time profiles of ivacaftor (Figure 10). There is no evidence of enterohepatic recirculation at the proposed therapeutic dose of 150 mg q12h.

2.5.10 What are the characteristics of drug excretion in urine?

Following oral administration of ivacaftor, elimination in urine is negligible. Of the 94.6% dose recovered in a mass balance study, only 6.6% was recovered in urine. Elimination as unchanged parent was negligible, and urinary metabolite M5 (hydroxy-ivacaftor glucuronide) was the major metabolite accounting for 3.5% of the total dose.

Following a single oral dose of 133 mg ^{14}C-ivacaftor, most urine concentrations of unchanged parent (i.e., ivacaftor) were below the limit of quantitation. Following a single oral dose of 500 mg ivacaftor, the maximum cumulative excretion of unchanged ivacaftor in the urine up to 24 hours postdose was 0.002% of the dose.

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

Dose proportionality was assessed using the non-compartmental analysis data from study 001. Figure 12 displays the natural log ($AUC_{0-\infty}$) and the natural log (C_{max}) versus the natural log (VX-770 or ivacaftor dose), in figures (A) and (B), respectively. The log-transformed $AUC_{0-\infty}$ and C_{max} values were fit to the log-transformed dose data using maximum likelihood approach. The proportionality estimate and 95% CI are shown in Table 10. For $AUC_{0-\infty}$, the 95% CI on the proportionality parameter contains 1.0, suggesting that increase in $AUC_{0-\infty}$ is dose-proportional for doses ranging from 25-800 mg. On the other hand, the 95% confidence interval for the proportionality parameter for C_{max} does not contain 1.0, suggesting that increase in C_{max} with increase in dose from 25-800 mg is not dose proportional.

Table 10: Statistical assessment of dose proportionality

Parameter	Proportionality Estimate	Approximate 95% confidence interval
Natural Log($AUC_{0-\infty}$)	1.05	(0.96, 1.14)
Natural Log(C_{max})	0.80	(0.69, 0.91)

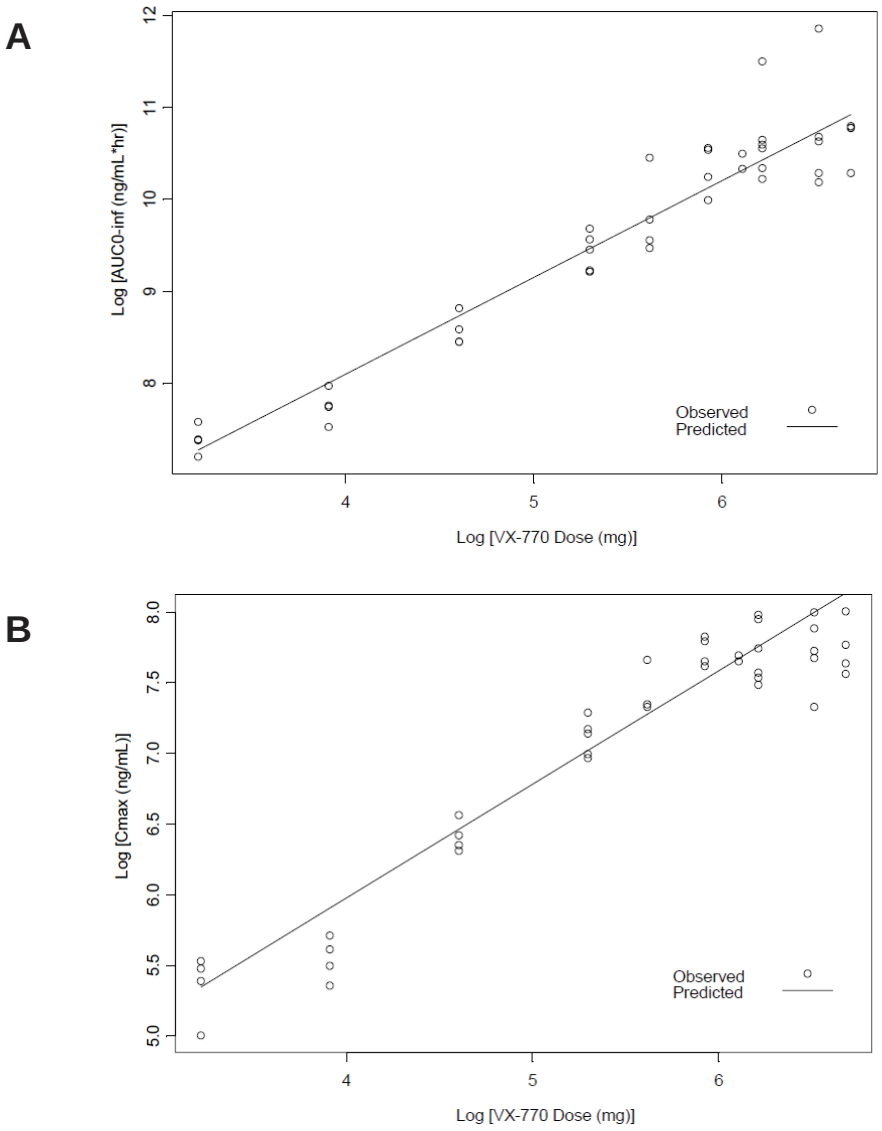


Figure 12: Assessment of dose proportionality for ivacaftor. (A) natural log ($AUC_{0-\infty}$) vs. natural log (Dose), and (B) natural log (C_{max}) vs. natural log (Dose)

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

There is no evidence for ivacaftor exposure to be affected by circadian rhythm.

In Study 809-005, in which ivacaftor was administered either alone or with another investigational CF drug being developed by Vertex (VX-809), PK samples were collected after the morning and evening doses of ivacaftor to provide an assessment of the potential diurnal variation of ivacaftor PK. Selected PK parameters for morning and evening doses of ivacaftor after 14 days of 150-mg q12h dosing, without coadministration of VX-809, are shown in Table 11. Morning and evening plasma concentration-time profiles were comparable.

Table 11: Comparison of PK parameters after morning versus evening doses of ivacaftor at steady-state

		C_{max} (ng/mL)		AUC_{0-12} (hr*ng/mL)	
Dose Regimen	**Statistic**	**AM**	**PM**	**AM**	**PM**
Multiple Dose (150 mg q12h, 14 days)	N	17	17	17	17
	Mean	1970	1690	17700	15700
	SD	1040	852	11700	10200
	Min	821	814	7490	6830
	Median	1810	1570	15600	13200
	Max	4600	3990	49800	44700
	CV%	52.7	50.3	66.0	65.1

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?

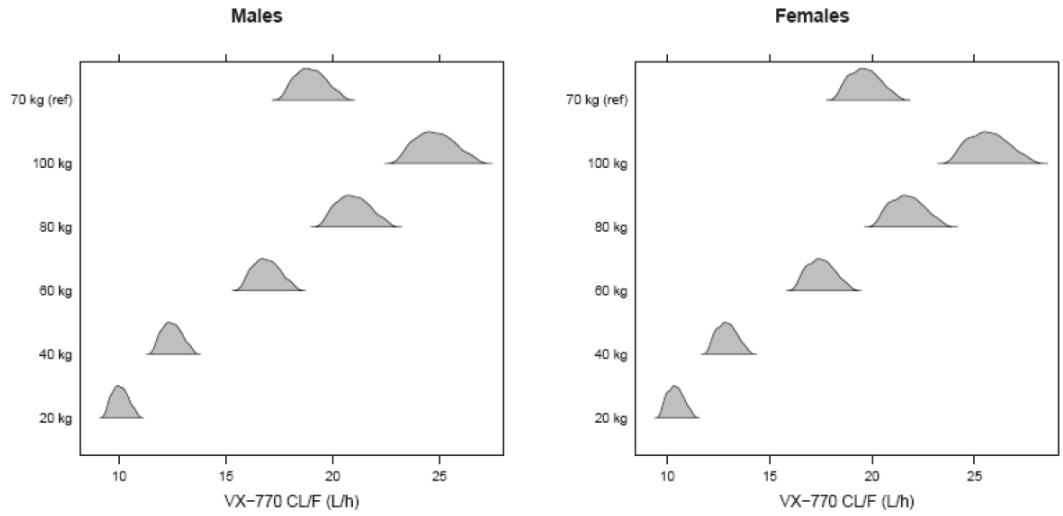
The effects of weight, gender, age, and disease status (healthy or CF) on ivacaftor PK were assessed in the population PK analysis. Population PK analysis was conducted on pooled data from Phase 2/3 studies (Study 101, Study 102, Study 103, and Study 104) and Phase 1 studies (Study 002, Study 007, and Study 010). Populations included among these studies were healthy subjects, CF subjects with the G551D mutation on at least one CFTR allele or homozygous for the F508del mutation, 6-11 year old subjects, 12-17 year old subjects, and adult subjects. Refer to Pharmacometrics review by Dr. Atul Bhattaram in Appendix 2 for detailed review of population PK analysis.

Weight

Weight was the most significant predictor of ivacaftor disposition. Predicted CL/F by body weight is shown in Table 12 and their relative distribution is shown in Figure 13. For a typical 20-kg subject, ivacaftor CL/F was about 50% of that of a 70-kg subject. For a typical 100-kg subject, ivacaftor CL/F was approximately 130% of that of a 70-kg subject. Similar to ivacaftor, variability in M1 CL/F was primarily explained by body weight.

Table 12: Bootstrap estimates of median and 95% CI for ivacaftor clearance estimates (L/h) by body weight

	Median	Lower 95%	Upper 95%
Male, 20 kg	10.02	9.23	11.10
Male, 40 kg	12.43	11.46	13.77
Male, 60 kg	16.85	15.53	18.66
Male, 80 kg	20.91	19.27	23.16
Male, 100 kg	24.72	22.78	27.38
Male, 70 kg (ref)	18.92	17.43	20.95
Female, 20 kg	10.39	9.57	11.44
Female, 40 kg	12.89	11.88	14.19
Female, 60 kg	17.47	16.10	19.24
Female, 80 kg	21.68	19.97	23.87
Female, 100 kg	25.63	23.61	28.22
Female, 70 kg (ref)	19.62	18.07	21.59



The distributions (5th and 95th percentiles) of the nonparametric bootstrap estimates are provided as density smooths for covariate values

Figure 13: Effect of body weight on ivacaftor clearance

Table 13: Effect of gender, age, and disease status

Parameter	Covariate	Estimate	%RSE	95% CI
Ivacaftor				
CL/F	Gender	1.03	9.13	(0.920,1.14)
CL/F	Age[a]	-0.114	46.9	(-0.219,0.0105)
CL/F	Healthy vs CF	1.03	9.13	(0.846,1.21)
M1				
CL/F	Gender	0.941	4.53	(0.857,1.02)
CL/F	Age[a]	0.0455	25.1	(-0.0511,0.142)
CL/F	Healthy vs CF	0.843	4.65	(0.766,0.920)
M6				
CL/F	Gender	0.947	5.71	(0.841,1.05)
CL/F	Age[a]	0.0652	67.5	(0.0210,0.151)
CL/F	Healthy vs CF	0.944	4.39	(0.863,1.03)

Age

Ivacaftor CL/F decreased with increasing age, with a point estimate (95% CI) of -0.114 (-0.219, 0.0105). The 95% CI on parameter estimate contained the null value of zero. Also CI was relatively wide with a high standard error for the parameter estimate (46.9%), suggesting that age effect was not well characterized with the available study data (population PK estimates in Table 13). The predicted trough concentrations (C_{min}) and AUC for different age groups are shown in Table 14 and are plotted in Figure 14. The mean and median C_{min} and AUC were higher for 6-11 years age group than adults; however, PK parameters in this age group were highly variable and showed substantial overlap with trough values for subjects aged 18 to 35 years.

Table 14: Summary statistics of individual predicted steady-state ivacaftor, M1, and M6 exposure for 150 mg q12h by age group

	Mean ± SD Median (Minimum, Maximum)		
Analyte	**6–11 years (n = 23)**	**12–17 years (n = 66)**	**Adults (n = 206)**
C_{min} (ng/mL)			
Ivacaftor	1180 ± 854 752 (316, 3600)	556 ± 356 492 (2.91, 1830)	774 ± 468 690 (3.36, 2920)
M1	5620 ± 2980 5520 (1480,12600)	3230 ± 1980 3120 (17.4,11300)	3440 ± 1780 3290 (57.3, 9620)
M6	1760 ± 1160 1460 (196, 4400)	967 ± 858 833 (2.03, 5100)	914 ± 710 738 (23.6, 4580)
AUC (ng*hr/mL)			
Ivacaftor	18120 ± 6547 16560 (7903, 30320)	8536 ± 3064 8122 (2951, 18670)	9508 ± 3763 8770 (3543, 26960)
M1	79220 ± 26370 79000 (38810, 137500)	41640 ± 15080 41590 (15520, 86620)	38110 ± 15210 35310 (6588, 89550)
M6	54140 ± 17930 54800 (28150, 93080)	28500 ± 10790 28270 (9969, 65150)	27320 ± 11760 25700 (4228, 67310)

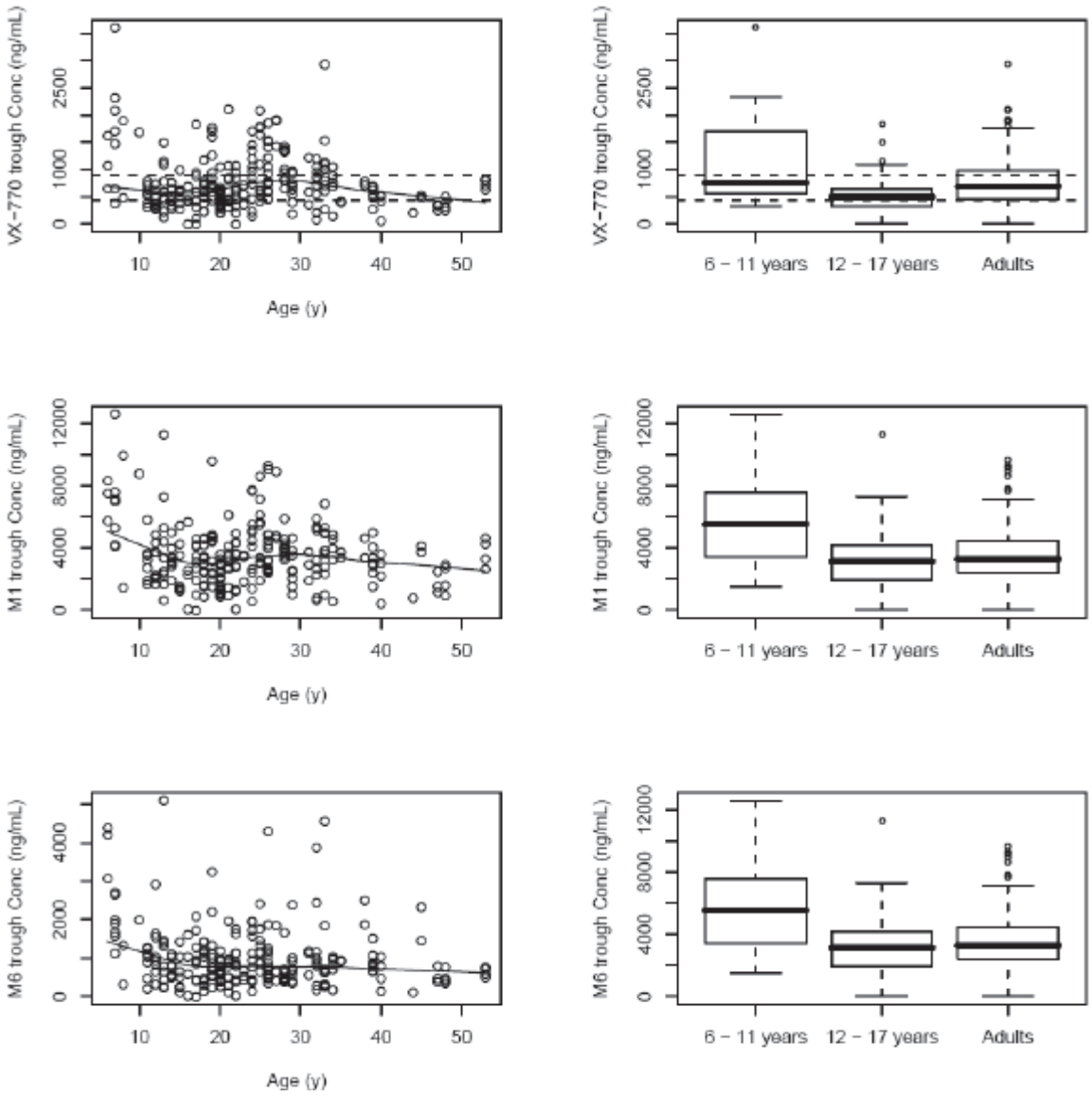


Figure 14: Ivacaftor, M1, and M6 trough concentrations vs. age

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

No dose adjustments are recommended based on severity of disease. Ivacaftor CL/F in healthy subjects was similar to that in subjects with CF, with an effect estimate of 1.03 (0.846, 1.21) (population PK estimates in Table 13).

2.6.2.2 Body Weight

Although body weight was a significant predictor of ivacaftor and M1 CL/F, no dose adjustments are recommended based on weight for CF patients ages 6 and above. A flat dose of 150 mg q12h is recommended for ages 6 and above based on evaluation of this dose in that age group in Phase 3 efficacy and safety clinical studies.

2.6.2.3 Elderly

The Phase 2b/3 studies (# 102, 103, and 104) enrolled patients with age ranging from 6 to 53 years. Ivacaftor's efficacy, safety, or PK has not been tested in elderly subjects.

2.6.2.4 Pediatric Patients

Phase 3 trials evaluating the efficacy and safety of ivacaftor in subjects with CF enrolled patients 6 years of age and older (Study 103: age 6-11 years (N=52), Study 102: age 12 years and older (N=161)). Therefore, the proposed dosing recommendations in age groups 6 years and above are based on observed efficacy and safety results. Safety and efficacy of ivacaftor has not been assessed in age group less than 6 years.

2.6.2.5 Race/Ethnicity

CF is most prevalent in Caucasians. The majority of subjects in the population PK dataset were White ("self-identified") with little representation in other racial categories; therefore, effect of race was not assessed in the population PK analysis.

2.6.2.6 Gender

No dose adjustments are recommended based on dose. In healthy subjects (studies 001, 008, 809-005), mean exposures of ivacaftor and M1 were similar in male and female subjects, and mean exposures of M6 (inactive metabolite) were higher in female subjects. However, M6 is an inactive metabolite. Population PK analysis of pooled data from healthy and CF subjects found no effect of gender on CL/F for ivacaftor, M1, or M6, likely because this analysis accounted for weight as a covariate. Ivacaftor CL/F was similar between males and females, with a point estimate of 1.03 (0.920, 1.14) (Table 13).

2.6.2.7 Renal Impairment

No dedicated study was conducted to assess the impact of mild, moderate or severe renal impairment or end stage renal disease on PK of ivacaftor and M1.

Only a small fraction of administered ivacaftor dose is eliminated by renal route (approximately 6.6% based on mass balance study). The urinary excretion of ivacaftor as unchanged parent was negligible with only 0.002% eliminated as parent following a single oral dose of 500 mg. Therefore, an effect of renal impairment on ivacaftor clearance is unlikely, and no dose adjustment is necessary for patients with mild or moderate renal impairment.

However, renal impairment may also affect some pathways of hepatic and gut drug metabolism and transport[†]; therefore, in absence of data from formal assessment in subjects with severe renal impairment or end stage renal disease, caution is recommended while using ivacaftor in these patients.

2.6.2.8 Hepatic Impairment

Impact of moderate hepatic impairment on ivacaftor PK was assessed in a non-randomized, open-label Study 013. Single dose of 150 mg ivacaftor was orally administered in subjects with moderate hepatic impairment (Child-Pugh Class B, Group A, n = 12) and matched healthy subjects (Group B, n = 12). The PK was compared in these two groups for ivacaftor, and main metabolites, M1 and M6, results of which are shown in Table 15. In addition to PK, for each patient, a blood sample was collected on day -1 to determine the fraction unbound for ivacaftor, M1, and M6, *in vitro*. Fraction of unbound or free drug (fu [%]) determined in these *in vitro* experiments was used in the calculation of individual PK parameters for unbound ivacaftor, M1, and M6 in subjects after dosing, which are shown in Table 16.

The geometric least squares mean ratio (GLSMR) for comparison of PK parameters between moderate hepatic impairment vs. healthy subjects is shown in Table 17. After single dose, the C_{max} for total and unbound ivacaftor and its metabolites M1 and M6 was similar in subjects with moderate hepatic impairment and matched healthy subjects, with geometric mean ratio close to 1. However, the $AUC_{0-\infty}$ for total and unbound ivacaftor was approximately 2-fold higher in subjects with moderate hepatic impairment than in matched healthy subjects, with geometric mean ratios of 1.96 (90%CI, 1.43-2.67) and 1.95 (90%CI, 1.36-2.78) for total and unbound drug, respectively. Total and unbound $AUC_{0-\infty}$ of ivacaftor metabolites, M1 and M6 were approximately 1.5- to 1.7-fold higher in moderate hepatic impairment subjects than in matched healthy subjects.

These results show that moderate hepatic impairment has no significant effect on absorption (C_{max}) of ivacaftor for single dose administration, but slows down the clearance (CL/F) and prolongs the terminal half-life ($t_{1/2}$) both by approximately two-fold of that in healthy subjects (Table 15). The mean apparent terminal half-life of metabolites, M1 and M6 in subjects with moderate hepatic impairment was prolonged to approximately 1.6-fold of that in healthy subjects (Table 15).

Sponsor performed simulations for steady-state based on nonparametric superposition to demonstrate that 150 mg once daily dose of ivacaftor in moderate hepatic impairment subjects would have PK parameters (C_{max}, C_{trough}, AUC_{0-24}) comparable to that for 150 mg q12h dose in matched healthy subjects. Results of simulations for steady-state concentrations of ivacaftor and active metabolite M1 are shown in Figure 15, and geometric mean ratio for comparison of PK parameters at steady-state is shown in Table 18. The geometric mean ratio for comparison of ivacaftor PK was close to 1, suggesting that reduction in dose to 150 mg once daily in moderate hepatic impairment brings down

[†] Guidance for Industry. Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling. Clinical Pharmacology, March 2010

the PK to close to that for 150 mg q12h dose in healthy subjects. Based on these simulations, the recommended dose in patients with moderate hepatic impairment was 150 mg once daily.

The impact of mild hepatic impairment (Child-Pugh Class A) and severe hepatic impairment (Child-Pugh Class C) on PK of ivacaftor, M1, and M6 has not been studied. However, mechanistically, for mild hepatic impairment, effect on metabolism is expected to be of smaller magnitude than moderate hepatic impairment (i.e., increase in AUC will be <2 fold); therefore, no dose adjustment is recommended. In absence of actual assessment in subjects with severe hepatic impairment, ivacaftor is not recommended for use, because the ivacaftor exposures would likely be higher than that for subjects with moderate hepatic impairment and is unknown.

Table 15: Summary of PK parameters for <u>total</u> ivacaftor (VX-770), M1, and M6 in subjects with moderate hepatic impairment and in matched healthy subjects after single dose of ivacaftor *[Numbers are Mean (SD) except for t_{max} which are Median (Min, Max)]*

Analyte	Group	C_{max} (ng/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0\text{-last}}$ (ng.hr/mL)	$AUC_{0\text{-}\infty}$ (ng.hr/mL)	CL/F (L/hr)	V_Z/F (L)	R_{AUC}
VX-770	A	735 (331)	4 (2, 5)	23.4 (11.8)	16500 (5980)	16800 (6140)	10.6 (5.34)	315 (126)	NA
VX-770	B	706 (300)	4 (3, 9)	11.8 (2.44)	8560 (3760)	8730 (3870)	20.7 (9.46)	343 (147)	NA
M1	A	1710 (647)	4 (4, 9)	25.6 (9.52)	33300 (14400)	33700 (14400)	NA	NA	2.27 (1.34)
M1	B	2000 (751)	4 (4, 5)	16.0 (2.63)	24500 (10500)	25400 (10900)	NA	NA	3.16 (1.48)
M6	A	628 (268)	7.5 (5, 9)	27.6 (10.7)	19100 (9550)	19300 (9570)	NA	NA	1.49 (1.20)
M6	B	674 (338)	6 (4, 12)	17.2 (3.32)	11300 (6770)	12000 (7490)	NA	NA	1.47 (0.730)

Group A: Moderate hepatic impairment; Group B: Healthy subjects
R_{AUC} = Metabolic ratio ($AUC_{metabolite}/AUC_{parent}$)

Table 16: Summary of PK parameters for <u>unbound</u> ivacaftor (VX-770), M1, and M6 in

subjects with moderate hepatic impairment and in matched healthy subjects after a single dose of ivacaftor. *[Numbers are Mean (SD) except for t_{max} which are Median (Min, Max)]*

Analyte	Group	f_u (%)	$C_{max,u}$ (ng/mL)	$AUC_{0\text{-last},u}$ (ng.hr/mL)	$AUC_{0\text{-}\infty,u}$ (ng.hr/mL)	CL_u/F (L/hr)	$V_{Z,u}/F$ (L)	$R_{AUC,u}$
VX-770	A	0.0350 (0.00674)	0.267 (0.149)	5.77 (2.14)	5.85 (2.16)	31600 (19000)	964000 (489000)	NA
VX-770	B	0.0358 (0.0108)	0.260 (0.154)	3.11 (1.89)	3.18 (1.95)	61300 (28100)	1030000 (529000)	NA
M1	A	0.177 (0.0512)	2.93 (1.04)	57.2 (23.4)	57.9 (23.6)	NA	NA	11.8 (8.1)
M1	B	0.178 (0.102)	3.84 (3.68)	48.0 (50.8)	49.6 (51.8)	NA	NA	19.5 (23.2)
M6	A	0.110 (0.0182)	0.701 (0.352)	21.3 (12.1)	21.5 (12.1)	NA	NA	5.18 (5.28)
M6	B	0.117 (0.074)	0.793 (0.635)	13.2 (11.1)	14.0 (11.8)	NA	NA	5.14 (4.25)

Group A: Moderate hepatic impairment; Group B: Healthy subjects
R_{AUC} = Metabolic ratio ($AUC_{metabolite}/AUC_{parent}$)

Table 17: Statistical comparison of PK parameters for ivacaftor, M1, and M6 between subjects with moderate hepatic impairment and healthy subjects

Analyte	Parameter	Unit	GLSMR (Group A:B)	90% Confidence Interval	
				Lower	Upper
VX-770	C_{max}	ng/mL	1.05	0.76	1.45
VX-770	$AUC_{0\text{-last}}$	ng.h/mL	1.97	1.44	2.68
VX-770	$AUC_{0\text{-}\infty}$	ng.h/mL	1.96	1.43	2.67
VX-770	$C_{max,u}$	ng/mL	1.05	0.70	1.56
VX-770	$AUC_{0\text{-last},u}$	ng.h/mL	1.96	1.37	2.79
VX-770	$AUC_{0\text{-}\infty,u}$	ng.h/mL	1.95	1.36	2.78
M1	C_{max}	ng/mL	0.87	0.65	1.16
M1	$AUC_{0\text{-last}}$	ng.h/mL	1.41	1.05	1.89
M1	$AUC_{0\text{-}\infty}$	ng.h/mL	1.37	1.02	1.84
M1	R_{AUC}		0.70	0.52	0.95
M1	$C_{max,u}$	ng/mL	0.91	0.62	1.32
M1	$AUC_{0\text{-last},u}$	ng.h/mL	1.47	1.01	2.15
M1	$AUC_{0\text{-}\infty,u}$	ng.h/mL	1.43	0.98	2.09
M1	$R_{AUC,u}$		0.74	0.47	1.17
M6	C_{max}	ng/mL	0.94	0.66	1.32
M6	$AUC_{0\text{-last}}$	ng.h/mL	1.74	1.19	2.55
M6	$AUC_{0\text{-}\infty}$	ng.h/mL	1.67	1.14	2.45
M6	R_{AUC}		0.86	0.52	1.41
M6	$C_{max,u}$	ng/mL	0.96	0.62	1.46
M6	$AUC_{0\text{-last},u}$	ng.h/mL	1.78	1.13	2.80
M6	$AUC_{0\text{-}\infty,u}$	ng.h/mL	1.71	1.08	2.69
M6	$R_{AUC,u}$		0.88	0.49	1.57

Group A: Moderate hepatic impairment; Group B: Healthy subjects
Subscript 'u' refers to unbound PK parameter
R_{AUC} = Metabolic ratio ($AUC_{metabolite}/AUC_{parent}$)

Table 18: Statistical comparison of the simulated ivacaftor (VX-770), M1, and M6 PK parameters at steady-state between subjects with moderate hepatic impairment after 150 once daily and healthy

subjects after ivacaftor 150 mg q12h dosing

Analyte	Parameter	Unit	GLSMR (Group HI:HS)	90% Confidence Interval Lower	Upper
VX-770	C_{max}	ng/mL	1.11	0.83	1.47
VX-770	C_{trough}	ng/mL	0.94	0.64	1.37
VX-770	AUC_{0-24}	ng.h/mL	0.97	0.71	1.33
M1	C_{max}	ng/mL	0.82	0.62	1.08
M1	C_{trough}	ng/mL	0.64	0.46	0.89
M1	AUC_{0-24}	ng.h/mL	0.68	0.51	0.92
M6	C_{max}	ng/mL	0.92	0.65	1.30
M6	C_{trough}	ng/mL	0.75	0.49	1.12
M6	AUC_{0-24}	ng.h/mL	0.83	0.57	1.22

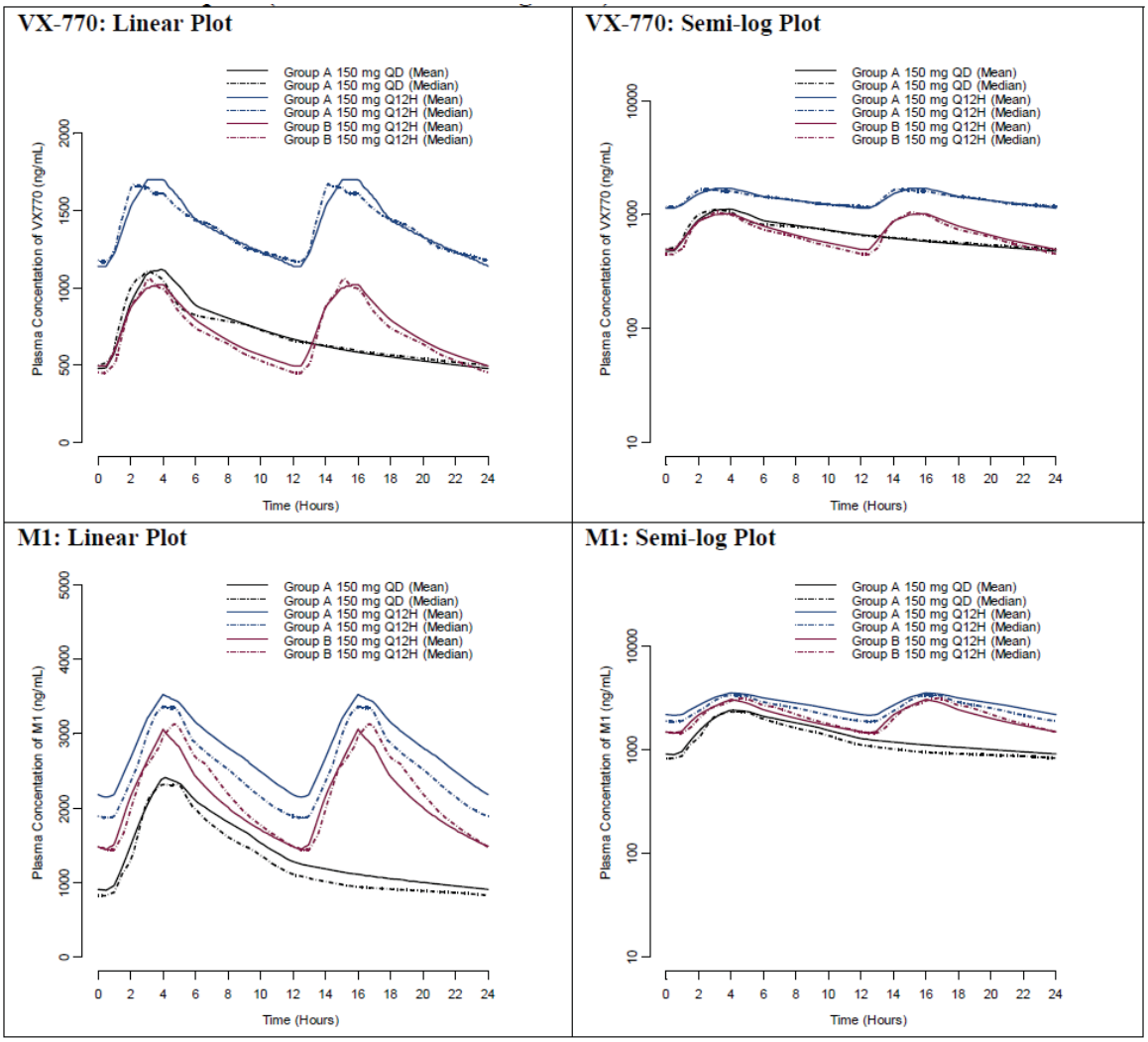


Figure 15: Simulated mean (solid lines) and median (dashed lines) steady-state plasma concentrations of ivacaftor (VX-770) and M1 in subjects with moderate hepatic impairment receiving 150 mg once daily and 150 mg q12h dosing, and in healthy subjects at 150 mg q12h dosing (Linear and Semi-log plots)

Sponsor proposed dosing adjustment was further assessed by performing simulations for different dosing scenarios using Berkeley Madonna simulation software. Ivacaftor

concentrations were simulated in a typical 18 year old subject with normal liver function or moderate hepatic impairment for 150 mg q12h or 150 mg once daily dosing regimen, respectively (Figure 16). These simulations were based on estimates of population PK parameters and fold change in clearance observed in hepatic impairment study 013. As shown in Figure 16, 150 mg once daily dosing in moderate hepatic impairment gives comparable exposure and $C_{min,ss}$ than 150 mg q12h dose in subjects with normal hepatic function. See Appendix 1 for further details on Berkeley Madonna simulations.

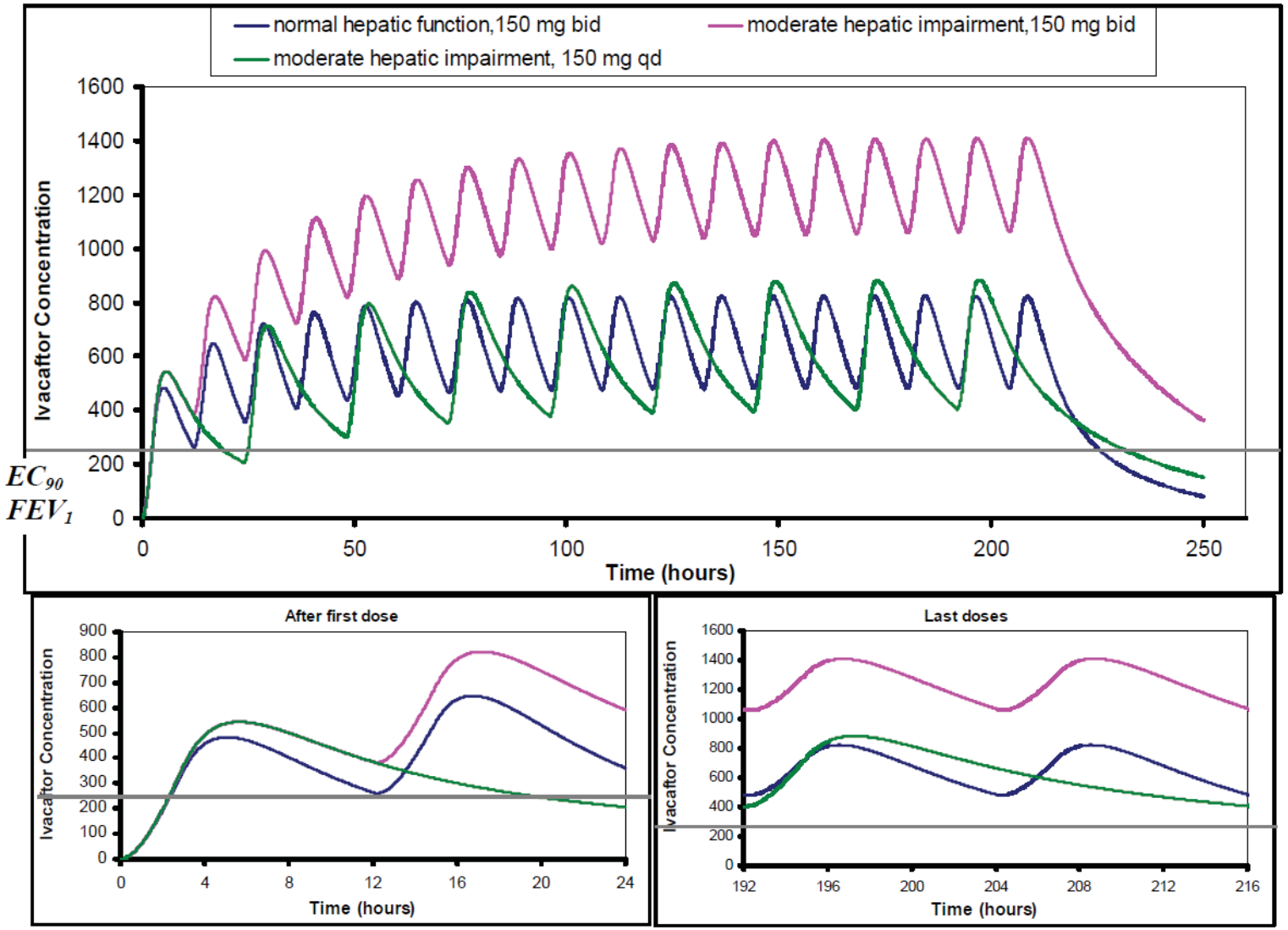


Figure 16: Simulation of different dosing scenarios for subjects with normal liver function and moderate hepatic impairment

2.6.3 Does genetic variation impact exposure and/or response?

The efficacy and safety of ivacaftor was assessed in CF patients with the G551D mutation in at least 1 allele of the *CFTR* gene in trials 102 and 103. The mutation in the second allele of the CFTR gene for most of these patients was F508del. Study 104 assessed the efficacy and safety of ivacaftor in subjects with CF who are homozygous for the F508del mutation. Ivacaftor was efficacious in subjects with the G551D mutation in one allele and the F508del mutation in the second allele, with mean change in percent predicted FEV_1 from baseline to week 24 was 11.1% in ivacaftor group and -0.7% in placebo group. Ivacaftor was not effective in subjects who were homozygous for the F508del mutation, with adjusted mean absolute change in FEV_1 from baseline through week 16 of 1.5% in ivacaftor group and -0.2% in placebo group, a treatment difference which was not statistically significant [1.72% (95% CI: -0.6, 4.1)].

In *in vitro* studies, ivacaftor increased chloride conductance through channels harboring a variety of CFTR gating mutations, as well as some non-gating CFTR mutations. Variability in response according to the second allele (on a background of G551D) was examined to assess whether ivacaftor is effective in non-G551D gating mutations and other non-gating mutation types. A total of 19 different CFTR mutations received treatment with ivacaftor. Only one subject that received ivacaftor was homozygous for gating mutations (G551D/G551D), and this subject did not demonstrate a FEV1 response (contrary to the expected additive effect of having two gating mutations). Major differences in FEV1 and sweat chloride responses were not apparent across non-gating mutation classes suggesting that the main effect is driven by G551D (Table 19). *In vitro* ivacaftor response phenotypes were not correlated with clinical ivacaftor responses (not shown). Overall, insufficient data are available to support a clinical effect in patients with gating mutations other than G551D and non-gating mutations.

Table 19: Clinical Endpoints at 24 weeks by CFTR Mutation Class in Trials 102 and 103

Endpoint (24 Wks)	CFTR Mutation Class of Second Allele	Placebo			Ivacaftor		
		N	Absolute change	Percent change	N	Absolute change	Percent change
FEV1	All Gating	1	-1.8	-3.9	1	-9.6	-9.5
	F508del Trafficking	**72**	**-1.6**	**-1.9**	**75**	**11.5**	**17.5**
	All Non-F508del Trafficking	**2**	**10.8**	**14.7**	**7**	**10.5**	**17.1**
	All Conductance	**2**	**1.9**	**-0.1**	**2**	**0**	**3.9**
	All Synthesis	**12**	**0.3**	**1.8**	**7**	**10.5**	**14.5**
	All Unknown	**1**	**1.1**	**0.8**	**1**	**5.4**	**9.2**
Sweat Cl-	All Gating	**1**	**2.0**	**2.0**	**1**	**-65.0**	**-50.8**
	F508del Trafficking	**68**	**-1.3**	**-0.8**	**74**	**-54.4**	**-54.0**
	All Non-F508del Trafficking	**2**	**0.0**	**0.2**	**7**	**-46.4**	**-46.9**
	All Conductance	**2**	**-5.25**	**-8.45**	**1**	**-32.5**	**-37.8**
	All Synthesis	**12**	**4.0**	**4.4**	**5**	**-62.0**	**-63.3**
	All Unknown	**1**	**-14.5**	**-14.2**	**1**	**-39.5**	**-40.5**

Results of population PK analysis showed that a dose of 150 mg q12h provided a similar exposure in subjects with the G551D mutation on at least 1 allele or subjects homozygous for the F508del mutation who are at least 12 years old

2.7 Extrinsic Factors

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

Yes, *in vitro* inhibition studies suggested that ivacaftor and M1 may have a potential for drug interactions through inhibition of CYP2C8, CYP2C9, and CYP3A4 enzymes, and P-gp transporter.

2.7.2 Is the drug a substrate of CYP enzymes?

Yes, ivacaftor and M1 are substrates for CYP3A enzymes, CYP3A4 and CYP3A5, while M6 is metabolically stable. The percentage of parent and metabolites remaining after 30 min incubation with recombinant CYP enzymes is shown in Table 20. 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 20: 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

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

In vitro studies of ivacaftor, M1, and M6 on isozyme-selective CYP activities in cultured human hepatocytes indicated that ivacaftor, M1, and M6 were not inducers of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5. However, ivacaftor and M1 were potential inhibitors of CYP2C8, CYP2C9, and CYP3A, whereas M6 was not a substantive inhibitor of CYP isozymes. Table 21 summarizes the results of possible inhibition potential of CYP450 isozymes by ivacaftor, M1, and M6.

Table 21: Inhibition of human CYP450 isozymes by ivacaftor and metabolites M1 and M6

Activities	CYPs	Ivacaftor		M1		M6	
		IC_{50} (μM)	K_i (μM)	IC_{50} (μM)	K_i (μM)	IC_{50} (μM)	K_i (μM)
Phenacetin *O*-deethylase	CYP1A2	>100	ND	>100	ND	>100	ND
coumarin 7-hydroxylase	CYP2A6	>100	ND	88.8	ND	>100	ND
bupropion hydroxylase	CYP2B6	>100	ND	>100	ND	>100	ND
amodiaquine N-deethylase	CYP2C8	3.8	3.4[a,b]	17.7	0.39/223[a,c]	63.1	ND
diclofenac 4-hydroxylase	CYP2C9	11.0	30.0[a,b]	27.9	14.2[a,c]	97.5	ND
S-mephenytoin 4-hydroxylase	CYP2C19	>100	ND	>100	ND	>100	ND
bufuralol 1-hydroxylase	CYP2D6	64.1	ND	>100	ND	>100	ND
chlorzoxazone 6-hydroxylase	CYP2E1	>100	ND	>100	ND	>100	ND
testosterone 6β-hydroxylase	CYP3A	41.0	36.9[c]	36.3	52.9[c]	>100	ND
midazolam 1-hydroxylase	CYP3A	47.4	36.8[c]	31.2	26.1[c]	99.4	ND

[a] Nonlinear
[b] Mixed type of inhibition
[c] competitive inhibition

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

In vitro experiments indicated that ivacaftor has potential to inhibit P-gp and M1 may also inhibit P-gp. The IC_{50} concentrations of ivacaftor and M1 towards digoxin transport in *in vitro* Caco-2 cell-based assay were 0.17 and 8.17 μM, respectively. For M6, the inhibitory effect on digoxin transport did not show a meaningful pattern and the IC50 value could not be determined. The C_{max} at steady-state following administration of 150 mg bid dose for 5 days in fed state was 1390 ng/mL (~3.5 μM).

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

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.

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

Among extrinsic factors, effect of coadministration with other drugs on ivacaftor, M1, and M6 PK was evaluated. Dose adjustment is specifically recommended when ivacaftor is coadministered with CYP3A inhibitors or inducers.

2.7.7 What are the drug-drug interactions?

Drug-drug interactions were assessed under following two categories:

- *Effect of coadministered drugs on ivacaftor PK*: Ketoconazole (strong CYP3A4 inhibitor), Fluconazole (moderate CYP3A4 inhibitor), Rifampin (strong CYP3A4 inducer), Oral contraceptives

- *Effect of ivacaftor on PK of coadministered drugs*: Midazolam (CYP3A4 probe substrate), Desipramine (CYP2D6 probe substrate), Rosiglitazone (CYP2C8 probe substrate), Ethinyl estradiol and Norethindrone (oral contraceptive)

Results of geometric mean ratios for comparison of C_{max}, AUC, C_{min} for these drug interaction studies are summarized in Table 22 and Table 23. In addition to the findings from drug-drug interaction studies with probe enzyme substrates, sponsor made some additional dosing recommendations, which are also summarized below.

Effect of co-administered drugs on ivacaftor PK

Strong CYP3A Inhibitors:

(Ketoconazole, Itraconazole, Posaconazole, Voriconazole, Telithromycin, and Clarithromycin)

Coadministration with ketoconazole, a strong CYP3A inhibitor, significantly increased the exposure of ivacaftor (C_{max} by 2.65 fold and AUC by 8.45 fold, see Table 21). Therefore, a reduction in ivacaftor dose to 150 mg twice-a-week is recommended when coadministered with strong CYP3A inhibitors such as ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin.

Reviewer's comment:
Using Berkeley Madonna simulation software, ivacaftor concentrations were simulated for 150 mg q12h given with or without ketoconazole for a typical 18 year old healthy subject (Prussian blue and pink profiles, respectively, in Figure 17). Simulations were also performed for ivacaftor 75 mg q12h and 250 mg q12h given without ketoconazole (red and violet profiles, respectively, in Figure 17). These doses were also effective based on results of the 28 days, Phase 2a study #101.

Two possible dosing scenarios for coadministration with ketoconazole were:

1. Ivacaftor 150 mg twice-a-week given with ketoconazole (simulations shown in green profile in Figure 17)
2. 75 mg once daily given with ketoconazole (simulations shown in light blue profile in Figure 17)

The 150 mg twice-a-week ivacaftor dosing with ketoconazole provided approximately similar steady-state concentrations ($C_{min,ss}$) as 150 mg q12h without ketoconazole; however, concentrations after initial doses were relatively low and Cmax after multiple

dose is higher. Still these low concentrations after initial doses were comparable with that for 75 mg q12h dose given without ketoconazole, a dose which was also shown to be effective in the dose ranging Phase 2a study #101. The higher Cmax after multiple doses was also lower than the Cmax for 250 mg bid dose at steady-state, which was found to be safe in 28-days study #101.

The alternative 75 mg once daily ivacaftor dose with ketoconazole provides comparable or higher steady-state concentrations ($C_{min,ss}$) than 150 mg q12h without ketoconazole, as shown in Figure 17. However, these high concentrations were comparable than that observed for 250 mg q12h dose given without ketoconazole, a dose which was shown to have similar safety profile following 28 days administration in dose finding Phase 2a study 101. See Appendix 1 for further details on Berkeley Madonna simulations.

Since there is only one, 150 mg, ivacaftor formulation strength proposed in current submission, 150 mg twice-a-week ivacaftor dosing is recommended when ivacaftor is to be coadministered with strong CYP3A inhibitors.

Moderate CYP3A inhibitors:

(Fluconazole and Erythromycin)

Coadministration with fluconazole, a moderate CYP3A4 inhibitor, significantly increased the exposure of ivacaftor (C_{max} by 2.47 fold, AUC by 2.95 fold, and C_{min} by 3.42 fold, see Table 22). Therefore, a reduction in ivacaftor dose to 150 mg once daily is recommended when coadministered with moderate CYP3A inhibitors such as fluconazole and erythromycin.

Reviewer's comment:
Using Berkeley Madonna simulation software, ivacaftor concentrations were simulated for 150 mg q12h given with or without fluconazole for a typical 18 year old healthy subject (Prussian blue and pink profiles, respectively, in Figure 18). Simulations were also performed for 250 mg q12h given without fluconazole (green profile in Figure 18), and 150 mg once daily given with fluconazole (light blue profile in Figure 18) to a typical 18 year old healthy subject. The 150 mg once daily ivacaftor dosing with fluconazole provided approximately similar or higher steady-state concentrations ($C_{min,ss}$) than150 mg q12h without fluconazole. However, these high concentrations were lower than the concentrations for 250 mg q12h, a dose which was shown to be comparably safe following 28 days administration in dose finding Phase 2a study 101. See Appendix 1 for further details on Berkeley Madonna simulations.

Therefore, based on practical consideration of available dose strength and available data on safety and efficacy, a 150 mg once daily dose is recommended when ivacaftor is to be coadministered with moderate CYP3A inhibitors.

Strong CYP3A inducers:

Rifampin, Rifabutin, Antiepileptic Agents (Phenobarbital, Carbamazepine, and Phenytoin), St. John's Wort, and Immune Modulators (Dexamethasone, High-dose Prednisone)

Coadministration with rifampin, a strong CYP3A inducer, significantly reduced the ivacaftor exposure (C_{max} by ~5 fold and AUC by ~9 fold, see Table 22), which would potentially diminish the effectiveness of ivacaftor. Therefore coadministration of ivacaftor with CYP3A inducers such as rifampin, rifabutin, phenobarbital, carbamazepine, and phenytoin is not recommended.

In addition, coadministration with St. John's Wort is not recommended, because it is an inducer of both CYP3A and P-gp activity, which may significantly reduce plasma concentrations of ivacaftor.

CYP3A substrates (oral contraceptives):
Coadministration of ivacaftor with oral contraceptives did not have any effect on ivacaftor, M1, and M6 exposures, with all geometric mean ratios and 90% CI being within 0.8 to 1.25 (Table 22). Therefore, no ivacaftor dose adjustments are needed or recommended.

Effect of ivacaftor on PK of co-administered drugs:

CYP3A and/or P-gp substrates:

Banzodiazepine Sedatives/Hypnotics (Midazolam, Triazolam, Diazepam, Alprazolam)

Coadministration of midazolam, a sensitive CYP3A substrate, with ivacaftor increased midazolam C_{max} by 1.38 fold and AUC by 1.54 fold (Table 23), which suggests that ivacaftor is a weak inhibitor of CYP3A. However, because of increased midazolam exposure adequate monitoring is recommended for benzodiazepine related side effects (such as prolonged or increased sedation or respiratory depression) during coadministration with ivacaftor, which may also apply for similar substrates triazolam, diazepam, and alprazolam.

Digoxin and Immune Modulators (Cyclosporine, Tacrolimus)
Similarly exposures may also increase for CYP3A and P-gp substrates such as digoxin, cyclosporine and tacrolimus following coadministration with ivacaftor, because in addition to being a weak inhibitor of CYP3A, in vitro studies showed that ivacaftor may be a strong inhibitor of P-gp at therapeutic concentrations. Therefore, adequate monitoring is recommended following coadministration of these drugs with ivacaftor (e.g., serum concentrations for digoxin, prolonged or increased immunosuppression for cyclosporine and tacrolimus).

Oral Contraceptives (Norethindrone and Ethinyl estradiol)
There was no significant effect on exposures of less sensitive CYP3A substrates, such as norethindrone and ethinyl estradiol (Table 23). Therefore, no adjustment in dose of oral contraceptive is recommended when coadministered with ivacaftor.

CYP2C8 substrate (e.g., Rosiglitazone):

No significant effect was observed on exposures of rosiglitazone following coadministration with ivacaftor, with geometric mean ratios and 90% CI for comparison of PK parameters being within 0.8 to 1.25 (Table 23). Therefore, no dose adjustments are recommended for rosiglitazone.

CYP2C9 substrate (e.g., Warfarin):

In vitro studies showed that iavacaftor has potential to inhibit CYP2C9. Given that warfarin, a substrate of CYP2C9, is a narrow therapeutic index drug, it is recommended that international normalization ratio (INR) be monitored whenever coadministration with ivacaftor is required.

Table 22: Summary of PK parameters for ivacaftor in the presence of co-administered drugs

Drug	Dose and Schedule		N	PK of	Effect	GLS Mean Ratio (90%CI) of ivacaftor, M1, M6 PK With/Without co-administered drug			Recommendation
	Drug	Ivacaftor				Cmax	AUC	Cmin	
Fluconazole (moderate CYP3A4 inhibitor)	400 mg on Day 1 and subsequently 200 mg qd for 8 days	Ivacaftor, 150 mg q12h for 8 days	18	Ivacaftor	↑	2.47 (1.93, 3.17)	2.95[d] (2.27, 3.82)	3.42 (2.61, 4.48)	Adjust ivacaftor dose to 150 mg qd when co-administered with fluconazole
				M1	↑	1.53 (1.22, 1.92)	1.86[d] (1.49, 2.32)	2.23 (1.80, 2.77)	
				M6	↓	0.84 (0.63, 1.11)	0.83[d] (0.63, 1.09)	0.91 (0.69, 1.20)	
Ketoconazole (strong CYP3A4 inhibitor)	Ketoconazole 400 mg qd 10 days	Ivacaftor, 150-mg single dose on Day 4 of ketoconazole Dosing	24[b]	Ivacaftor	↑	2.65 (2.21, 3.18)	8.45[c] (7.14, 10.01)	NA	Reduce dose to 150 mg twice-a-week when co-administered with ketoconazole
				M1	↑	0.23 (0.18, 0.28)	1.69[c] (1.49, 1.92)	NA	
				M6	↓	0.062 (0.048, 0.081)	0.30[c] (0.25, 0.36)	NA	
Oral Contraceptive	Norethindrone/ ethinyl estradiol 0.5 mg/0.035 mg qd for 21 days	Ivacaftor, 150 mg q12h for 28 days	22	Ivacaftor	↔	0.98 (0.90, 1.06)	0.99[d] (0.92, 1.06)	1.00 (0.92, 1.07)	No dose adjustment
				M1	↔	0.99 (0.92, 1.06)	0.99[d] (0.93, 1.06)	1.02 (0.93, 1.11)	
				M6	↔	1.07 (0.96, 1.20)	1.08[d] (0.97, 1.21)	1.12 (098, 1.28)	
Rifampin (strongCYP3A4 inducer)	600 mg qd for 10 days	Ivacaftor, 150-mg single dose on Day 6 of rifampin Dosing	20[e]	Ivacaftor	↓	0.20 (0.17, 0.24)	0.11[c] (0.10, 0.14)	NA	Co-administration not recommended
				M1	↓	0.61 (0.54, 0.70)	0.25[c] (0.22, 0.29)	NA	
				M6	↑	4.75 (4.21, 5.36)	1.88[c] (1.68, 2.11)	NA	

Abbreviations
NA: not applicable
[a]↔: drug has no effect on ivacaftor exposure (AUC GLS mean ratio and 95% CI fall within 0.80-1.25)
↑: drug increases ivacaftor exposure (AUC); ↓: drug decreases ivacaftor exposure (AUC)
[b]N = 23 for AUC0-∞
[c]$AUC_{0-\infty}$; [d]AUC_{0-12}
[e]N = 15 for $AUC_{0-\infty}$

Table 23: Summary of PK parameters for co-administered drugs in the presence of ivacaftor

Drug	Dose and Schedule		N	Effect on drug PK[a]	GLS Mean Ratio (90%CI) of Drug PK With/Without Ivacaftor			Recommendation
	Drug	Ivacaftor			Cmax	AUC	Cmin	
Desipramine (CYP2D6 probe substrate)	50-mg, single dose, on Day 5 of ivacaftor dosing	Ivacaftor, 150 mg q12h for 9 days	24[d]	↔	1.00 (0.94, 1.07)	1.04[b] (0.99, 1.10)	NA	No dose adjustment
Midazolam (CYP3A4 probe substrate)	2-mg, single dose, on Day 6 of ivacaftor dosing	Ivacaftor, 150 mg q12h for 6 days	24	↑	1.38 (1.26, 1.52)	1.54[b] (1.39, 1.69)	NA	Use with caution and monitor for benzodiazepine-related side effects during coadministration.
Rosiglitazone (CYP2C8 probe substrate)	4-mg, single dose, on Day 7 of ivacaftor dosing	Ivacaftor, 150 mg q12h for 7 days	20	↔	0.93 (0.86, 1.00)	0.98[b] (0.90, 1.06)	NA	No dose adjustment
Ethinyl estradiol	EE 0.035 mg + 0.5 mg NE, qd for 21 days	Ivacaftor, 150 mg q12h for 28 days	22	↔	1.22 (1.10, 1.36)	1.07[c] (1.00, 1.14)	1.04 (0.90, 1.22)	No dose adjustment
Noretindrone	EE 0.035 mg + 0.5 mg NE, qd for 21 days	Ivacaftor, 150 mg q12h for 28 days	22	↔	1.09 (1.01, 1.19)	1.05[c] (0.99, 1.12)	1.16 (0.98, 1.38)	No dose adjustment

Abbreviations
EE: ethinyl estradiol, NA: not applicable, NE: norethindrone
[a] ↔: Ivacaftor has no effect on substrate exposure (AUC GLS Mean Ratio and 90% CI fall within 0.80 – 1.25);
↑: drug increases substrate exposure (AUC); ↓: drug decreases substrate exposure (AUC)
[b] $AUC_{0-\infty}$
[c] AUC_{0-24}
[d] N = 23 for AUC

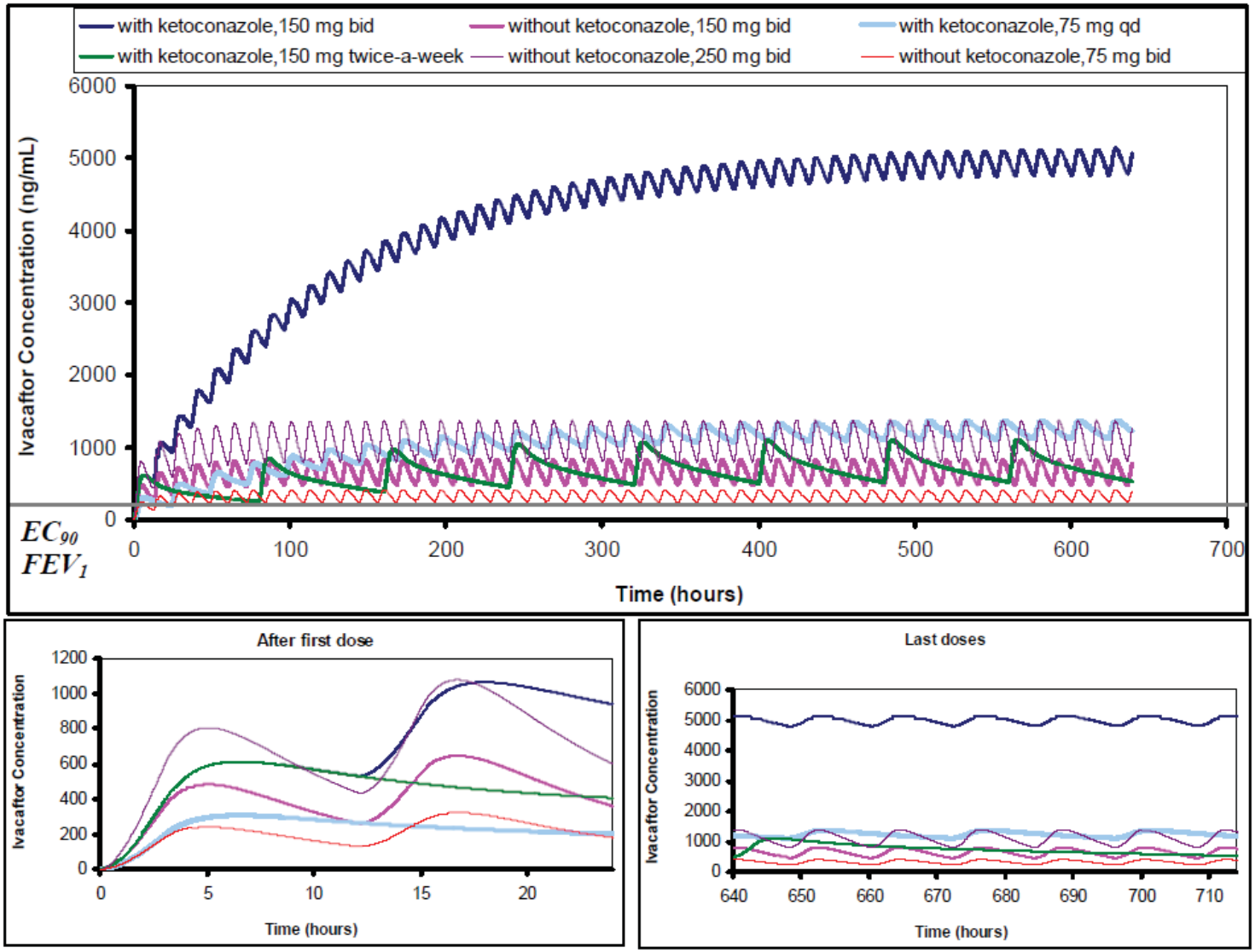


Figure 17: Simulations for different dosing scenarios with and without ketoconazole

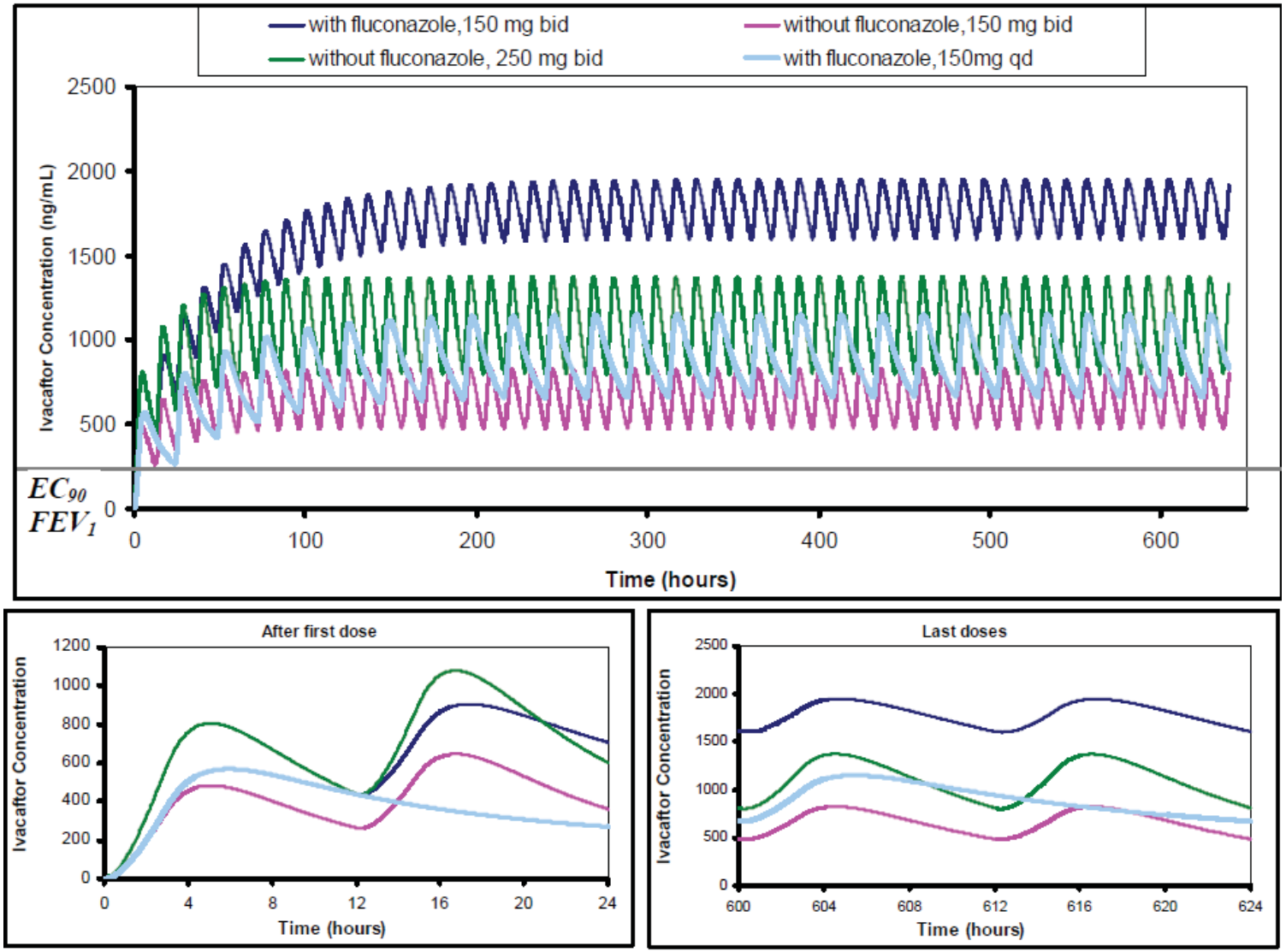


Figure 18: Simulations for different dosing scenarios with and without fluconazole

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

The label does not specify administration of ivacaftor with any particular drug.

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

Based on data from Phase 3 trials 102 and 103, the most commonly prescribed comedications were: azithromycin, ciprofloxacin, tobramycin, omeprazole, salbutamol, fluticasone, Vit K, Vit D, ascorbic acid, pancrelipase, ibuprofen, colecalciferol, paramecatol.

2.8 General Biopharmaceutics

The formulations used in different in vivo clinical studies are listed in Table 24.

Table 24: Formulations of ivacaftor used in clinical studies

Clinical Study Number (Abbreviated)[a]			Formulation Description (Abbreviated)	Formulation Description
Phase 1	Phase 2	Phase 3		
001, 002[b], 003				(b) (4)
002[b], 005, 006, 007[c] 809-005	101		(b) (4)	25-mg or 50-mg tablet (b) (4) (b) (4)
007[c]			(b) (4) tablet (b) (4) ablet	T1: 150-mg tablet (b) (4) (b) (4)
				T2: 150-mg tablet (b) (4) (b) (4)
		102[d], 103[e]	Film-coated tablet	Film-coated 100-mg or 150-mg tablet, (b) (4) (b) (4)
008, 009, 010, 011, 012, 013	104	102[d], 103[e], 105	Waxed, film-coated tablet (Intended Commercial Tablet)	Waxed, film coated 150-mg tablet (b) (4) (b) (4)
004[f]				(b) (4)
				(b) (4)

[a]Study numbers are abbreviated as specified to last 3 digits
[b]Study 002 was a comparative bioavailability study comparing (b) (4) tablets (b) (4)
[c]Study 007 was a comparative bioavailability study comparing (b) (4) (b) (4) tablets.
[d]Some subjects in Study 102 received both film-coated and waxed, film-coated 150-mg tablets.
[e]Subjects in Part A of Study 103 received film-coated 100 mg tablets, and subjects in Part B of Study 103 received waxed, film-coated 150-mg tablets.
[f]Study 004 was a taste profiling study

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?

There is not sufficient information on permeability to classify ivacaftor according to biopharmaceutic classification system (BCS). However, given that ivacaftor is insoluble is water, it would be either a BCS Class 2 (low solubility/high permeability) or Class 4 (low solubility/low permeability) drug.

In vitro experiments indicate to a possibly high permeability of ivacaftor in Caco-2 cell based assay; however, sponsors state that due to experimental limitations a definitive determination of permeability according to BCS criteria could not be made.

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

The intended to-be-marketed formulation is a waxed, film-coated tablet. Phase 3 studies used both the waxed and unwaxed film coated 150 mg ivacaftor tablets. The only difference between waxed and unwaxed tablets (b) (4) These changes are not expected to impact the dissolution or relative bioavailability of tablet formulation.

In initial clinical studies, (b) (4) formulation was used and in the subsequent study a tablet formulation with (b) (4) was used. Bioavailability study 002 found a higher relative bioavailability (72% higher C_{max} and 57% higher AUC) for (b) (4) compared to (b) (4) formulation. However, bioavailability of (b) (4) formulation was almost double following administration with food which was considered comparable to (b) (4) see section 2.8.3, Table 24). Subsequently tablet formulations (b) (4) DL (b) (4) and (b) (4) DL (b) (4) were developed. Bioavailability study 007, demonstrated that tablet formulation (b) (4) DL (b) (4) was bioequivalent to the (b) (4) tablet formulation (b) (4) (b) (4)

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

Coadministration with food significantly affected the exposures of ivacaftor for all formulations used during clinical program (Table 25). Coadministration with food increased AUC by approximately 2-3 fold and Cmax by 2-4 fold. Phase 2 (# 101 and 104) and Pivotal Phase 3 studies (# 102, 103, and 105) were conducted with ivacaftor following diet appropriate for CF patients, and the label also recommends taking ivacaftor with fat-containing food.

Exposure of metabolite M1 and M6 also increased following coadministration with food. Geometric mean ratio (90% CI) for $AUC_{0-\infty}$ and C_{max} of M1, for comparison of (b) (4)

formulation in fed state vs. fasted state, were 2.06 (1.82, 2.33) and 1.58 (1.30, 1.91), respectively. Geometric mean ratio (90% CI) for $AUC_{0-\infty}$ and C_{max} of M6, for comparison of (b) (4) formulation in fed state vs. fasted state, were 1.86 (1.51, 2.29) and 1.59 (1.22, 2.06), respectively.

Table 25: Effect of food on bioavailability of different ivacaftor formulations tested during clinical development program

Trial	N	Test	Reference	Geometric mean ratio (90% CI)	
				$AUC_{0-\infty}$	C_{max}
002	18/18	(b) (4) tablet, food	(b) (4) tablet, fasted	2.06 (1.81, 2.34)	2.28 (1.85, 2.81)
007	36/36	(b) (4), food	(b) (4) fasted	2.55 (2.26, 2.87)	2.83 (2.14, 3.76)
		(b) (4), food	(b) (4), fasted	2.34 (1.85, 2.96)	2.38 (1.92, 2.94)
012	18/18	Film-coated, waxed tablet*, food	Film-coated, waxed tablet*, fasted	2.98 (2.56, 3.48)	3.89 (3.12, 4.86)

*intended final formulation

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?

Ivacaftor, and its metabolites M1 and M6, were measured in plasma and urine samples using the LC-MS/MS bioanalytical methods.

Ivacaftor, M1, and M6 analysis in plasma (VX-770-DMPK-VAL-033)

The method for analysis was based on a liquid-liquid extraction method using tertiary butyl-methyl ether (MTBE), chromatographic separation by reversed-phase high performance liquid chromatography using a 5.0 µm XTerra C18 column (2.1 x 50 mm), mobile phases consisting of 0.1% formic acid in water and 0.1% formic acid in acetonitrile, with appropriate internal standards, and detection by positive ion mode using a turbo ion spray (ESI+) interface with MS/MS detection. This method used a common internal standard for metabolites M1 and M6.

Ivacaftor, M1, and M6 analysis in plasma (b) (4)

The method VX-770-DMPK-VAL-033 was modified to have separate internal standards for metabolites M1 and M6.

Ivacaftor, M1, and M6 analysis in urine (b) (4)

This method was also based on a liquid-liquid extraction method using MTBE, chromatographic separation by reversed-phase high performance liquid chromatography using a 5.0 µm Sunfire C18 column (2.1 x 50 mm), mobile phases consisting of 0.1% formic acid in water and 0.1% formic acid in acetonitrile, with appropriate internal

standards, and detection by positive ion mode using a turbo ion spray (ESI+) interface with MS/MS detection.

2.9.2 Which metabolites have been selected for analysis and why?

Metabolite M1 and M6 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?

The bioanalytical methods used for the analysis of ivacaftor, M1, and M6 in different clinical studies are listed in Table 26. Brief description of methods for analysis of ivacaftor, M1, and M6 in plasma and urine (VX-770-DMPK-VAL-033, (b) (4) is provided in section 2.9.1. The remaining methods were used to measure only ivacaftor in plasma or urine.

Table 26: Bioanalytical method validation reports for ivacaftor, M1, M6, and other metabolites

Report Number Date of Report	Analyte/Matrix Linear Range (LR) of Quantitation	Clinical Study Identifier (Abbrev.)
Vertex C201 VX-770-DMPK-VAL-006 15Dec2006	Ivacaftor/Human Plasma 2 to 2000 ng/mL	001 and 002
(b) (4) 10Jan2008	Ivacaftor/Human Plasma 1 to 2000 ng/mL	003
Vertex C202 VX-770-DMPK-VAL-013 15Dec2006	Ivacaftor/Human Urine 1 to 1000 ng/mL	001
(b) (4) 10Jan2008	Ivacaftor/Human Urine 1 to 2000 ng/mL	003
Vertex E053 VX-770-DMPK-VAL-033 20May2009	Ivacaftor, M1, and M6/Human Plasma 2 to 2000 ng/mL	007, 101, 102, 103A, 103B, 104, 105, 106, 107, 012 and 809-005
(b) (4) 28Jan2009	Ivacaftor, M1, and M6/Human Plasma 2 to 2000 ng/mL	005, 006, 008, 009, 010, 011, and 013
(b) (4) 28Jan2009	Ivacaftor, M1, and M6/Human Urine 1 to 1000 ng/mL	006

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

The standard curve range or linear range of quantification for different methods used for analysis is shown in Table 26. Calibration curves were generated for peak area ratios

using a weighted ($1/x^2$) linear least-squares regression curve fitting method.

2.9.5.1 What are the lower and upper limits of quantitation?

The lower limit of quantitation (LOQ) for the method of quantitation for the analytes ivacaftor, M1, and M6 in plasma was 2 ng/mL and the upper limit of quantitation (ULQ) was 2000 ng/mL.

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

For the method used for analysis of ivacaftor, M1, and M6 in plasma, QC samples were tested at 6, 15, 100, 400, 1200, 1800 ng/mL concentrations. Inter-assay bias and imprecision was less than ±10% for ivacaftor, less than ±12% for M1 (also known as VRT-837018), and less than ±10% for M6 (also known as VRT-842917) based on tested QC concentrations.

Intra-assay bias and imprecision was less than ±10% for ivacaftor, ±12% for M1, and less than ±10% for M6 based on tested QC concentrations.

For dilution samples (concentration 10000 ng/mL), bias was within ±20% and imprecision was <20%.

These inter- and intra-assay accuracy and bias met the recommendations for bioanalytical methods by the FDA.

Selectivity was assessed with analysis of LLOQ samples from six different lots of blank plasma. These samples had mean accuracy of ±20% of the nominal value and the precision (%CV) was <15%, demonstrating the method was selective for the analytes of interest in the intended concentration range.

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

Results of stability testing for the method used for analysis of ivacaftor, M1, and M6 in plasma from method VX-770-DMPK-VAL-033 are as follows:

Bench-top stability (Room temperature):	6 hours
Freeze-thaw stability (-70°C):	3 cycles
Auto sampler stability (4°C):	13 days
Stock solution stability (-70°C):	1 year, 20 days[1] (VX-770)
	133 days[1] (VRT-837018)
	133 days[1] (VRT-842917)
Long term frozen stability (-70°C):	1 year[2] (VX-770)
	2 months[3] (VRT-837018)
	2 months[3] (VRT-842917)

VRT-837018 is also known as M1
VRT-837017 is also known as M6

Appendix 1
Berkeley Madonna code for simulations
The code below was used to simulate different dosing scenarios to determine the appropriate dose adjustments for special population (hepatic impairment) and drug-drug interaction cases (for coadministration with ketoconazole, fluconazole etc).

The typical parameter estimates from population PK analysis[3] were used to simulate the ivacaftor plasma concentration – time profile for an 18 year old, 70 kg, male CF subject, administered the (b) (4) tablet. The model which descried the PK of ivacaftor was a two compartmental model with a zero order infusion input in absorption phase. The parameter estimates (95% CI) were: apparent (oral) clearance (*CL/F*) - 19.0 (17.5, 20.5) L/h, apparent (oral) central volume of distribution (*Vc /F*) - 186 (170, 202) L, apparent (oral) peripheral volume of distribution (*Vp/F*) - 118 (100, 136) L, apparent (oral) intercompartmental clearance (*Q/F*) - 9.38 (6.17, 12.6) L/h, zero-order dose duration (D1) - 2.99 (2.85, 3.13) h, and absorption rate constant (*ka*) - 0.546 (0.456, 0.636) h^{-1}.

The fold change in clearance from actual studies (i.e., for example for coadministration with rifampin clearance increased from 19.6 L/hr to 170 L/hr, which is by ~8.5 fold) was used to simulate ivacaftor plasma concentration – time profile for those situations; only CL/F was changed and other parameters were kept unchanged. Under these altered CL/F conditions, different dose regimens, such as 150 mg qd, 75 mg q12h, 75 mg qd, were simulated to find a suitable dosing regimen.

(b) (4)

[3] Report number g198. "Population pharmacokinetics and pharmacodynamics of VX-770 in subjects with cystic fibrosis". NDA 203188

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Appendix 2

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 Summary of Findings

1.1 Key Review Questions

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

1.1.1 Is the proposed dose and dosing regimen of VX-770 (150 mg every 12 hours) acceptable?

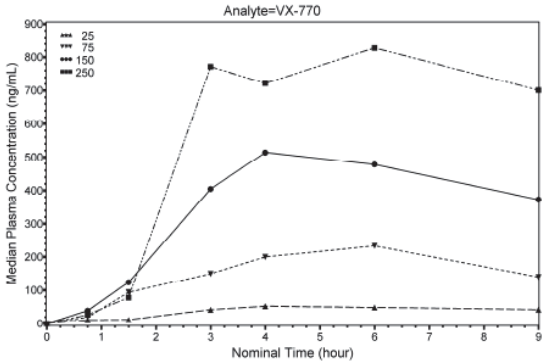
Yes, the proposed dose and dosing regimen of VX-770 (150 mg every 12 hours) in patients (6 years and older) is acceptable, if the treatment effects (benefit/risk) are clinically acceptable. The basis for dose/dosing regimen selection and findings from registration trials is discussed below.

Dose/Dosing regimen selection in adults (age>18 years)

The selection of 150 mg every 12 hours in registration trials is based on findings from in vitro studies and dose-finding study (vx06-770-101) in patients (age>18 years).
The effective concentration range of 60 to 400 μg/L was shown to potentiate the CFTR channel in vitro. In the dose finding study, 75-mg q12h dose was chosen as the most likely dose to achieve an optimal pharmacologic effect with the 25-mg q12h dose being just high enough to induce some increase in chloride conductance and the 150-mg q12h dose within a safe range but potentially supra-maximal with respect to CFTR potentiation.

Figure 19 shows the time course of VX-770 plasma concentrations on Day 1 in dose finding study and parameters describing the time course of VX-770 plasma concentrations using NONMEM® software.

Figure 19. Median VX-770 Plasma Concentrations on Day 1. VX-770 Population PK Model Fixed Effects Parameter Estimates

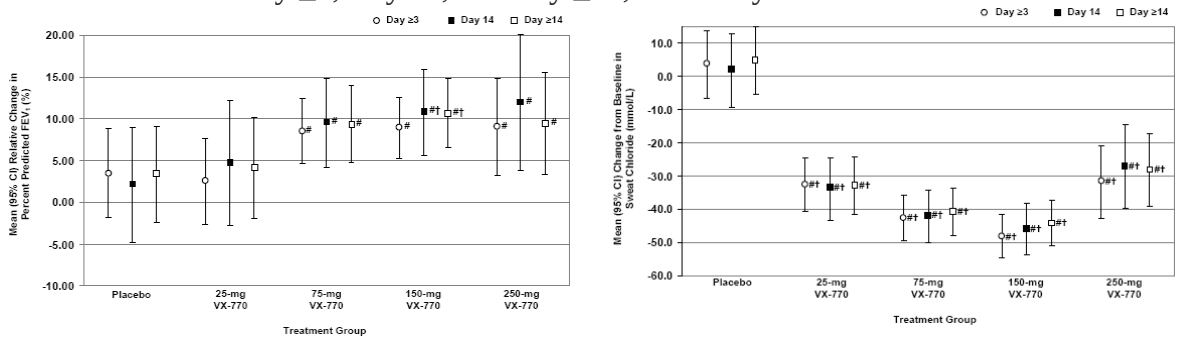


Model Parameters	Parameter Description	Units	Estimate	Standard Error	%SEM
θ_1	Clearance (CL)	L/hr	15.1	1.79	11.9
θ_2	Volume of Distribution (V)	L	219	17.2	7.9
θ_3	First order absorption rate constant (k_a)	hr^{-1}	0.487	0.0801	16.4
θ_4	Lag time in absorption	hr	0.649	0.0173	2.7
θ_5	Power of relative bioavailability F as a function of dose/150	-	0.194	0.042	21.6
θ_6	Allometric coefficient of CL (power of CL as a function of weight/60)	-	0.772	0.576	74.6
θ_7	Allometric coefficient of V (power of V as a function of weight/60)	-	1.33	0.353	26.5

Source: Figure 11-1 on page 97, Table 11-1 on page 104 from vx06-770-101-csr-body.pdf
Figure 20 shows the relationship between dose and changes in efficacy measures (percent

predicted FEV1, sweat chloride). The data suggest that 150 mg every 12h is the optimal dose.

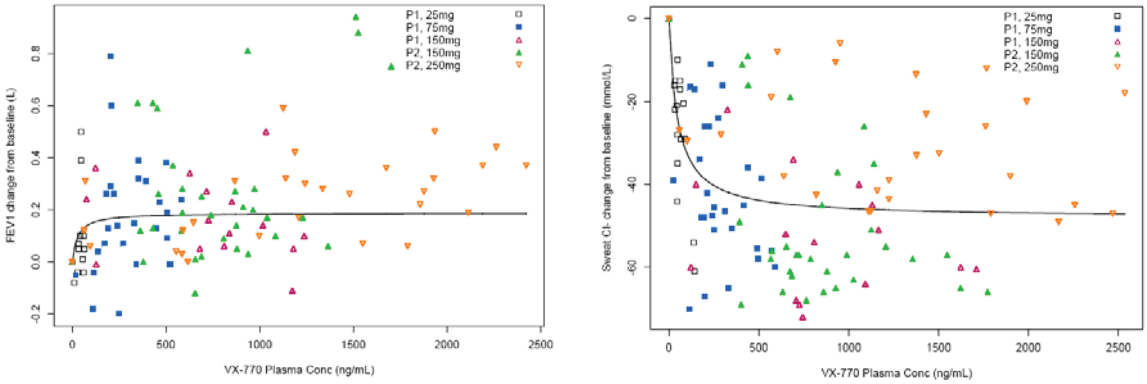
Figure 20. Mean (95% CI) Change from Baseline in percent predicted FEV1(%), Maximum Sweat Chloride for Day ≥3, Day 14, and Day ≥14, Full analysis dataset.



Source: Figure 11-6 on page 108, Figure 11-8 on page 128 from vx06-770-101-csr-body.pdf

The relationship between VX-770 concentrations and changes in FEV1, sweat chloride were analyzed as shown in Figure 21.

Figure 21. Study 101: Predicted Population Mean and Observed FEV1, Sweat Chloride Change From Baseline Versus VX-770 Exposure

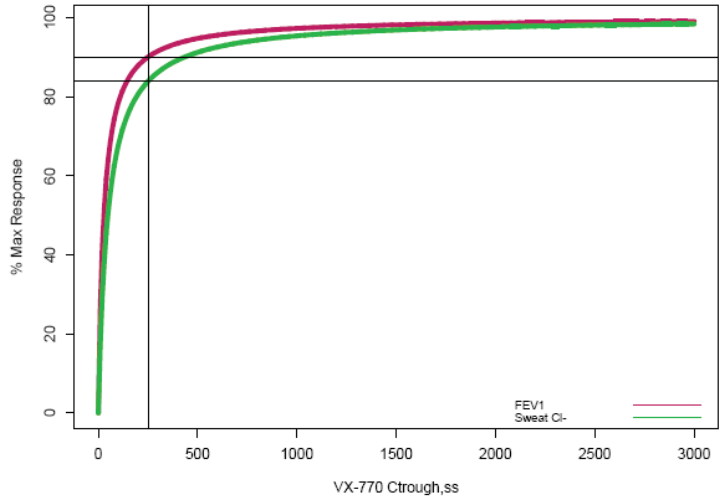


Source: Figure 7-1 on page 8, Figure 7-2 on page 9 from h171.pdf

The sponsor evaluated the relationship between VX-770 concentrations and changes in FEV1, sweat chloride by including or excluding data from 250 mg dose group. The estimated maximum effect (as change from baseline) and EC_{50} values were 0.19 L and 28 ng/mL for FEV_1, and -48 mmol/L and 48 ng/mL for sweat chloride.

The doses for Study 102 (12 years and older patients) and Study 103 Part A (6-11 year old patients) were selected on the expectation that they would provide an average (in terms of median) VX-770 $C_{min,ss}$ of at least the predicted EC_{90} for FEV_1 (250 ng/mL, corresponding to the predicted EC_{84} for sweat chloride as shown in Figure 22).

Figure 22. Study 101: Simulated Exposure-Response Curves for FEV_1 (L) and Sweat Chloride (mmol/L)



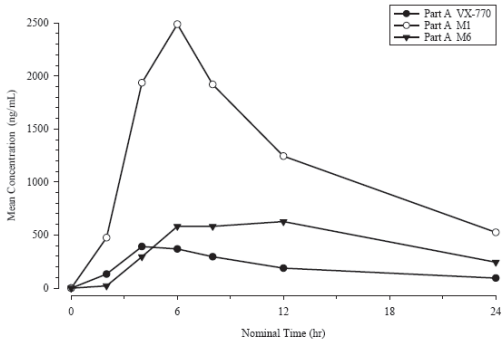
Source: Figure 7-3 on page 10 from h171.pdf

Dose/Dosing regimen selection in pediatrics

Age: 6-11 years

Based on PK/PD modeling and simulations using data from Studies 101 and 007, the VX-770 dose selected for Study 103 Part A (lead-in PK, subjects aged 6 to 11 years) was 100 mg as a single dose. Mean plasma concentration-time profiles of VX-770, M1, and M6 after a single oral dose administration of 100 mg in subjects 6 to 11 years of age are presented in Figure 23.

Figure 23. Part A: Mean Concentration-Time Profiles of VX-770, M1, and M6 Following a Single Dose of VX-770 100 mg in Subjects 6 to 11 years of age.



	VX-770
N	10
C_{max} (ng/mL), mean ± SD	434 ± 118
t_{max} [a] (h), mean ± SD	4.04 (1.93;11.88)
$AUC_{0-\infty}$ (h•ng/mL), mean ± SD	4740 ± 1380 [b]
$t_{1/2\lambda z}$ (h), mean ± SD	6.56 ± 1.40 [b]
CL/F (L/h), mean ± SD	23.0 ± 7.59

Source: Figure 11-1 on page 130, Table 11-6 on page 131 from vx06-770-103-csr-body.pdf

To determine or confirm the dose for Part B of Study 103, preliminary nonlinear mixed effects modeling was performed on the pooled PK data of VX-770 as a new film-coated tablet formulation from Part A of Study 103 (a single oral dose of VX-770 100 mg in subjects aged 6 to 11 years with CF following a standard high-fat high-calorie CF breakfast) and treatment T1F in Study 007 (a single oral dose of VX-770 150 mg in healthy adult subjects in the fed state). A 2-compartment linear PK model with lag time

in absorption appeared to be the best structural model for the data. Allometric scaling based on body weight was included on clearances and volumes. The allometric coefficients for clearances and volumes were estimated to be 0.384 and 0.796, respectively. These values were subsequently used in the simulations to determine the dose for Part B of Study 103. The simulations indicated that, at 100 mg q12h, the projected steady-state concentration of VX-770 in these subjects would be lower than expected; thus, an upward adjustment of the dose for Part B was necessary. A dose regimen of 150 mg q12h would be needed to achieve an average steady-state VX-770 trough concentration of at least the estimated concentration at which effect is at 90% of the maximum (EC_{90}).

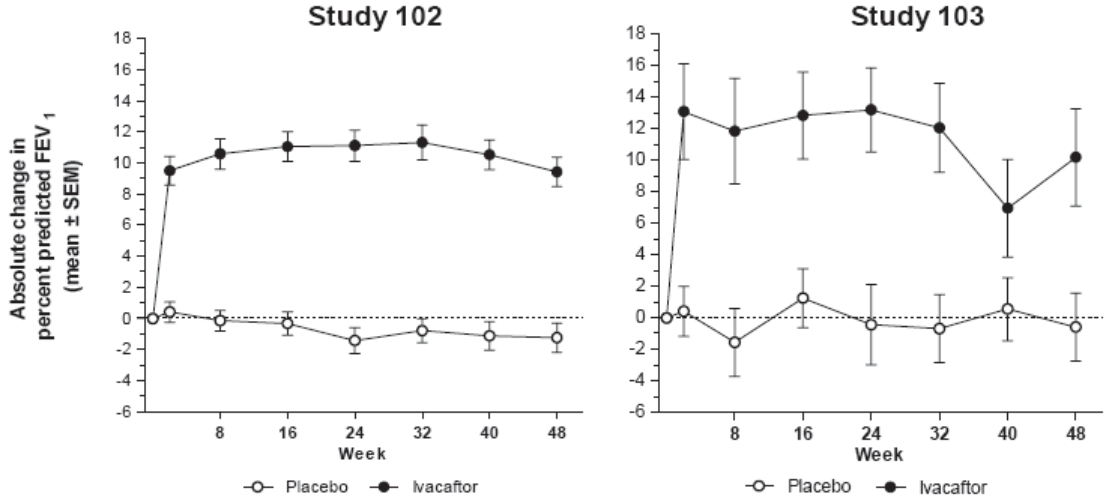
Age: 12-18 years

Based on PK/PD modeling and simulations using data from Studies 101 and 007, the VX-770 dose selected for Study 102 (subjects aged 12 years and older) was 150 mg q12h.

Changes in FEV1 in registration trials

The clinical benefit of ivacaftor in subjects with CF who have the G551D mutation in the *CFTR* gene was demonstrated for subjects age 12 years and older in Study 102 and for subjects age 6 to 11 years in Study 103. In both studies the primary endpoint was absolute change in percent predicted FEV_1 through Week 24 (Figure 24).

Figure 24. Absolute Change in Percent Predicted FEV_1 From Baseline Through Week 48 in Studies 102 and 103.



Source: Figure 6 on page 34 from clinical-overview.pdf

1.1.2 Are the proposed labeling statements based on population pharmacokinetic analysis acceptable?

The following labeling statements are derived based on population pharmacokinetic analysis.

Section 12.3 Pharmacokinetics

(b) (4)

(b) (4)

Special populations

Gender

The effect of gender on KALYDECO pharmacokinetics was evaluated using population pharmacokinetics of data from clinical studies of KALYDECO. No dose adjustments are necessary based on gender.

Reviewer's comments: The labeling statements regarding gender effects are acceptable.

1.2 Recommendations

NA

1.3 Label Statements

NA

2 PERTINENT REGULATORY BACKGROUND

VX-770 is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the *CFTR* gene. The recommended dose of KALYDECO for both adults and pediatric patients age 6 years and older is 150 mg taken orally every 12 hours (300 mg total daily dose) with fat-containing food. The proposed dose and dosing regimen is based on exposure-response analysis of dose finding study (vx06-770-101). The dose, identified based on exposure-response analysis, was further evaluated in 2 registration trials (Study 102 in patients 12 years and older; Study 103 in patients 6-11 years).

3 RESULTS OF SPONSOR'S ANALYSIS

Population pharmacokinetic-pharmacodynamic analysis was conducted by the sponsor using data from the following studies:

Study Number VX06-770-002: A Bioavailability and Food Effect Study of a Tablet Formulation of VX-770 Relative to a Solution Formulation of VX-770 in HealthyMale Subjects

Study Number VX08-770-007: A Phase 1, Randomized, Open-Label Study to Evaluate the Bioavailability and Food Effect of 2 New Tablet Formulations of VX-770 Relative to a VX06-770-101 Tablet Formulation in HealthyMale Subjects

Study Number VX09-770-010: An Open-Label Phase 1 Study to Examine the Effect of VX-770 onMidazolam and Rosiglitazone and the Effect of Fluconazole on VX-770 in Healthy Subjects

Study Number VX06-770-101: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study of VX-770 to Evaluate Safety, Pharmacokinetics, and Biomarkers of CFTR Activity in Cystic Fibrosis (CF) Subjects with Genotype G551D

Study Number VX08-770-102: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-770 in Subjects with Cystic Fibrosis and the G551D Mutation

Study Number VX08-770-103: A Phase 3, 2-Part, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Pharmacokinetics, Efficacy and Safety of VX-770 in Subjects Aged 6 to 11 Years with Cystic Fibrosis and the G551Dmutation

Study Number VX08-770-104: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel- Group Study to Evaluate the Safety and Efficacy of VX-770 in Subjects Aged 12 Years and OlderWith Cystic Fibrosis who are Homozygous for the F508del-*CFTR*Mutation

Table 27 and Table 28 summarize the continuous and categorical covariates in the population pharmacokinetic dataset.

Table 27. Continuous Covariate Summary for All Subjects in the VX-770 Population PK Dataset

	Covariate	N	Mean	Range
All Studies	Baseline Weight (kg)	315	60.3 ± 17.5	18.7–107
	Age (y)	315	24.8 ± 11.5	6–53
	Baseline AST (U/L)	315	26.2 ± 10.2	11–87
	Baseline ALT (U/L)	315	27.2 ± 15.6	7–167
	Baseline CRCL (mL/min)	315	119 ± 23.1	56.6–150
002	Baseline Weight (kg)	18	80.5 ± 7.37	68.2–89.1
	Age (y)	18	33.3 ± 10.7	20–53
	Baseline AST (U/L)	18	24.1 ± 6.23	15–41
	Baseline ALT (U/L)	18	21.9 ± 7.42	9–43
	Baseline CRCL (mL/min)	18	123 ± 13.2	101–150
007	Baseline Weight (kg)	17	80.8 ± 7.52	66.6–91.6
	Age (y)	17	33.6 ± 9.83	20–48
	Baseline AST (U/L)	17	26.1 ± 5.87	21–41
	Baseline ALT (U/L)	17	22.7 ± 7.78	9–39
	Baseline CRCL (mL/min)	17	118 ± 21.2	86.2–150
010	Baseline Weight (kg)	24	72.5 ± 13.3	50.4–97.6
	Age (y)	24	35.8 ± 8.34	22–52
	Baseline AST (U/L)	24	20 ± 4.12	12–28
	Baseline ALT (U/L)	24	20.3 ± 7.56	9–36
	Baseline CRCL (mL/min)	24	128 ± 19	87–150
101	Baseline Weight (kg)	31	63.4 ± 12.5	46.9–86.6
	Age (y)	31	28.2 ± 9.44	18–51
	Baseline AST (U/L)	31	23.3 ± 7.34	13–39
	Baseline ALT (U/L)	31	26.3 ± 12.7	7–60
	Baseline CRCL (mL/min)	31	104 ± 24.4	59.8–150
102	Baseline Weight (kg)	80	61.4 ± 14.5	30.2–107
	Age (y)	80	25.8 ± 9.5	12–53
	Baseline AST (U/L)	80	23.6 ± 7.26	11–54
	Baseline ALT (U/L)	80	24.7 ± 13.5	9–69
	Baseline CRCL (mL/min)	80	121 ± 22.2	83–150
103	Baseline Weight (kg)	33	31.7 ± 9.27	18.7–62
	Age (y)	33	8.88 ± 2.01	6–12
	Baseline AST (U/L)	33	30.8 ± 6.61	21–51
	Baseline ALT (U/L)	33	25.4 ± 10.2	14–68
	Baseline CRCL (mL/min)	33	112 ± 23.8	75.1–150
104	Baseline Weight (kg)	112	58.2 ± 13.5	35.1–99.8
	Age (y)	112	22.8 ± 10.2	12–52
	Baseline AST (U/L)	112	29.1 ± 13.6	11–87
	Baseline ALT (U/L)	112	32.8 ± 20.1	13–167
	Baseline CRCL (mL/min)	112	121 ± 23.9	56.6–150

Source: Table 3 on page 51 from g198.pdf

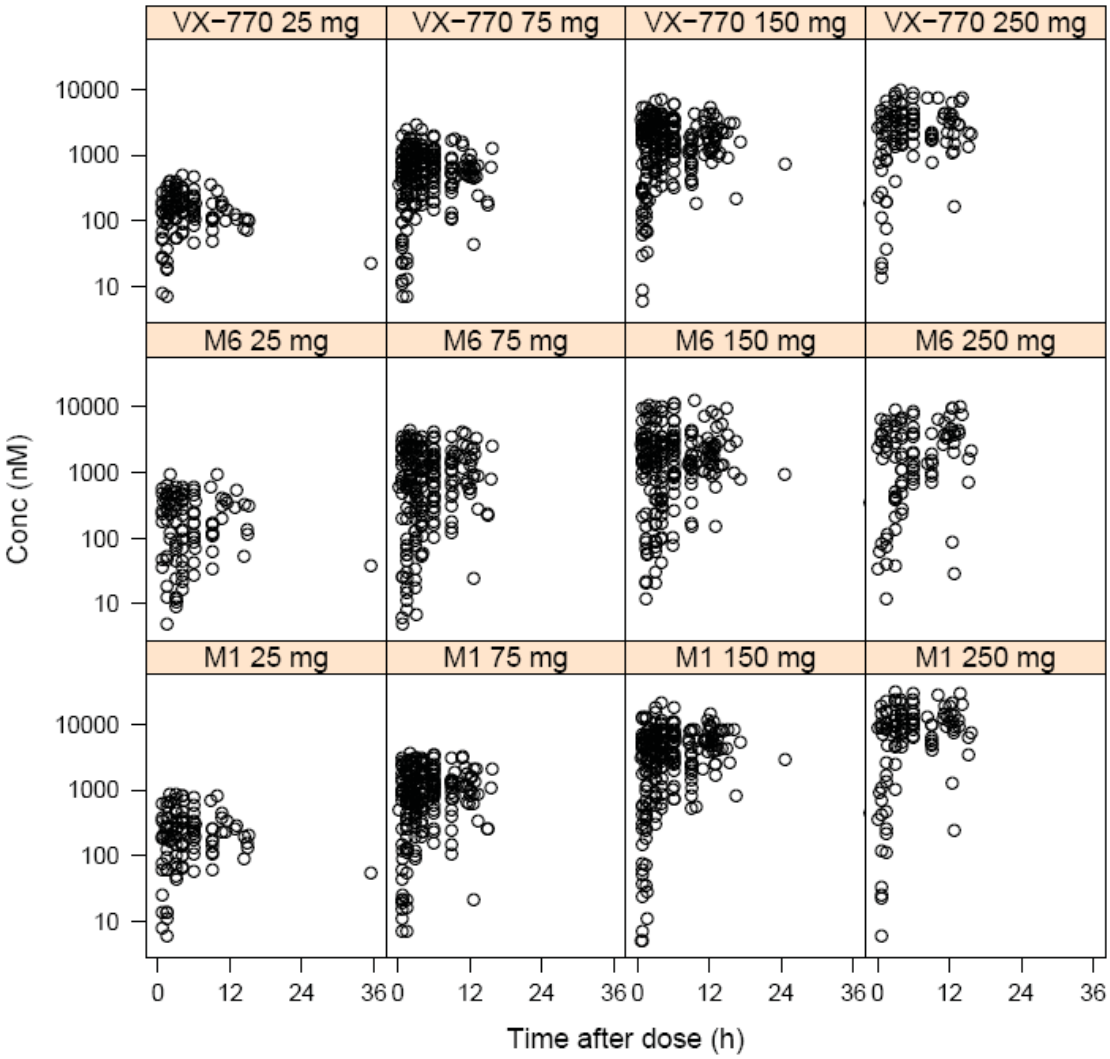
Table 28. Categorical Covariate Summary for All Subjects in the VX-770 Population PK Dataset

	All	Study 002	Study 007	Study 010	Study 101	Study 102	Study 103	Study 104
Gender								
Female	144	0	0	9	17	43	21	54
Male	171	18	17	15	14	47	12	58
Race								
Caucasian	291	15	10	17	31	78	29	111
African American	15	2	7	5	0	0	0	1
Asian	3	1	0	2	0	0	0	0
Unknown	6	0	0	0	0	2	4	0
Formulation								
SDD	49	18	0	0	31	0	0	0
$80\%DL-SDD$	266	0	17	24	0	80	33	112
Subject Status								
Healthy	59	18	17	24	0	0	0	0
CF	256	0	0	0	31	80	33	112
AST > 40 U/L								
<= 40 U/L	292	17	16	24	31	77	31	96
>40 U/L	23	1	1	0	0	3	2	16
ALT > 40 U/L								
<= 40 U/L	277	17	17	24	27	70	91	0
>40 U/L	38	1	0	0	4	10	2	21

Source: Table 4 on page 54 from g198.pdf

Figure 25 shows the time course of plasma concentrations of VX-770 and its metabolites in study 101 (VX06-770-101).

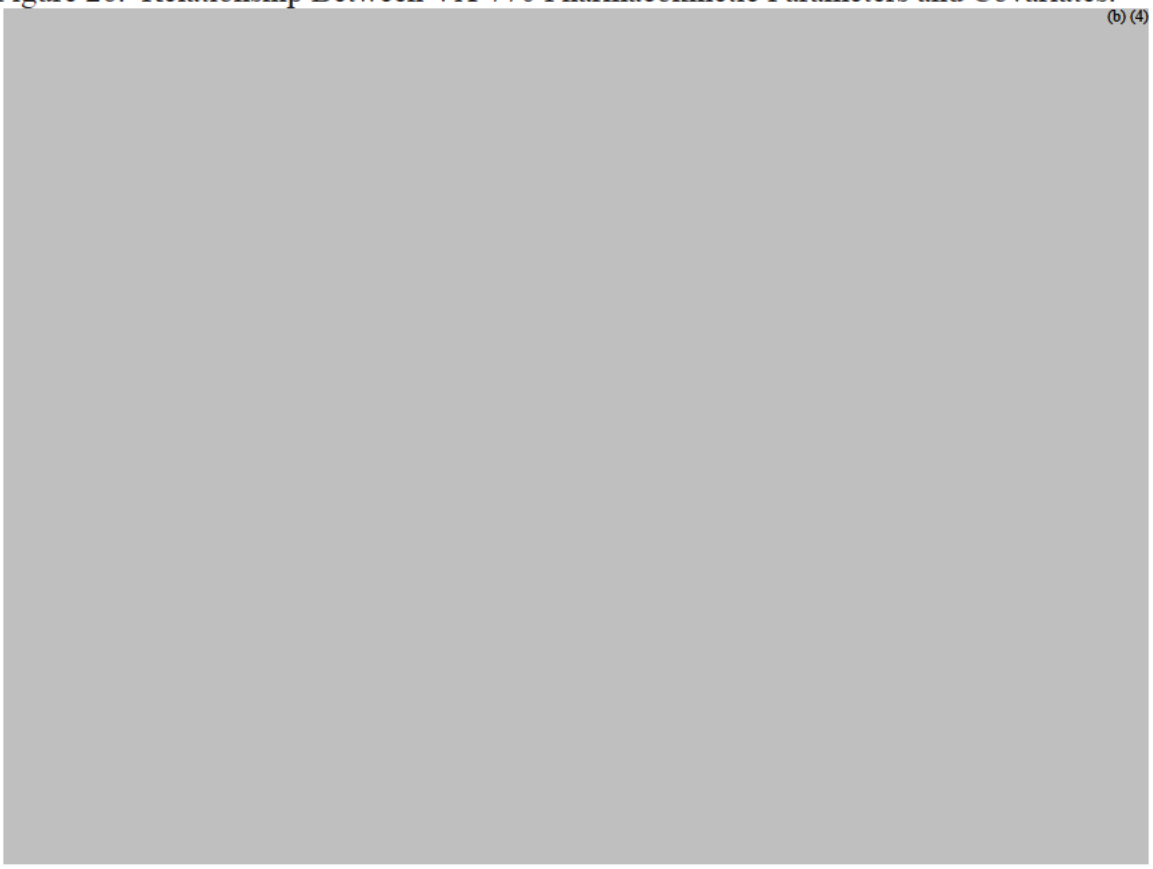
Figure 25. Plasma Concentrations of VX-770 and its Metabolites (M1, M6) in Study 101.



Source: Figure 8 on page 90 from g198.pdf

A two-compartment model with zero-order delivery to the absorption compartment and subsequent first order absorption was chosen as the VX-770 base structural model. The pharmacokinetic parameters are shown in Figure 26.

Figure 26. Relationship Between VX-770 Pharmacokinetic Parameters and Covariates.



Source: Equation 6 on page 31 from g198.pdf

The estimates of parameters based on the population pharmacokinetic analysis are shown in Table 29.

Table 29. Parameter Estimates from the VX-770 Full Population Pharmacokinetic Model (Run 200). The reference subject is 70 kg, male, 18 years, administered the [redacted] (b) (4) tablet, and CF subject.

	Point Estimate	%RSE	95% CI	IIV	IOV
CL/F	19.0 (L/h)	3.97	(17.3, 20.7)	39.4 (CV%)	
Vc/F	186 (L)	4.34	(170, 200)		
Vp/F	118 (L)	7.75	(77.2, 187)		
Q/F	9.38 (L/h)	17.5	(5.48, 13.0)		
$D1$	2.99 (h)	2.40	(2.88, 3.11)		
k_a	0.546 (h^{-1})	8.42	(0.484, 0.611)	59.9 (CV%	98.8 $(CV\%)$
$F1$	1	$Fixed$			46.8 $(CV\%)$
Inter-individual Variance					
$\omega^2_{CL/F}$	0.155	10.5	(0.125, 0.192)		
ω^2_{ka}	0.359	25.8	(0.219, 0.548)		
Inter-occasion Variance					
ω^2_{F1}	0.219	4.89	(0.163, 0.271)		
ω^2_{ka}	0.976	11.1	(0.769, 1.18)		
Residual Variance					
σ^2_{prop}	0.0311	2.50	(0.0243, 0.0409)		
σ^2_{add}	11500	4.12	(6442, 16933)		
Prop. Error CV	17.6 (CV%)				
Add. Error SD	107 (nM)				

$\%RSE$ = percent relative standard error of the parameter estimate, CL/F = apparent oral clearance, Vc/F = apparent volume of distribution in the central compartment, Vp/F = apparent volume of distribution in the peripheral compartment, Q/F = apparent inter-compartmental clearance, k_a = first-order absorption rate, $D1$ = zero-order absorption duration, $F1$ = bioavailability, ω^2 = between-individual or inter-occasion variance, σ^2_{prop} = proportional residual variance, σ^2_{add} = additive residual variance

Source: Table 6 on page 56 from g198.pdf

Figure 27 shows the relationship between population predicted, individual predicted versus observed VX-770 concentrations. If the model fits the data reasonably well, the predicted concentrations will be equally distributed along the line of identity.

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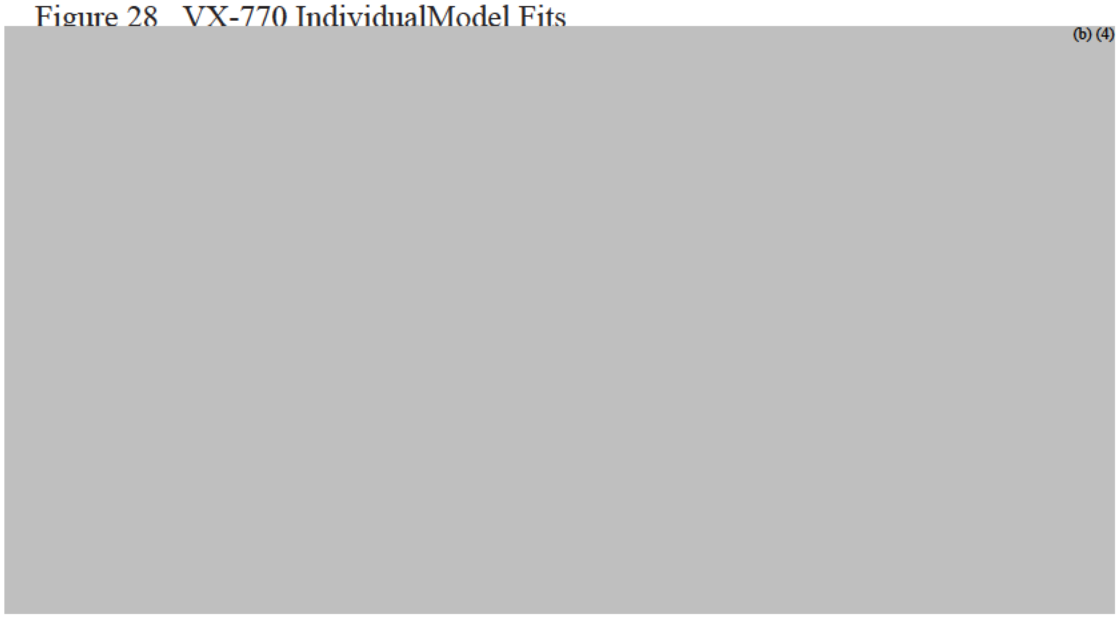
Figure 28 VX-770 IndividualModel Fits



Conclusions based on population pharmacokinetic analysis

1. Absorption was highly variable both between and within subjects.
2. The PK model of VX-770 demonstrated that weight was the major influence on the *CL/F*. *CL/F* did not differ between females and males nor was there a difference between CF subjects and healthy subjects (Table 30).
3. PK parameters from subjects with G551D and F508del did not differ. No firm conclusions could be reached regarding age as the outcome parameters were poorly defined.

Table 30. Covariate Parameter Estimates from the VX-770 Full Population PharmacokineticModel (Run 200). The reference subject is 70 kg, male, 18 years, administered the (b) (4) tablet, and CF subject.

Parameter	Covariate	Estimate	%RSE	95% CI
CL/F	$Gender$	1.03	9.13	(0.920, 1.14)
CL/F	Age	−0.114	46.9	(−0.219, 0.0105)
CL/F	$Healthy$	1.03	9.13	(0.846, 1.21)
$F1$	$Formulation$	1.03	4.84	(0.932, 1.13)

$\%RSE$ = percent relative standard error of the parameter estimate, CL/F = apparent oral clearance, $F1$ = bioavailability

4. A secondary covariate analysis of the effect of CrCL on VX-770 and its metabolites was conducted. No effect was expected nor detected. However most subjects in the analysis datasets had CrCL greater than 80 mL/min.
5. Exploratory analysis was performed to evaluate the effects of concomitant medications on the PK of VX-770. The magnitude of changes in *CL/F* was at most 20% and thus not clinically important. Caution is warranted when interpreting these results, since these studies were not designed to evaluate the effects of concomitant medications.

Reviewer's Comments: The sponsor's analysis methodology is acceptable. The

pharmacokinetic model submitted by the sponsor was run using NONMEM® (Ver 7.1.2) to confirm labeling statements. The proposed labeling statements regarding gender effects are acceptable.

4 REVIEWER'S ANALYSIS

NA

4.1 Introduction

Sponsor proposed a labeling statement regarding influence of gender on ivacaftor pharmacokinetics using nonlinear mixed effects analysis.

4.2 Objectives

Analysis objectives are:
To confirm sponsor's proposed labeling statements regarding gender effects.

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 31.

Table 31. Analysis Data Sets

Study Number	Name	Link to EDR
G198.pdf	Population Pharmacokinetics and Pharmacodynamics of VX-770 in Subjects with Cystic Fibrosis	

4.3.2 Software

NONMEM (Ver 7)

4.3.3 Models

Sponsor's PK model without interoccasion variability was used for analysis.

4.4 Results

The results from reviewer's analysis are similar to sponsor's analysis.
Reviewer's analysis findings:
Females had a similar *CL/F* when compared to males, with a point estimate of 1.07 (95%CI: 0.94-1.19).
Sponsor's analysis findings
Females had a similar *CL/F* when compared to males, with a point estimate of 1.03 (0.920, 1.14).

The labeling statement, as proposed by sponsor, regarding gender effects on ivacaftor pharmacokinetics are acceptable.

5 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
sponsormodel_noiov_foceint_sig2.ctl	PK model used by reviewer	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Ivacaftor_NDA203188_VAB\PPK Analyses
sponsormodel_noiov_foceint_sig2.lst	Output file	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Ivacaftor_NDA203188_VAB\PPK Analyses\sponsormodel_noiov_foceint_sig2 nm7

Appendix 3

OFFICE OF CLINICAL PHARMACOLOGY

GENOMICS GROUP REVIEW

NDA Number	203188
Submission Date	27 July 2011
Drug Name	Ivacaftor
Applicant	Vertex Pharmaceuticals
Primary Reviewer	Hobart L. Rogers, Pharm.D., Ph.D.
Secondary Reviewer	Michael Pacanowski, Pharm.D., M.P.H.

Executive Summary

Ivacaftor is a new molecular entity for the treatment of cystic fibrosis (CF) in subjects who carry at least one copy of the *CFTR* G551D allele. Patients with gating mutations other than G551D were not enrolled in Phase 3 trials. The purpose of this review is to evaluate variability in ivacaftor response across different *CFTR* mutation types (e.g., gating, trafficking vs. conductance) to determine whether ivacaftor is effective in patients who carry non-G551D gating mutations, or other non-gating mutations. In two Phase 3 trials, ivacaftor significantly increased FEV1 and decreased sweat chloride in patients with the G551D mutation; no effect over placebo was observed in a Phase 2 trial in patients with F508del. Few subjects in Phase 3 trials were heterozygous for mutations other than F508del, and only one subject was homozygous for gating mutations. Overall, the second mutation did not appear to contribute significantly to response variability in terms of spirometry or changes in sweat chloride suggesting that the main effect is driven by G551D. A relationship between *in vitro* chloride conductance responses to ivacaftor and these clinical response endpoints could not be established to support activity in other mutation types. Taken together, while *in vitro* data suggest that subjects with other gating alleles might benefit from ivacaftor, insufficient data are available to support a clinical effect in patients with gating mutations other than G551D, or other non-gating mutations.

1 Background

Cystic Fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that result in loss of chloride ion transport at epithelial cell membranes. Over 1800 mutations in *CFTR* are known (PMIDs: 19359498, 2475911). CF mutations are generally classified as follows (American College of Medical Genetics; PMID: 12973375): Class I – failure to synthesize full length CFTR, or "defective synthesis"; Class II – CFTR misfolding and reduced delivery, or "trafficking",

of CFTR to the cell surface; Class III – defects in chloride ion channel conduction, or "gating"; Class IV – reduced ability of chloride to pass through the CFTR, or "conductance"; and Class V – reduced CFTR mRNA expression and correctly spliced transcripts, or "reduced synthesis".[4] In the U.S., approximately 95% of CF patients have mutations that affect CFTR trafficking to the cell membrane, while the remaining 5% of patients have mutations that affect CFTR gating. The most common mutation resulting in CF is the F508del trafficking mutation, which is present in approximately 90% of all CF patients. The most common gating mutation is G551D, which makes up around 4% of the CF patient population. Other gating mutations account for less than 1% of the CF patient population.

Ivacaftor is a CFTR potentiator developed for the treatment of CF in patients with at least one copy of the G551D gating mutation because of its purported effect of increasing chloride conductance through the CFTR. Ivacaftor effectively improved FEV1, sweat chloride, weight, and other patient reported outcomes compared to placebo in patients with the G551D mutation. Patients with other gating mutations were not enrolled in Phase 3 clinical trials of ivacaftor; ivacaftor was not effective in a Phase 2 clinical trial of patients with the F508del mutation.

Ivacaftor is to be indicated only for patients who carry the G551D gating mutation. Since so few patients with other gating mutations are available for clinical trials, the purpose of this review is to evaluate whether the indication should be expanded to all non-gating mutations by 1) evaluating the efficacy of ivacaftor on clinical and pharmacodynamic endpoints in patients with various *CFTR* genotypes, particularly those with two gating mutations, based on response variability according to the second mutated allele, and 2) assessing whether *in vitro* ivacaftor response phenotypes translate to clinical ivacaftor responses.

2 Submission Contents Related to Genomics

Ivacaftor safety and efficacy was evaluated in one Phase 2 trial (104) and two Phase 3 trials (102 and 103). *CFTR* genotype was determined in all subjects. Trials 102 and 103 required that subjects carry at least one copy of the G551D allele. Trial 104 required that subjects were homozygous for the F508del mutation. All of the trials were randomized, double-blind, placebo-controlled, parallel group trials, as shown below. The primary endpoint was the absolute change from baseline in percent predicted FEV1 through week 24. Key secondary endpoints were the change in sweat chloride, weight and CFQR scores.

[4] Throughout this document, the functional categorization will be used rather than the mutational class.

Table 32: Summary of Phase 2 and 3 Trials

Trial	Phase	Mutations Included	Sample Size		Primary Endpoint
			Placebo	Ivacaftor	
102	3	At least one copy of G551D	78	83	Absolute change in percent predicted FEV1 at 24 weeks
103	3	At least one copy of G551D	26	26	Absolute change in percent predicted FEV1 at 24 weeks
104	2	Homozygous for F508DEL	28	112	Absolute change in percent predicted FEV1 at 16 weeks

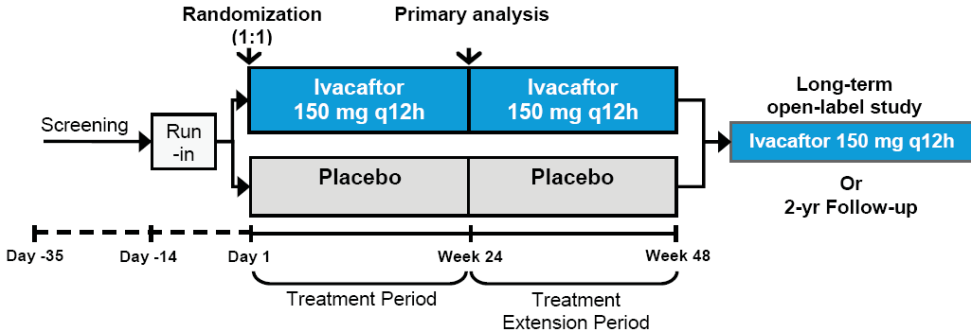


Figure 29: Phase 3 trial schematic

3 Key Questions and Summary of Findings

3.1 Is ivacaftor effective in patients with *CFTR* mutations other than G551D?

Only patients that carried at least one G551D mutation were enrolled in Phase 3 clinical trials. Ivacaftor's effectiveness in patients with non-G551D gating mutations (e.g. G178R, S549N, G970R) or other mutation cannot be established from the available data.

- *In vitro data suggest that ivacaftor increases chloride conductance through the CFTR in channels with gating defects. Ivacaftor also increased chloride conductance in some other non-gating mutations such as the R117H and D110H "conductance" mutations, and the R1070W and F1074L "trafficking" mutations.*
- *Clinical data for CFTR mutations other than F508del as the second allele were limited given the small number of subjects; no data were available for non-G551D gating mutations as the second allele, and only one G551D homozygote received ivacaftor (who did not have a FEV1 response). Clinically, responses within non-gating mutation subgroups were variable, and no consistent differences in response across the mutation classes were observed (e.g., for trafficking, where smaller responses might be expected).*
- *In vitro ivacaftor responses do not appear to correlate with clinical responses (FEV1 and sweat chloride changes). However, in vitro response data were available for a small subset of the mutations identified in the clinical trials.*

3.1.1 In vitro ivacaftor responses

The applicant used *in vitro* models using Fisher Rat Thyroid (FRT) cells that expressed various *CFTR* mutations to study the effects of ivacaftor on chloride transport. Consistent with the proposed mechanism, ivacaftor increased chloride transport in FRT cells expressing *CFTR* gating mutations (i.e., G551D, G178R, G551S, S1251N; range of 16- to 1050-fold increase over baseline, mean [SD] 152 [317]) However, in cell lines expressing *CFTR* conductance mutations (i.e., R117H, D110H, R334W) or trafficking mutations (i.e., F508del, I507del, R560T, N1303K), ivacaftor did not consistently increase chloride transport (range of 2.8- to 54-fold increase for non-gating mutations, mean [SD] 8.0 [10.1]).

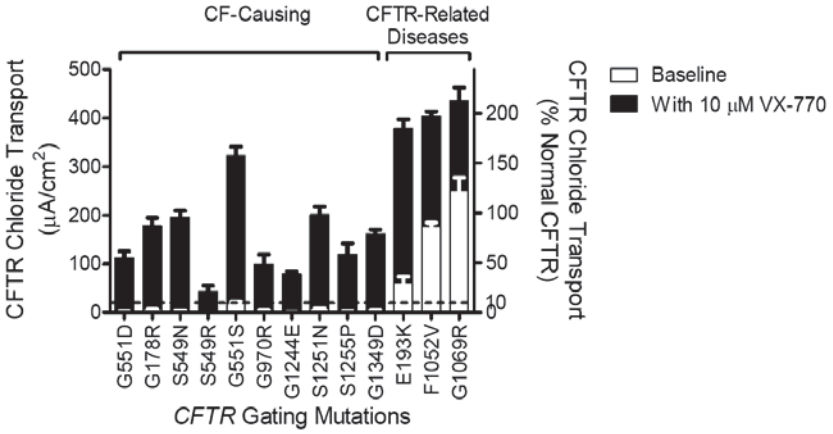


Figure 30: Baseline chloride transport and the VX-770 response in FRT cells expressing CFTR forms encoded by CFTR gating mutations

The applicant also used human bronchial epithelia (HBE) cell models obtained from airway scrapings of CF patients to show that ivacaftor increased chloride transport in cells from subjects with the G551D mutation. The largest change in chloride transport was from the HBE cells from a G551D/F508del heterozygote, while the G551D homozygous model showed only a modest response. Increased chloride transport in response to ivacaftor were limited in a number of other *CFTR* genotypes, including G542X/F508del (defective synthesis), F508del/F508del (trafficking), R117H/F508del (conductance) and 2789+5G-A/508del (reduced expression).

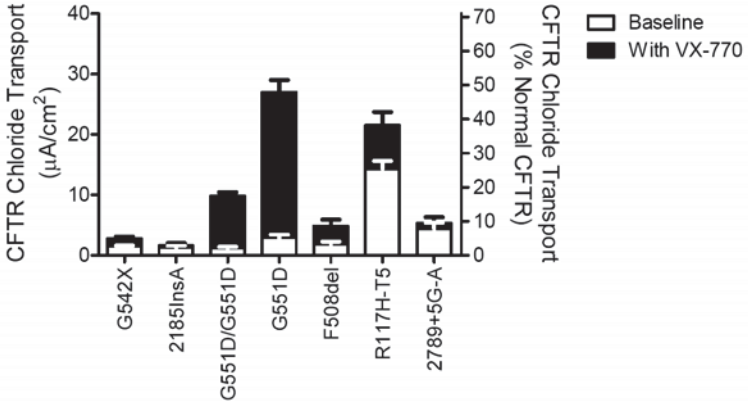


Figure 31: Baseline chloride transport and the VX-770 response in cultured CF HBE. All alleles are in combination with F508del except G551D/G551D

In vitro data suggest that ivacaftor potentiates the chloride ion channel, increasing chloride conductance across multiple gating mutations, but having limited effects on the other classes of mutations. The G551D heterozygous HBE cells had a larger increase in chloride conductance than the G551D homozygous HBE cells. Whether these *in vitro* findings translate into clinically significant changes in CF has yet to be determined for mutations other than G551D and F508del.

3.1.2 Clinical responses to ivacaftor

To support the efficacy and safety of ivacaftor, the applicant conducted two Phase 3 trials in subjects with at least one copy of the G551D mutation. Consistent with the known *CFTR* allele frequencies, the majority of subjects were F508del/G551D heterozygotes. However, 23 subjects with *CFTR* mutations other than F508del as the second allele were enrolled and treated with ivacaftor, including one subject who was homozygous for G551D; a total of 19 different *CFTR* genotypes received treatment with ivacaftor. Considering that all subjects have the same allele on one chromosome (i.e., G551D), variability in response according to the second allele may support efficacy in other, non-G551D gating mutations, or other functionally similar non-gating mutations. It would be expected that subjects harboring two gating mutations (rather than heterozygous for gating mutations) would have the largest clinical responses. Conversely, subjects with a defective synthesis mutation, for example, would be expected to have the smallest response considering the pharmacology of ivacaftor.

A summary of responses is provided below for each genotype. Data were pooled from both Phase 3 trials. Except for F508del, no more than five subjects in either treatment group had the same genotype. No gating mutations other than G551D were available to evaluate effects in this mutation class; only one subject was homozygous for gating mutations and this subject did not demonstrate a FEV1 response (but sweat chloride decreased). Responses to ivacaftor were similar across the non-gating *CFTR* mutation classes for the primary endpoint of absolute change in percent predicted FEV1 and sweat chloride. However, responses within each genotype class were highly variable. All mutation classes demonstrated some benefit from ivacaftor, although no single mutation class had substantially larger effects than the others. Given the small sample sizes and variable responses, limited conclusions can be drawn from these results.

Table 33: Summary of FEV1 Findings According to Second Allele in Subjects Treated with Ivacaftor in Trials 102 and 103

Type	Genotype	N	Placebo		N	Ivacaftor	
			Absolute change	Percent change		Absolute change	Percent change
Gating	G551D	1	-1.8	-3.9	1	-9.6	-9.5
	All Gating	**1**	**-1.8**	**-3.9**	**1**	**-9.6**	**-9.5**
Trafficking	F508del	72	-1.6	-1.9	75	11.5	17.5
	N1303K	1	-1.3	-2.9	3	10.9	19.3
	R560T	1	22.9	32.3	2	5.1	7.8
	I507del				1	28.9	42.5
	1158X				1	2.1	3.8
	All Trafficking	**74**	**-1.6**	**-1.9**	**82**	**11.4**	**17.5**

Type	Genotype	N	Placebo		N	Ivacaftor	
			Absolute change	Percent change		Absolute change	Percent change
Conductance	R347H				1	-5.4	-6.0
	R347P	1	9.7	9.9			
	R117H				1	6.0	13.9
	R792G*						
	1251 f508C*						
	P67L	1	-5.9	-10.1			
	All Conductance	**2**	**1.9**	**-0.1**	**2**	**0.3**	**3.9**
Synthesis	W1282X	1	-2.2	-3.5	1	16.5	20.5
	R553X	1	-0.5	-0.7	1	6.1	7.3
	E60X*				1	2.7	4.9
	2183AA>G	1	7.8	9.8	1	25.5	37.9
	G542X	3	0.3	6.1	1	3.6	4.7
	1717 G>A	2	2.9	7.4	1	7.6	11.4
	1078DEL				1	11.3	15.2
	G621 G>T*	2	-5.7	-12.2			
	E585X	1	4.9	10.6			
	3272-26A>G	1	-1.6	-3.7			
	All Synthesis	**12**	**0.3**	**1.8**	**7**	**10.5**	**14.5**
Unknown	3791DEL				1	15.3	32.3
	EX14A_15DEL	1	2.2	5.9			
	All unknown	**1**	**2.2**	**5.9**	**1**	**15.3**	**32.3**

* = withdrawal before 24 weeks of treatment
All subjects that completed 24 weeks per protocol were included in the table; data presented as mean values

Table 34: Summary of Sweat Chloride Findings According to Second Allele in Subjects Treated with Ivacaftor in Trials 102 and 103

Type	Genotype	N	Placebo		N	Ivacaftor	
			Absolute change	Percent change		Absolute change	Percent change
Gating	G551D	1	2.0	2.0	1	-65	-50.8
	All Gating	**1**	**2.0**	**2.0**	**1**	**-65.0**	**-50.8**
Trafficking	F508del	68	-1.3	-0.8	74	-54.4	-54.0
	N1303K	1	-3.5	-3.2	3	-37.5	-35.4
	R560T	1	3.5	3.5	2	-58.3	-67.6
	I507del				1	-54.5	-50.2
	1158X				1	-41.0	-36.6
	All Trafficking	**70**	**-1.3**	**-0.8**	**81**	**-53.7**	**-53.4**
Conductance	R347H				1	-32.5	-37.8
	R347P	1	-1.5	-1.4			
	R117H						
	R792G*						
	1251_f508C*	1	-9.0	-15.5			
	P67L						
	All Conductance	**2**	**-5.3**	**-8.5**	**1**	**-32.5**	**-37.8**
Synthesis	W1282X	1	2.0	2.2			
	R553X	1	7.5	7.5	1	-32.0	-35.0
	E60X*						

Type	Genotype	N	Placebo		N	Ivacaftor	
			Absolute change	Percent change		Absolute change	Percent change
	2183AA>G	1	14.5	14.5	1	-59.5	-63.6
	G542X	3	4.1	4.8	1	-67.0	-74.4
	1717 G>A	2	-6.3	-6.0	1	-84.0	-77.8
	1078DEL				1	-67.5	-65.9
	G621 G>T*	2	9.0	9.7			
	E585X	1	13.0	13.8			
	3272-26A>G	1	-7.0	-6.7			
	All Synthesis	**12**	**4.0**	**4.4**	**5**	**-62.0**	**-63.3**
Unknown	3791DEL				1	-39.5	-40.5
	EX14A_15DEL	1	-14.5	-14.2			
	All unknown	**1**	**-14.5**	**-14.2**	**1**	**-39.5**	**-40.5**

* = withdrawal before 24 weeks of treatment

All subjects that completed 24 weeks per protocol were included in the table; data presented as mean values

The primary endpoint of absolute change in percent predicted FEV1 is shown by mutation type in the figure below. No statistically significant differences were identified among the mutation class groupings.

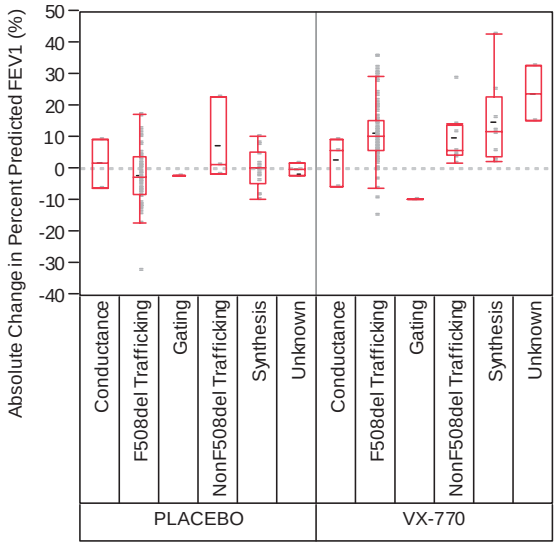


Figure 32. Absolute change in percent predicted FEV1 by *CFTR* mutation type

3.1.3 Correlation between in vitro and in vivo ivacaftor responses

To evaluate the correlation between *in vitro* changes in chloride conductance and clinical endpoints, the *in vitro* chloride conductance for each individual subject was plotted against the percentage change from baseline in both FEV1 and sweat chloride at 24 weeks. *In vitro* conductance measures were only available for a limited number of *CFTR* mutations enrolled in the Phase 3 clinical trials. Genotypes with the largest *in vitro* responses did not appear to have the largest clinical responses. *In vitro* responses do not appear to correlate with clinical responses, as shown in the figures below (sweat chloride r^2=0.09; FEV1 r^2=0.14). Most of the subjects in the plots had *CFTR* mutations with little or no *in vitro* conductance, thus making it likely that the results were driven solely by the

effect of ivacaftor on the G551D allele. Consistent with the small effect of ivacaftor *in vitro*, the one G551D homozygous subject did not have an improvement of FEV1 at 24 weeks, despite having a decrease in sweat chloride at 24 weeks.

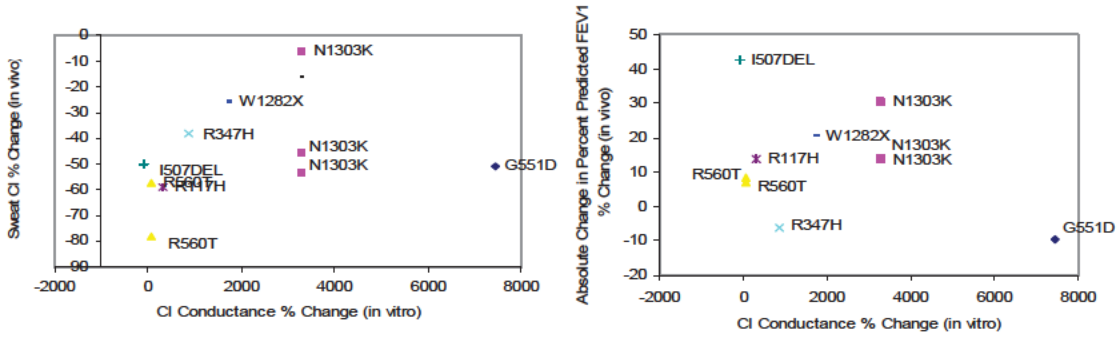


Figure 33. Percent change in *in vitro* chloride conductance of the non-G551D allele vs. percentage change in sweat chloride (left) and FEV1 (right). Pre- and/or post-treatment conductance values were less than zero for N1303K, W1282X, and I507del; a value of 0.05 μA/cm2 was used for these mutations in place of zero values.

4 Summary and Conclusions

4.1 *In vitro* data provided by the applicant suggest that ivacaftor may be beneficial in subjects carrying other *CFTR* gating mutations than G551D and some non-gating mutations. Ivacaftor significantly increased chloride conductance in the *in vitro* rat thyroid cell model for all the gating mutations. Ivacaftor also increased chloride conductance in some conductance mutations.

4.2 Only patients that carried at least one G551D mutation were enrolled in Phase 3 clinical trials. No clinical trials have directly evaluated the clinical efficacy of ivacaftor on subjects with gating mutations other than G551D (e.g. G178R, S549N, G970R). No subjects with a second gating mutation other than G551D were enrolled in either of the pivotal Phase 3 trials; only one G551D homozygote received ivacaftor without FEV1 response. Thus, no additive effect of having two gating mutations rather than one gating mutation could be established to support efficacy in other gating mutations. For other mutation types, no consistent trends in responses according to the second mutation or mutation class were observed (e.g., trafficking; where smaller responses might be expected) suggesting that most of the effect is meditated by the G551D mutation.

4.3 No robust correlation between *in vitro* response and clinical responses for to ivacaftor for the various mutations was observed. *In vitro* ivacaftor response phenotype data were available for only a limited number of mutations. Therefore, a correlation between *in vitro* ivacaftor responses and clinical responses (FEV1 or sweat chloride) could not be definitively established for non-G551D *CFTR* mutations or *CFTR* mutation classes.

5 Recommendations

Despite the plausibility of the *in vitro* data submitted by the applicant, *in vitro* responses do not appear to correlate with *in vivo* responses. The current submission does not support the effectiveness of ivacaftor in subjects with non-G551D gating mutations or other non-gating mutations. Additional experience may be accumulated through ongoing clinical trials, particularly crossover trials, to support efficacy in other mutations and/or mutation types.

5.1 Post marketing studies

None.

5.2 Labeling

None.

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/s/

LOKESH JAIN
01/18/2012

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01/18/2012

CHANDRAHAS G SAHAJWALLA
01/18/2012

BIOPHARMACEUTICS FILING REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 203-188 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D.	
Division:	DPARDP		
Applicant:	Vertex Pharmaceuticals Inc.	**Biopharmaceutics Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	--		
Generic Name:	Ivacatfor (VX-770) Film-Coated IR Tablets	**Date Assigned:**	Rolling NDA- Aug 9, 2011
Indication:	Cystic Fibrosis	**Date of Review:**	Dec 2, 2011
Formulation/strength	Immediate Release Tablet/150 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
Rolling NDA Jul 21, 2011 Original NDA Oct 18, 2011	July 27, 2011 Oct 18, 2011	July 27, 2011 Aug 9, 2011	April 18, 2012 (Priority)
Type of Submission:	Rolling NDA		
Type of Consult:	• Dissolution method and acceptance criterion • Role of dissolution on QbD		

REVIEW SUMMARY:

Ivacaftor is a selective potentiator of the CFTR protein that is being proposed "for the treatment of cystic fibrosis in patients age 6 years and older who have a G551D mutation in the CFTR gene. It was granted Fast Track status (IND 74,633) and Orphan Drug Designation. Ivacafor drug product is an immediate-release film-coated tablet for oral administration. Each tablet contains 15- mg of ivacaftor drug substance.

(b) (4) Ivacatfor is practically insoluble in water (<0.05 µg/mL in water) and meets the definition of low solubility with respect to the Biopharmaceutics Classification System (BCS), (b) (4) .

The product and process development of ivacaftor was conducted under a Quality by Design (QbD) paradigm to ensure desired product performance in terms of quality, safety, and efficacy. Dissolution was identified as one of the CQAs for the drug product. (b) (4)

This review focuses on the evaluation of; **1)** the role of dissolution on the construction of the design space for ivacaftor film-coated tablets, **2)** the acceptability of the dissolution method and acceptance criterion and **3)** the role of dissolution as a methodology that ensures control of physical form (b) (4) of ivacaftor tablets.

a) Dissolution Method and Acceptance Criterion:
The proposed dissolution method and acceptance criterion for avacaftor IR tablets is a follows:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance criterion
II	65 rpm	900mL 3-prong sinker	37°C	50 mM sodium Posphate buffered 0.7% (w/v) SLS	Q (b) (4) at 20 min

The acceptability of the dissolution method will be review issue. A preliminary analysis indicates that the method lacks discriminating ability. The sponsor is requested to provide additional information to support the acceptability of the method. The proposed acceptance criterion of Q= (b) (4) at 20 min appears to be permissive. Tighter acceptance criterion may be recommended.

b) Role of dissolution as a methodology that ensures control of physical form (b) (4) of ivacaftor tablets

(b) (4)

The proposed (b) (4) dissolution (mean of (b) (4) in 20 minutes specification; Stage 1, n=6) for the methodology was also derived from release data (% Dissolved at 20 minutes) from 10 GMP lots (b) (4).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Role of dissolution on the construction of the design space
In this submission the Applicant proposes to use dissolution as a CQA in the construction of the design space. During development of the ivacaftor drug product. (b) (4)

The following summarizes the Biopharmaceutics review issues identified:

1. Discriminatory power of the dissolution method is questionable.
    - Applicant will be requested to submit additional information
2. Proposed dissolution specification may be tighten
    - Need BA/BE data to aid in setting clinically relevant dissolution specifications
3. Dissolution may be used to monitor physical form
    - Proposed time point dissolution specification is questionable
        - Applicant will be requested to submit additional information
4. The validity of the dissolution model for compression is questionable
    - Used dissolution at Q=20 min, which seems not to be discriminating
    - Need additional data to support the predictive power of the model

RECOMMENDATION:
The ONDQA-Biopharmaceutics team has made a preliminary assessment of the data submitted in NDA 203-188 for Ivacaftor IR tablets. We found this NDA filable from Biopahrmaceutics perspective. The following comments should be conveyed to the Applicant as part of the 74-Day letter:

The following information is needed to support your proposed dissolution method and acceptance criterion:

1. The dissolution method report including the complete dissolution profile data (individual, mean, SD, profiles) collected during the development and validation of the proposed dissolution method.
2. The information included to support the discriminating power of the method is insufficient. Provide additional data supporting this claim (b) (4)
3. Submit the complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for the proposed product.
4. Submit the dissolution profile data (raw data and mean values for the drug product batches used in PK studies VX08-770-102 and VX08-770-007 (formulations (b) (4) 20QB02001A.HQ00001; (b) (4) 20QB02001B.HQ00001, and 50 mg tablet).

(b) (4)

(b) (4)

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Lead
Office of New Drug Quality Assessment

cc: DHenry

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/s/

SANDRA SUAREZ
12/05/2011

ANGELICA DORANTES
12/05/2011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 203118

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**203188**	**Brand Name**	**Kalydeco**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Ivacaftor (VX770)**
Medical Division	**DPARP (OND-570)**	**Drug Class**	**Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulator**
OCP Reviewer	**Partha Roy**	**Indication(s)**	**Cystic Fibrosis**
OCP Team Leader (Acting)	**Suresh Doddapaneni**	**Dosage Form**	**Tablet**
Pharmacometrics / Pharmacogenomics Reviewer	**Atul Bhattaram / Hobart Rogers**	**Dosing Regimen**	**Twice daily (BID), i.e. every 12h**
Date of Submission	**10/18/2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**3/09/2012**	**Sponsor**	**Vertex**
Medical Division Due Date	**3/25/2012**	**Priority Classification**	**P**
PDUFA Due Date			

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**	**24**		**Includes method validation and trial-specific bioanalytical reports**
I. Clinical Pharmacology				
Mass balance:	**x**	**1**		
Isozyme characterization:	**x**	**4**		
Blood/plasma ratio:				
Plasma protein binding:	**x**	**1**		
Pharmacokinetics (e.g., Phase I) -	**x**			
Healthy Volunteers-	**x**			
single dose:	**x**	**8**		
multiple dose:	**x**	**4**		
Patients-				
single dose:	**x**	**1**		
multiple dose:	**x**	**2**		
Dose proportionality -				
fasting / non-fasting single dose:	**x**	**1**		
fasting / non-fasting multiple dose:	**x**	**1**		
Drug-drug interaction studies -				
In-vivo effects on primary drug:		**2**		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 203118

In-vivo effects of primary drug:		**3**		
In-vitro:		**4**		
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:		**1**		
geriatrics:	**x**			
renal impairment:	**x**			
hepatic impairment:		**1**		
PD -				
Phase 2:	**x**	**1**		
Phase 3:	**x**	**2**		
PK/PD -				
Phase 1 and/or 2, proof of concept:	**x**	**1**		
Phase 3 clinical trial:		**2**		
Population Analyses -				
Data rich:	**x**			
Data sparse:	**x**	**1**		
II. Biopharmaceutics				
Absolute bioavailability	**x**	**1**		
Relative bioavailability -				
solution as reference:	**x**	**1**		
alternate formulation as reference:	**x**	**1**		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies		**3**		
Bio-waiver request based on BCS				
BCS class		**ND**		
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**x**	**1**		**Proposed for ≥12y in the original submission; plan for 6-11y submitted**
Literature References	**x**			
Total Number of Studies		**51**		**Includes all clinical, nonclinical and bioanalytical reports**

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	Commercial form used in pivotal clinical trials
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	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 203118

	allow substantive review to begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	x			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Pediatric studies (≥12y) part of adult submission
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
____Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Not Applicable

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 203118

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Based on this filing review, there are two comments that need to be communicated to the Sponsor.

1. With regard to the submitted draft labeling
   Under Section 12.3
   Pharmacokinetics

   Forest plots are generally used to capture changes in observed PK data as a result of intrinsic and extrinsic factors from in vivo studies. Therefore, hepatic impairment: simulated steady state data should be deleted from Figure 2.

2. *Submit the NONMEM control streams as .txt files.*

Background

This is a 505(b)(1) new drug application for a new molecular entity (NME) submitted by Vertex Pharmaceuticals for Ivacaftor (VX-770) intended for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the CFTR gene. This small molecule drug candidate represents a proposed new class of drugs known as "CFTR Modifier". The drug candidate's mechanism of action is to potentiate CFTR activity in patients with CF due to a mutation in which the CFTR protein is transported intact to a cell's epithelial membrane, but which has low activity (class 3, gating mutation).The proposed formulation is an oral tablet and the proposed clinical dose is 150 mg twice daily (BID), i.e. dosed every 12 hours. The clinical data for this NDA is developed under IND 74633. Ivacaftor received an orphan drug designation and priority review status. The advisory committee meeting for this application is scheduled on February 24, 2012. The filing meeting took place on November 9, 2011.

Overview of Clinical Pharmacology submission and data

The ivacaftor development program consists of a total of 23 clinical trials, with 17 completed trials (including one Phase 2 and two Phase 3 trials in subjects with CF). There are 12 clinical pharmacology trials included in the total for completed clinical trials.

Highlights of the Clinical Pharmacology and Biopharmaceutics program include:

1. The sponsor conducted substantial formulation development concurrent with clinical development and optimized the final formulation prior to pivotal Phase 2/3 clinical trials.
2. The final formulation had significant food effect and all clinical trials were conducted with high fat-containing diet appropriate for CF patients. Labeling calls for the drug to be taken with fat containing food.
3. Ivacaftor and its metabolites (M1 and M6) are substrates of CYP3A and P-gp and potential inhibitors of CYPs 3A, 2C8 and 2D6 resulting in significant clinical drug-drug interactions (DDI) that prompted dose adjustments in the proposed drug label.

4. Sparse sampling data were obtained from Phase 2/3 trials to assess the effects of demographic characteristics and other covariates on Ivacaftor PK and to characterize the exposure-response relationships for FEV_1 and sweat chloride using population PK and PK/PD.
5. Dose selection for pivotal Phase 3 trials (≥12y and 6-11y) was based on PK/PD modeling and simulations from earlier trials.
6. A Thorough QT study was conducted to study the effect of ivacaftor on the electrocardiogram (ECG) QT interval.

Attached are slides depicting a brief overview of the clinical pharmacology submission, including items that will require further evaluation in the formal review process.

(b) (4)

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/s/

PARTHA ROY
12/04/2011

SURESH DODDAPANENI
12/04/2011