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RESEARCH**

APPLICATION NUMBER:

203188Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Addendum to CDTL Review for NDA 203188

To: NDA 203188 (Vertex Pharmaceuticals, Inc., VX-770, ivacaftor)

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Date: January 30, 2012

Elevated sweat chloride has historically been the means by which CF is diagnosed and it was used as an endpoint in the Vertex clinical trials as an indicator of CFTR function. However, change (decrease) in sweat chloride did not correlate with improvement in lung function (FEV₁). Because this lack of correlation seems counterintuitive, I have included some additional discussion regarding the determination and analyses of sweat chloride in the Vertex VX-770/ivacaftor program.

Changes in Sweat Chloride

Changes in sweat chloride concentration were evaluated at Day 1, Day 15, and at Weeks 8, 16, 24, 32, 40, and 48 in Studies 102 and 103B. All sweat chloride testing was measured by quantitative pilocarpine iontophoresis and sweat samples were collected using the Macroduct collection system. All samples were sent to a central laboratory for testing, interpretation of results, and entry of results into the database. Individual sweat chloride results were not disclosed to the study sites. Change from baseline in sweat chloride concentration through week 24 was a key secondary endpoint for both Studies 102 and 103B. Results are listed in the Table below.

Changes in Sweat Chloride Measurements Through Weeks 24 and 48, Full Analysis Set								
Result		n	Baseline value (mmol/L)	Post-baseline value	Absolute change from baseline LS mean ^a	Difference Between treatment groups	95% CI	p-value
<i>Change in Sweat Chloride Through Week 24</i>								
Study 102								
	Placebo	74	100.1	100.9	-0.8			
	VX-770	78	100.4	50.8	-48.7	-47.93	-51.3, -44.5	<0.0001
Study 103								
	Placebo	23	105.0	104.7	-1.2			
	VX-770	23	104.4	47.9	-55.5	-54.3	-61.8,-46.8	<0.0001
<i>Change in Sweat Chloride Through Week 48</i>								
Study 102								
	Placebo	74	100.1	100.7	-0.6			
	VX-770	78	100.4	50.8	-48.7	-48.1	-51.5,-44.7	<0.0001
Study 103								
	Placebo	23	105.0	103.8	-2.6			
	VX-770	23	104.4	47.3	-56.0	-53.5	-60.9,-46.0	<0.0001
a= estimates from Mixed Effects Model for Repeated Measurements [Source: Module 5.3.5.1.3, Clinical Study Report 102, Tables 14.2.2.2.1.1 and 14.2.2.2.1.2, and Clinical Study Report 103, Tables 14.2.2.2.1.1 and 14.2.2.2.1.2]								

Vertex provided analyses which evaluated the correlation of sweat chloride concentration with changes in FEV1. There was minimal to no correlation between change from baseline percent predicted FEV1 and sweat chloride. FDA analyses reached the same conclusion.

Vertex also performed subgroup analyses on sweat chloride data for both Studies 102 and 103. For Study 102, there were no meaningful differences in absolute change from baseline in sweat chloride through weeks 24 or 48 between VX-770-treated patients based on geographic region, baseline percent predicted FEV1, or age, with less than a 3mmol/L difference between subgroups. There was a small difference between males and females, with male patients receiving VX-770 (n=37) having a decrease in sweat chloride of -42.8 and -42.5mmol/L at weeks 24 and 48, respectively, and female patients receiving VX-770 (n=41) having a decrease in sweat chloride of -53.8 and -53.8mmol/L at weeks 24 and 48, respectively. [Source: Module 5.3.5.1.3, Clinical Study Report 102, Tables 14.2.2.2.2.1 and 14.2.2.2.2.2] The clinical meaning of a roughly 10mmol/L difference in sweat chloride values is not known, since there is no data regarding what would determine a clinically-meaningful change, and if such value would be a threshold, or if sequential decrease in chloride concentration would correlate with incremental clinical benefit.

For Study 103, the overall study numbers are small, so these analyses need to be interpreted with caution; subgroup analysis noted no meaningful differences in absolute change from baseline in sweat chloride through weeks 24 or 48 between VX-770-treated patients based on geographic region, age, or gender. In contrast to Study 102, they note less than 5mmol/L difference between genders, with male patients receiving VX-770 (n=8) having a decrease in sweat chloride of -60.3 and -59.5mmol/L at weeks 24 and 48, respectively, and female patients receiving VX-770 (n=15) having a decrease in sweat chloride of -55.7 and -54.5mmol/L at weeks 24 and 48, respectively. When comparing a pooled group of patients with FEV1 less than or equal to 90% predicted at baseline to those patients with FEV1 >90% predicted, the difference in VX-770-treated patients with FEV1 \leq 90% (n=14) was -51.6 and -53.7mmol/L at 24 and 48 weeks, respectively, versus the difference in VX-770-treated patients with FEV1 >90% (n=9) of -66.6 and -66.5mmol/L at 24 and 48 weeks, respectively. [Source: Module 5.3.5.1.3, Clinical Study Report 103, Tables 14.2.2.2.2.1 and 14.2.2.2.2.2]

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/s/

ANTHONY G DURMOWICZ
01/30/2012

Cross-Discipline Team Leader Review

Date	January 27, 2012
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 203188
Supplement#	
Applicant	Vertex Pharmaceuticals
Date of Submission	October 18, 2011
PDUFA Goal Date	April 18, 2012
Proprietary Name / Established (USAN) names	Kalydeco/ivacaftor
Dosage forms / Strength	Oral tablet/150 mg
Proposed Indication(s)	"... indicated for the treatment of cystic fibrosis in patients age 6 years and older who have a G551D mutation in the CFTR gene"
Recommended:	Approval

1. Introduction

Vertex submitted a 505(b)(1) new drug application (NDA 203188) on October 18, 2011, for the use of VX-770 (ivacaftor) at a proposed dose of 150 mg mcg twice daily for “the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene”. The term VX-770, which will be used to refer to the drug in this review, was the name used for most of the clinical program with ivacaftor later used to identify the drug substance and Kalydeco the trade name. The clinical development program was conducted under IND 74,633 which was submitted on March 13, 2006. The PDUFA date for this application is April 18, 2012. VX-770 is not currently marketed for any indication in the United States or other country.

This review will provide an overview of the application with a focus on the determination of efficacy and safety in patients with CF who have a G551D mutation in the CFTR gene as well as additional efficacy and safety information in patients with CF who possess the most common genotype that results in the disease (homozygous for the f508 deletion in the CFTR gene). Summaries will also be provided for discipline-specific reviews that were conducted.

2. Background

VX-770 is a new molecular entity which has been classified as a cystic fibrosis transmembrane conductance regulator “potentiator”. The CFTR protein is an epithelial chloride ion channel, encoded by the CFTR gene, which aids in the regulation of salt and water absorption and secretion throughout the body. The proposed indication for VX-770 is for the treatment of CF in patients age 6 years and older who have a G551D mutation in the CFTR gene. The proposed chronic dosing regimen is 150mg every 12 hours, to be taken with fat-containing food.

Cystic fibrosis is an autosomal recessive, progressive, and usually fatal genetic disease most common in the Caucasian population. It occurs in approximately one out of every 3,500 children born in the United States and is an orphan drug population. Lack of properly functioning CFTR is responsible for the clinical sequelae of CF, including malabsorption of nutrients, and the presence of tenacious respiratory secretions which are difficult to mobilize, leading to recurrent/chronic pneumonia and lung damage. There is no cure for CF, treatment is limited to alleviation of symptoms and treatment of complications. Over the past several decades, with improved care, life expectancy has increased significantly, with the current median age of survival to the early-mid thirties. Death is typically due to respiratory failure. There are over 1800 mutations in the CFTR gene which, when present in both CFTR alleles, results in the clinical constellation that is CF. VX-770 has been developed to treat a specific mutation in the CFTR, called the G551D mutation, in which the mutated CFTR protein reaches the cell surface, but does not activate normally resulting in a low probability of being open. If approved, it would be the only drug which acts to treat the underlying defect in the CFTR ion channel which is the cause of CF, albeit in the small subpopulation of patients with CF with at least one copy of the G551D mutation in the gene.

Current therapies used by patients with CF to help manage their disease include mucolytics such as inhaled DNase, beta-agonist bronchodilators, inhaled antibiotics (tobramycin, aztreonam), and pancreatic enzyme supplements.

The regulatory history for VX-770 began with the submission of IND# 74,633 on March 13, 2006. Initial safety review noted that preclinical data did not support doses over 500 mg, the IND-opening protocol was subsequently amended and the study was allowed to proceed. Fast Track designation was requested in March, and granted on May 4, 2006. On December 20th, 2006, Orphan drug product designation was also granted to VX-770 for the treatment of patients with CF. Clinical development continued, and on June 30, 2008, an End-of-Phase-1 meeting was held. Key points discussed included:

- The Division raised concerns regarding the use of sweat chloride as a primary efficacy variable because the clinical relevance of sweat chloride as a biomarker/clinical endpoint in CF has not been demonstrated and recommended FEV1 or another clinically meaningful endpoint instead.
- Controlled data for 1 year would better support durability of treatment effect
- Recommendation for one year of safety data in the NDA
- Given the small number of patients with CF who have a G551D mutation, that the proposed small pediatric study showing a positive trend would be adequate to support a positive result in the proposed study in adolescents and adults.
- That Vertex would also conduct a large clinical study in CF patients aged 12 and older that are homozygous for the F508del-CFTR mutation to assess safety and clinical activity of VX-770 in this patient population and to guide clinicians' understanding of how to appropriately prescribe the drug product.

In December 2008, Vertex submitted 3 protocols under a Special Protocol Assessment (SPA) for phase 3 clinical trials. However, review of the non-clinical data showed that there was not adequate non-clinical support for the proposed trials because of a lack of chronic toxicity data to support the proposed duration of the trial. On January 9, 2009, the Division placed the clinical studies on clinical hold for lack of non-clinical support and Vertex withdrew the studies the same day. After adequate nonclinical support was provided, Vertex submitted protocols for 3 new clinical studies (not under a SPA) which would provide the basis for demonstrating the safety and efficacy of VX-770 in the indicated population (studies 102, 103, and 104). End-of-Phase 2 meeting comments were sent to Vertex on April 13, 2009, which reflected that positive results from study 102 and positive trending efficacy data from 103, and 48-week safety data including study 104 would be adequate for filing an NDA.

On June 17, 2011, a Clinical Pre-NDA meeting was held with the Applicant, during which the Division stated that, because of the likelihood of a priority review, 48-week data would be needed at the time of NDA submission and that CDRH would be consulted with regard to potential genetic testing issues. The possibility of early submission of the CMC module of the NDA was also discussed. Vertex submitted the CMC module on July 27, 2011; the NDA submission was complete on October 18, 2011.

3. CMC/Device

From a CMC perspective, the application is recommended for approval.

The manufacturing process for VX-770 employed Quality-by-Design (QBD) elements meant to ensure that production of a consistent drug product was built into the manufacturing process. One of the significant issues in the QBD framework was the fact that

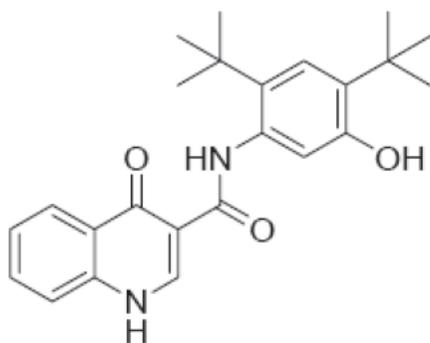
(b) (4)
(u) (4)

Because of the critical nature of this procedure, the CMC and Biopharm teams have recommended tighter dissolution specifications which were accepted by the company.

Another issue which had to be resolved was the potential for the presence of a number of (b) (4) impurities, (b) (4), and residual solvents in the drug substance. This issue was evaluated by Timothy Robison, Ph.D., D.A.B.T., from the Pharmacology/Toxicology team in consultation to the CMC team. It was subsequently determined that the potential (b) (4) impurities, (b) (4), and residual solvents found in the drug substance, (b) (4) and/or drug product were qualified from a toxicologic perspective.

The drug substance is VX-770 (ivacaftor), the first drug substance of a new pharmacologic class “CFTR Potentiator”. The chemical name is: (N-(2,4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide). Its molecular formula is “C₂₄H₂₈N₂O₃” and molecular weight is 392.49 grams.

Structure of VX-770 (ivacaftor)



All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The drug product will be supplied as light blue, film-coated, capsule-shaped tablet containing 150 mg of VX-770. Inactive standard compendial excipients include colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium

stearate, microcrystalline cellulose, and sodium lauryl sulfate. Currently the proposed expiration dating period for the drug product is 30 months.

4. Nonclinical Pharmacology/Toxicology

The Applicant has submitted all required nonclinical data and studies needed to characterize the nonclinical safety profile of VX-770 and support its approval from the nonclinical perspective. Following is a brief summary of the more salient aspects of the toxicology program.

General Toxicity

General toxicology studies were conducted in the mouse, rat, and dog up to 3-months, 6-months, and 12-months, respectively. The liver was identified as a target organ of toxicity in 3 month studies with relatively high doses in rats and mice; however, no liver toxicity was observed in chronic studies with rats and dogs or lifetime studies with rats and mice. Liver toxicity appeared to be monitorable. The gastrointestinal tract and heart (ECG findings) were identified as target organs in the chronic toxicity study with dogs. These findings were also considered monitorable in a clinical setting and were not used in safety factor determinations for clinical doses. Drug exposure in nonclinical test species and humans was composed of exposure to the parent drug, VX-770, and its metabolites, M1 and M6. In humans, plasma levels of M1 and M6 were significantly greater than the parent drug, VX-770; however, exposures to parent drug were significantly higher than M1 and M6 in toxicity studies with mouse, rat, and dog. Thus, M1 and M6 were regarded as disproportionate metabolites in humans. The proposed human dose has adequate safety margins for the animal toxicity findings. The chronic rat and dog studies provided adequate clinical coverage (greater than one on an AUC basis) for the parent drug, VX-770. The rat study also provided adequate coverage for the M1 and M6 metabolites.

Carcinogenicity

Two-year mouse and rat carcinogenicity studies were conducted with VX-770. In the mouse study, animals received oral doses of VX-770 at 25, 75, and 200 mg/kg/day. Vehicle control groups (0.5% w/v methylcellulose with 0.5% w/v sodium lauryl sulfate in water) with and without 0.01% simethicone were also included in the study. In the rat study, animals received oral doses of VX-770 at 5, 15, and 50 mg/kg/day. Vehicle control groups were also included in this study. It is notable that during the course of this study, after review of preliminary findings of high mortality in some dosing groups, early termination of study groups (at week 89 of dosing) due to high mortality was recommended by the Agency's Executive Carcinogenicity Assessment Committee (ECAC). The ECAC reviewed the final results of the two studies and concurred with the Applicant's interpretation that there were no drug-related neoplasms apparent in either study. It was noted, however, that male rats dosed at 50 mg/kg/day had statistically significant lower survival in comparison to simethicone controls.

Genotoxicity

VX-770 was negative in a complete battery of genetic toxicity tests including a bacterial reverse mutation assay, a Chinese hamster ovary chromosomal aberration assay and in an *in vivo* mouse micronucleus assay.

Reproductive toxicity

Reproductive and developmental toxicity studies of VX-770 were completed in rats and rabbits. These studies evaluated the effects of VX-770 on fertility in rats, teratogenicity in rats and rabbits, and peri- and post-natal development in rats. While VX-770 decreased fertility indices in males and females in rats, the drug was non-teratogenic in rats and rabbits. Fertility effects occurred at very high doses (200 mg/kg/day) and are considered a general toxicity. They did not occur at doses \leq 100 mg/kg/day. VX-770 had no effects on peri- or post-natal development in rats.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology team has concluded that the data submitted by the Applicant to characterize the clinical pharmacology and biopharmaceutic profile of VX-770 is adequate to support its approval from the clinical pharmacology perspective. There is one post-marketing study being recommended. Since VX-770 has been demonstrated to be a P-gp inhibitor in vitro, the Applicant should evaluate and submit data to be included in label on the potential for in vivo drug-drug interaction of VX-770 with sensitive P-gp substrates.

Following is a brief summary of the relevant clinical pharmacology data including the effects of roflumilast on the QT interval.

Pharmacokinetics

Absorption

As there is no intravenous preparation, the absolute bioavailability of VX-770 has not been evaluated. Exposure (AUC) to VX-770 is dose-proportional for doses ranging from 25-800 mg, however, increases in C_{max} were not dose proportional. The median time to reach maximum plasma concentrations of VX-770 (t_{max}) is approximately 4 hour when taken with food. Food intake (particularly food containing fat) increases VX-770 exposure (AUC) and C_{max} by 3 and 4-fold, respectively. Pharmacokinetics were similar between healthy volunteers and patients with CF.

Distribution

Plasma protein binding of VX-770 and its M1 and M6 metabolites is >98%. It is extensively distributed in tissues with volume of distribution (V_z/F) of 203 L and 220 L in subjects with CF and healthy subjects, respectively. VX-770 does not affect the protein binding of warfarin and does not bind to human red blood cells.

Metabolism and Elimination

VX-770 is extensively metabolized by CYP3A enzymes. Metabolism primarily involves oxidation to M1 (hydroxymethyl-VX-770) and M6 (VX-770-carboxylate). The M1 metabolite is considered active and possesses approximately 1/6th of the potency of VX-770, the M6 metabolite is considered inactive. The metabolite to parent ratio for M1 and M6 at steady-state were 4.89 and 1.73, respectively. VX-770 is primarily eliminated through feces with minor elimination through renal route (approximately 6-7%).

Pharmacokinetics in Special Populations

Renal Impairment

VX-770 has not been studied in patients with renal impairment. Since it is metabolized almost exclusively by the liver (6-7% renal) and excreted in feces, no dose adjustment is felt to be necessary for patients with mild to moderate renal impairment. However, it is the recommendation by the clinical pharmacology team that caution be exercised if VX-770 is to be used in a patient with severe renal impairment or end stage renal disease.

Hepatic Impairment

VX-770 has been studied in subjects with moderate liver impairment (Child-Pugh Class B, score 7 to 9). While these subjects had similar VX-770 C_{max}, there was an approximately 2-fold increase in AUC_{0-∞} compared with healthy subjects. As a result, it will be recommended that the dose of VX-770 should be reduced to 150 mg once daily for patients with moderate hepatic impairment. VX-770 has not been studied in subjects with mild or severe liver disease. For those with mild impairment any change in exposure is expected to be small and no dose adjustment is recommended. For those with severe liver impairment, exposure is expected to be substantially higher and, therefore, VX-770 should be used with caution, after weighing its risks versus the potential benefit, at a starting dose of 150 mg once daily or less frequently.

No clinically significant differences in pharmacokinetics of VX-770 were identified based on age, weight or gender.

Drug-Drug Interactions

In vitro metabolism studies using human liver microsomes and *in vivo* drug-drug interaction studies indicated that VX-770 is mainly metabolized by CYP3A4. Therefore, the exposure of VX-770 is expected to increase when inhibitors of CYP3A4 are co-administered and decrease when inducers of CYP3A4 are co-administered.

CYP3A Inhibitors

Drug-drug interaction studies were conducted with the following drugs: midazolam, erythromycin, ketoconazole, fluconazole, rifampicin, rosiglitazone, desipramine, and oral contraceptives. Co-administration of VX-770 with ketoconazole, a strong CYP3A inhibitor, significantly increased VX-770 exposure [measured as area under the curve (AUC)] by 8.5-fold. Therefore, a reduction of the VX-770 dose to 150 mg twice weekly is recommended when strong CYP3A inhibitors, such as ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin will be administered concomitantly. The moderate CYP3A inhibitor, fluconazole, increased VX-770 exposure by approximately 3-fold. As a result, the dose of VX-770 should be reduced to 150 mg once daily in patients taking moderate CYP3A inhibitors concomitantly (e.g., fluconazole and erythromycin). Because grapefruit juice contains one or more components that moderately inhibit CYP3A and its intake may increase exposure of VX-770, food containing grapefruit or Seville oranges should be avoided by patients receiving VX-770.

CYP3A Inducers

Co-administration of VX-770 with rifampin, a strong CYP3A inducer, significantly decreased exposure to VX-770 by approximately 9-fold. As this much reduction in exposure is very likely to impact the efficacy of VX-770, use of strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's Wort is not recommended when patients are receiving VX-770.

CYP3A and P-gp Substrates

VX-770 and its M1 metabolite have the potential to inhibit CYP3A and P-gp. As such, administration of VX-770 may increase systemic exposure of drugs which are substrates of CYP3A and/or P-gp and increase or prolong their effects. Co-administration of VX-770 with the CYP3A substrate, midazolam, increased VX-770 exposure by a factor of approximately 1.5. Therefore, caution should be exercised and patients monitored for increased effects when VX-770 is administered with CYP3A and/or P-gp substrates, such as benzodiazepines, digoxin, cyclosporine, and tacrolimus.

Co-administration of VX-770 with desipramine, rosiglitazone, or oral contraceptives does significantly effect not require any dose adjustment.

Thorough QT Study

A thorough QT study was conducted for this program and reviewed by the QT study interdisciplinary review team. The study consisted of 2 parts, Part A in which 8 subjects were enrolled to evaluate the safety and tolerability of increasing doses of VX-770 up to 450 mg every 12 hours (q12h) followed by Part B to determine if therapeutic or suprathreshold systemic exposure to multiple doses of VX-770 up to 450 mg q12h prolongs the mean Fridericia-corrected QT (QTcF) interval by more than 5 milliseconds. No significant toxicities were identified in Part A. The actual effect of multiple doses of VX-770 150 mg and 450 mg on QTc was evaluated in Part B; a double-blind, randomized, placebo- and active-controlled, single center, 4-period crossover study in which 72 subjects received VX-770 150 mg q 12h, VX-770 450 mg q 12h, placebo, and moxifloxacin 400 mg (the active comparator). The study was appropriately designed; the suprathreshold dose of 450 mg q 12h produced mean C_{max} approximately 4 times higher than the mean C_{max} for the therapeutic dose of 150 mg q 12h. No significant QTc prolongation effect of VX-770 at the doses tested was detected. The largest upper bounds of the 2-sided 90% CI for the mean differences between VX-770 150 mg and placebo, and between VX-770 450 mg and placebo were below 10 ms (the threshold for regulatory concern). Assay sensitivity was demonstrated as the largest lower bound of the 2-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for the active comparator moxifloxacin was greater than 5 ms (see table below).

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for VX-770 150 mg b.i.d., VX-770 450 mg b.i.d. and the Largest Lower Bound for Moxifloxacin on Day 5 of Dosing

Treatment	Time (h)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
VX-770 150 mg b.i.d.	0.5	0.8	(-1.5, 3.1)
VX-770 450 mg b.i.d.	0.5	-0.5	(-2.9, 1.8)
Moxifloxacin 400 mg*	3	9.7	(7.4, 12.1)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 6.8 ms.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

Overview of the clinical program

Vertex Pharmaceuticals has submitted the results from two Phase 3 studies (102 and 103 Part B) to support the regulatory approval of VX-770 (ivacaftor) at a dose of 150 mg every 12 hours for the treatment of CF patients age 6 years and older who have a G551D mutation in the CFTR gene. Support for the dose selected is provided by the findings from the proof of concept/dose selection study (study 101). Additional supportive safety data and demonstration of lack of efficacy for the most common mutation in the CFTR to result in CF (homozygous for the F508-CFTR mutation) is provided by the findings from study 104. The general design of the clinical studies relevant for VX-770 in patients with CF can be found in Table 2.

Table 2 Relevant Clinical Studies for VX-770 in Cystic Fibrosis Patients

Study/ Years conducted	Study Type	Study Duration	CF Mutation	Pt age (yr)	Baseline FEV1 ^a	Treatment groups	N (ITT)	Countries
<i>Dose-ranging and Proof of Concept</i>								
Study 101 ^b 2007-2008	Dose- ranging, PK, PD	4 weeks	G551D	≥ 18	≥ 40%	Part 1: VX-770 25, 75, 150, 250 mg Placebo	20	North America, Germany
						Part 2: VX-770 150, 250 mg Placebo	19	
<i>Phase 3 and Supportive Studies</i>								
Study 102 2009-2011	Safety and Efficacy	48 weeks	G551D	≥ 12	40-90%	VX-770 150 mg Placebo	83 78	North America, Europe, Australia
Study 103B ^c 2009-2011	Safety and Efficacy	48 weeks	G551D	6-11	40-105%	VX-770 150 mg Placebo	26 26	North America, Europe, Australia
Study 104A ^d 2009-2010 Supportive	Safety and Efficacy	16 weeks	F508/ F508	≥ 12	≥ 40%	VX-770 150 mg Placebo	112 28	North America (US)
Study 105 Supportive	Safety	Up to 96 weeks	G551D	≥ 6	≥ 40%	VX-770 150 mg open label	≈ 144	North America, Europe, Australia
a FEV1 as per cent predicted value b Study 101 Part 1 was crossover for 2 weeks of treatment in each arm; Part 2 was of parallel group design with a 4 week treatment period c Study 103 consisted of 2 parts A and B. Part A assessed single dose PK in 9 patients to confirm the dose level for Part B d Study 104 also consisted of 2 parts A and B. Part B enrolled "responders" from Part A, the study was terminated for futility after Week 40								

Design and conduct of the studies

Dose Selection

Dose selection for the VX-770 Phase 3 program was primarily based on PK/PD modeling and simulations using data from study 101 and PK data from healthy volunteers. Study 101 was a randomized, double-blind, placebo-controlled, 28-day dose-finding and proof-of-concept study in 39 patients with cystic fibrosis > 18 years of age and FEV1 \geq 40% predicted with at least one copy of the G551D mutation in the CFTR gene. It was conducted in two parts. Part 1 was of placebo-controlled, cross-over design and consisted of a 14 day treatment period followed by a 7-28 day washout period before crossing over. Treatments consisted of VX-770 at doses of 25, 75, and 150 mg and placebo. Part 2, conducted in a separate set of patients, was of parallel group design in which patients received either VX-770 150, 250, or placebo every 12 hours for 28 days. The major clinical and pharmacodynamic endpoints relevant for dose selection included FEV1, nasal potential difference (NPD), and sweat chloride. Twenty patients were studied in Part 1 and 19 in Part 2. Results from study 101 demonstrated that doses of 75 and 150 mg every 12 hours for 14 days clearly separated from the 25 mg dose and demonstrated statistically significant changes in FEV1, NPD, and sweat chloride concentrations compared to placebo. Improvements in % predicted FEV1 were 9 and 10% above placebo for the 75 and 150 mg doses, respectively. Changes in NPD and sweat chloride were very similar between the 75 and 150 mg doses with changes in the range of -4.7 to -5.4 millivolts for NPD and -40 to -42 mmol/L for sweat chloride. The 250 mg dose did not provide any additional benefit over the 150 mg dose. The 150 mg dose was chosen to carry forward in development based on slight nominal differences between the 75- and 150 mg doses and lack of any additional safety concerns.

Dose selection for children 6-11 years of age was based on PK data in 9 pediatric patients with CF obtained in Part A of study 103 who received VX-770 100 mg as a single dose. Based on pharmacokinetic modeling data, the 150 mg dose every 12 hours was maintained for the 6-11 year old population.

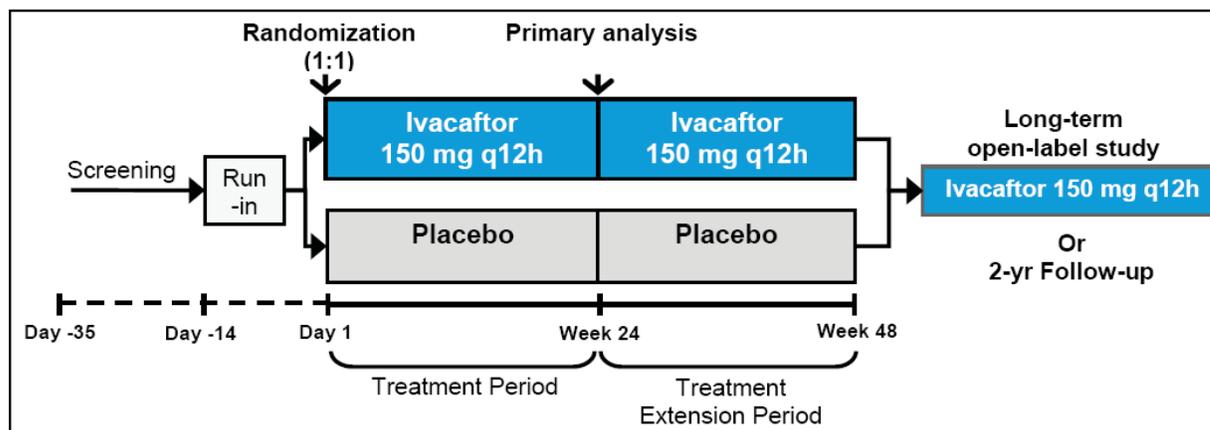
Establishment of a once daily dosing regimen was based on the results of a pharmacokinetic data in healthy volunteers and patients with CF which demonstrated that VX-77 had a terminal half-life of approximately 12-14 hours. Dosing intervals less than or greater than 12 hours were not evaluated in clinical trials.

Efficacy Studies

Studies 102 and 103B were of almost identical design, albeit in different age populations. Both were randomized, double blind, placebo-controlled, parallel group studies designed to assess the efficacy and safety of 48 weeks of treatment with VX-770 150 mg every 12 hours (taken with fat-containing food) in patients ages 12 years and older (study 102) and 6 to 11 years (study 103B) with CF and a G551D mutation in the CFTR gene. After initial screening, patients entered a 14 day run-in period during which patient stability and adherence with the current medical regimen was documented and adjustment of the dosing timing of allowed concomitant medications such as inhaled antibiotics. Patients were then randomized 1:1 to receive VX-770 (ivacaftor) 150 mg orally with fat-containing food every 12 hours or placebo. Of note, study 102 was originally planned for a maximum of 24 weeks, but subsequent amendments allowed for an additional 24 week double blind, placebo-controlled 'extension' period after the initial 24 week follow-up period in order to investigate the 'durability' of response to treatment and secondary endpoints. Evaluations were made at baseline, day 15,

week 8, week 16, week 24, week 32, week 40, and week 48. Similarly, in study 103B, the first 24 weeks were designated as the ‘treatment’ period and the second 24 weeks was the ‘extension period’ during which the double blind was preserved and secondary endpoints assessed (see Figure 1).

Figure 1: General Design of Studies 102 and 103B



Note: Schematic shown represents Studies 102 and 103 Part B. The long-term open-label study is Study 105.

Pertinent inclusion criteria included a sweat chloride of at least 60 mmol/L or 2-CF-causing mutations and chronic sino-pulmonary disease or GI/nutritional abnormalities. In addition, patients enrolled in study 102 were to have FEV1 between 40 and 90% predicted while pediatric patients in study 103 studied pediatric patients with FEV1 between 40 and 105% predicted. Patients who had persistent Burkholderia cenocepacia, dolosa, or Mycobacterium abscessus at screening and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥ 3 times the upper limit of normal were excluded. In general, patients were allowed to continue their chronic medication regimens. Chronic cycled inhaled antibiotics (such as inhaled tobramycin) were allowed but the treatment cycles adjusted such that the Day 1 study visit occurred at the end of an off-cycle. Use of inhaled hypertonic saline, a commonly used but not FDA-approved mucolytic/expectorant, was excluded.

The primary efficacy endpoint in both studies was improvement in lung function as determined by the mean absolute change from baseline in percent predicted predose FEV1 through 24 weeks of treatment. Covariates were age and baseline % predicted FEV1.

Prespecified key secondary endpoints included:

1. absolute change from baseline in sweat chloride through Week 24
2. absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain through Week 24
3. time to pulmonary exacerbation through Week 48 (study 102 only)
4. change from baseline in weight to Week 48 in study 102 and from baseline to Week 24 in study 103

Study Efficacy Findings

For studies 102 and 103B, sixty per cent of the study population was from North America while 40 per cent was from the European Union or Australia. As would be expected for CF, the demographics of the overall patient populations are notable for a study population that was almost exclusively Caucasian (98% in study 102 and 86% in study 103). For study 102 other demographics were similar between treatment groups with mean age of 26 years, and baseline mean FEV1 64% predicted, weight 61.5 kg, and sweat chloride of 100 mmol/L. For study 103B, conducted in the younger 6-11 year old age group, demographics were also similar between groups but patients were younger than in Study 102 with a mean age of 9 years and pulmonary function was better with baseline mean FEV1 84% predicted. Baseline mean weight was 30.9 kg and sweat chloride was 105 mmol/L.

The dropout rate was low in both of the two 48-week efficacy studies with 94% of patients in both studies 102 and 103B completing dosing through week 24 and 90% and 92% of patients in studies 102 and 103B, respectively, completing dosing through 48 weeks. Of note is that in study 102, fewer patients treated with VX-770 discontinued early (7) compared to patients who received placebo (15) although 6 of the patients who discontinued in the placebo group did so on Day 1 because they were determined to be ineligible.

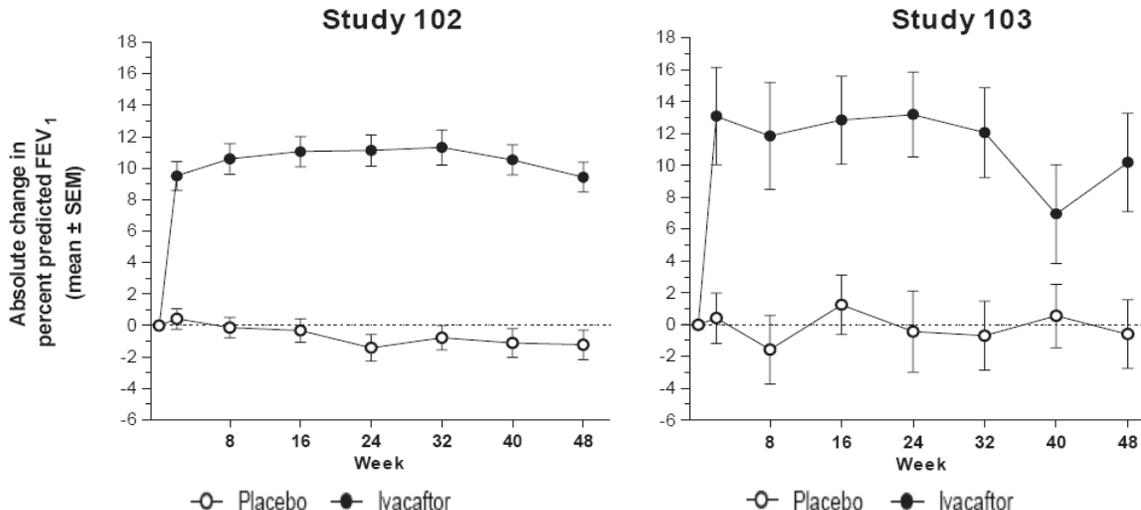
The most common reasons for early withdrawal in study 102 were due to adverse events (6), requirement for a prohibited medication (4), and noncompliance with study requirements and withdrawal of consent (2 each). For study 103B, a total of 4 patients failed to complete the 48 week treatment period, all in the placebo group. Reasons for discontinuation included withdrawal of consent, adverse event, requirement for a prohibited medication, and Other (1 patient in each category).

Treatment compliance, as determined by pill counting, was reported to be $\geq 93\%$ for all treatment groups across both studies. Mean treatment exposure in the VX-770 and placebo group was similar in both studies.

Primary Endpoint: Change from Baseline in Per Cent Predicted FEV1 at 24 Weeks

In both studies, treatment with VX-770 resulted in a significant improvement in FEV1. The treatment difference between VX-770 (labeled as ivacaftor in the figure below) and placebo for the mean absolute change in percent predicted FEV1 from baseline through Week 24 was 10.6 % ($p < 0.0001$) in study 102 and 12.5% ($p < 0.0001$) in study 103B. Because the overall dropout rate at Week 24 was low (6% in each study), we did not expect missing data to be an issue for this application. In fact, when different analytical methods and imputation strategies were applied, the results were consistent and highly significant. The results are visually depicted in the figure below.

Figure 2: Mean Absolute Change from Baseline in Percent Predicted FEV₁ by Treatment for Studies 102 (A) and 103 (B)



Analysis of subpopulations demonstrated that improvements in percent predicted FEV₁ were observed regardless of age, disease severity (as measured by lung function), sex, and geographic region. Additional subgroup analyses performed to determine if there was a difference in efficacy between patients with CF with the G551D/ Δ F508 genotype versus those with G551D/ non-F508 genotype also demonstrated no difference.

FEV₁ Non-Responders

While the overall efficacy data notes a statistically and clinically significant improvement in per cent predicted FEV₁ by 10% percent in study 102 and 12% in study 103B at week 24, there was a group of patients who did not demonstrate such an improvement. In examining data from study 102, there were a total of 18 patients who received VX-770, but did not achieve a change from baseline of at least 5% in percent predicted FEV₁ by week 24. Examination of baselines and genotype did not reveal any pattern of covariates such as age, sex, pulmonary function, geographic location, etc. which may account for 'non-responders'. Patient compliance or plasma concentration of VX-77 also did not explain a lack of response in FEV₁. However, the lack of response in FEV₁ may not predict lack of response in other clinically meaningful endpoints as 15 of the 18 FEV₁ non-responders had a response in weight gain (response defined as gain in weight \geq 50 % of the mean increase in weight for the study population).

Secondary endpoints

As described above major secondary endpoints for studies 102 and 103B included change from baseline in sweat chloride and CFQ-R (respiratory domain) through Week 24, time to pulmonary exacerbation through Week 48 (study 102 only), and change from baseline in weight to Week 48 in study 102 and from baseline to Week 24 in study 103B. Analysis of all key secondary endpoints were also statistically significant in favor of VX-770 in both studies, with the exception of the improvement in CFQ-R respiratory domain score through Week 24 ($p = 0.11$) in study 103B (see Table 3). Following are some specific comments regarding the clinical applicability of several of the endpoints.

Table 3 Results of Secondary Endpoints for Studies 102 and 103B

Secondary Endpoint	Study 102		Study 103	
	Treatment Difference	P value	Treatment Difference	P value
Absolute change from baseline in CFQ-R respiratory domain through Week 24 ^a	8.1 points	<0.0001	6.1 points	0.1092
Absolute change from baseline in sweat chloride through Week 24	-47.9 mmol/L	<0.0001	-54.3 mmol/L	<0.0001
Absolute change from baseline in weight at Week 48	2.7kg	<0.0001	1.9kg ^b	0.0004
Time-to-first Pulmonary Exacerbation through Week 48 (hazard ratio)	0.46	0.0012	NA	NA

^a The CFQ-R respiratory domain was used as an assessment tool for clinically relevant respiratory symptoms such as cough, wheeze, congestion, sputum production, and difficulty breathing
^b Weight change at Week 48 was the key endpoint for Study 102 and at Week 24 for Study 103
 [Source: Module 2.5, Clinical Overview, Sections 4.2 and 4.3, Tables 4 and 5]

Change in Weight

Since CF is a disease that affects multiple organs, given the mechanism of action of VX-770, during discussion over the design of the Phase 3 studies, the Division strongly recommended Vertex include a clinically relevant non-pulmonary endpoint in the phase 3 studies. Discussion focused on the gastrointestinal system with the possibility of assessing fecal fat as a measure of fat malabsorption. However, this endpoint had significant logistical problems and an assessment of weight as a measure of possible improvement in GI function was agreed upon. An improvement of 2-3 kg of weight in patients with CF is highly clinically significant for a population that has difficulty in weight gain as a result of fat and protein malabsorption and, possibly, the metabolic burden of the disease itself. Of note, weight data, when expressed as body mass index normalized for age and sex in patients <20 years of age, was consistent with absolute change from baseline in weight.

Time to First Pulmonary Exacerbation

Time-to-first pulmonary exacerbation through Week 48 was a key secondary endpoint for study 102. While there is no universally agreed upon definition of what constitutes an exacerbation of CF, the definition used consisted of documentation of increases in specific CF-related signs, symptoms, and therapies and was a slight adaptation from the definition of exacerbation used in clinical studies that supported regulatory approval of other CF therapies. A pulmonary exacerbation-free rate of 67% in the VX-770 group versus 41% in the placebo group from baseline through Week 48 is clinically meaningful and, again, supports the efficacy of VX-770 in CF patients with a G551D mutation in the CFTR gene.

Cystic Fibrosis Questionnaire-Revised Respiratory Domain Score

The CFQ-R is a disease-specific, patient reported, health-related quality of life measure for cystic fibrosis consisting of generic and CF-specific scales. While it is a commonly used patient reported outcome measure (PRO) for patients with CF, it has not met the criteria for validation outlined in the Agency's Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, December 2009. For the Applicant's clinical program, the respiratory domain of the CFQ-R was used as a secondary endpoint. While the single respiratory domain, again, has not been validated in this context of use, it does assess respiratory symptoms that are clinically relevant to patients with

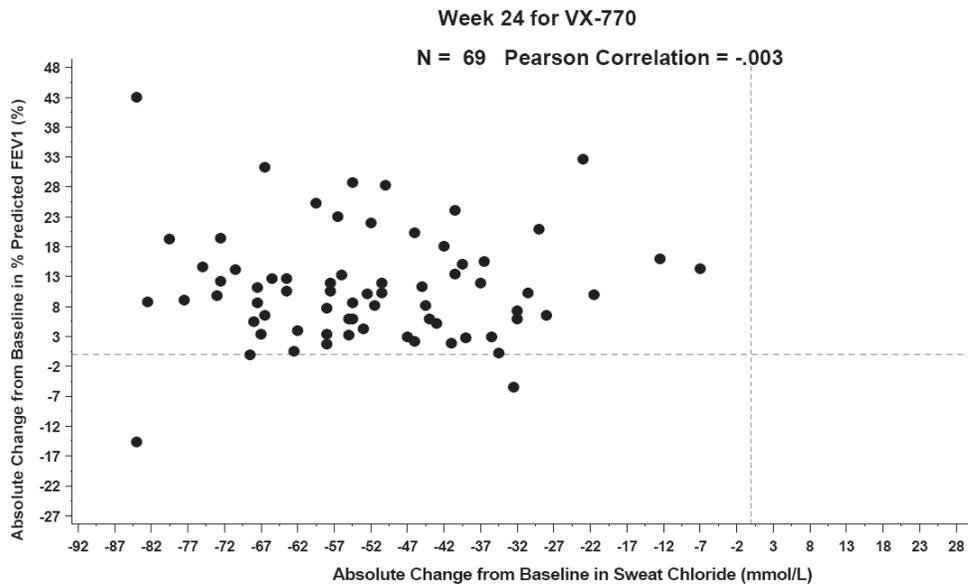
CF such as cough, wheeze, congestion, sputum production, and difficulty breathing. Improvements in the respiratory domain scores, therefore, provide additional support for a positive treatment effect for VX-770.

Sweat Chloride

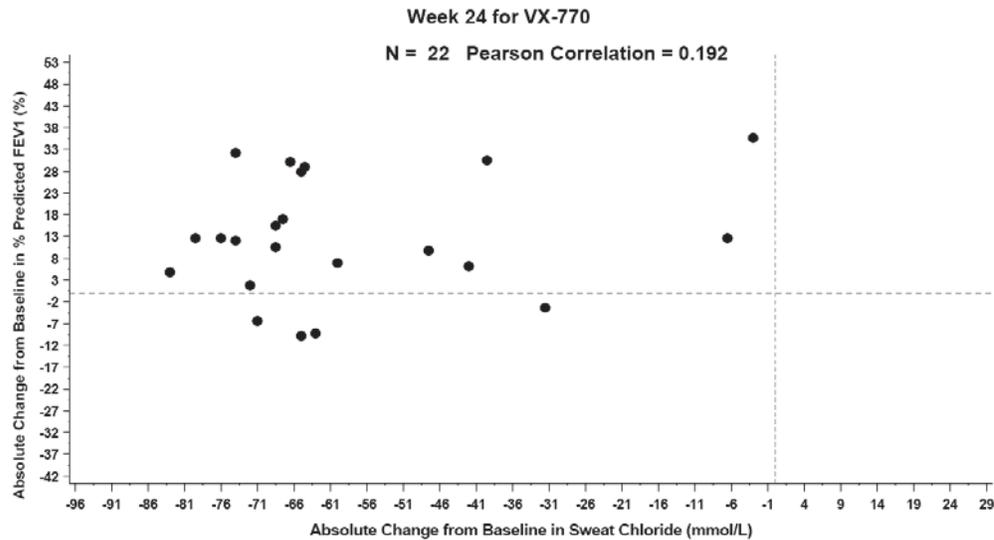
An elevated sweat chloride (generally > than 60 mmol/L), along with the expected clinical constellation of symptoms, has historically been the means by which CF is diagnosed. For the VX-770 program, it was a pharmacodynamic endpoint used as a surrogate measure of CFTR function. In this vein of thought, a marked and sustained decrease in sweat chloride by approximately half, as was demonstrated in studies 102 and 103B, would result in improved CFTR function, which, in turn, should lead to improved pulmonary function. While improvement in several disease parameters has been demonstrated for the VX-770 program, the hypothesis that decreases in sweat chloride, in and of itself, could be used to predict improvement in pulmonary function does not appear to be correct. As Figure 3 below demonstrates, there was no direct correlation between a decrease in sweat chloride levels and improvement in lung function (FEV1). Therefore, change of sweat chloride, while of interest, does not seem to be predictive of clinical outcome.

Figure 3 Scatter Plots of Absolute Change from Baseline in % Predicted FEV1 vs Absolute Change from Baseline in Sweat Chloride at Week 24 for Studies 102 (A) and 103B (B)

A



B



Adapted from Figure 14.2.4.1 Trial 102 CSR, page 1300/3623 and Figure 14.2.2.2 Trial 103 CSR, page 991/2366

Efficacy in Patients with CF Homozygous for the F508del Mutation in the CFTR Gene (Study 104)

Study 104 was a 16-week randomized, double-blind, placebo-controlled, parallel-group trial in 140 patients with CF age 12 years and older who were homozygous for the F508del mutation in the CFTR gene and who had FEV1 ^{(b) (4)} predicted. Patients were randomized 4:1 to receive VX-770 150 mg (n=112) every twelve hours or placebo (n=28) in addition to their prescribed CF therapies. The mean age of patients enrolled was 23 years and the mean baseline FEV1 was ^{(b) (4)} predicted (range ^{(b) (4)}). As in Studies 102 and 103B, patients who had persistent Burkholderia cenocepacia, dolosa, or Mycobacterium abscessus at screening isolated from sputum and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥ 3 times the upper limit of normal were excluded. The use of inhaled hypertonic saline was also not permitted.

The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline through Week 16 in percent predicted FEV1. Treatment with VX-770 resulted in no improvement in FEV1 relative to placebo in patients with CF homozygous for the F508del mutation in the CFTR gene (mean absolute change from baseline through Week 16 in percent predicted FEV1 was ^{(b) (4)} for patients in the VX-770 and placebo-treated groups, respectively (p = 0.15). There were no meaningful differences between patients treated with VX-770 compared to placebo for secondary endpoints (change in CFQ-R respiratory domain score, change in weight, or change in sweat chloride concentration). The results of this study convincingly demonstrate the lack of efficacy in patients with CF homozygous for the F508del mutation, the most common mutation in the CFTR gene resulting in CF.

Summary of Efficacy

For the patients with CF and a G551D mutation in the CFTR gene in trials 102 & 103B, the results from the analysis of the primary endpoint (absolute change in percent predicted FEV1 through Week 24) showed a statistically significant treatment effect for both studies through

Week 24 which was persistent through Week 48. Both trials indicated that the median change from baseline in the primary endpoint was approximately 10 % in the VX-770 group and zero in the placebo group through 24 and 48 weeks. Analysis of key secondary endpoints (CFQ-R respiratory domain score through weeks 24 and 48, change in sweat chloride concentration through weeks 24 and 48, time to first pulmonary exacerbation through weeks 24 and 48, and change in weight at weeks 24 and 48) also supported the efficacy of VX-770, with the exception of the improvement in CFQ-R respiratory domain score through Week 24 ($p = 0.11$) in study 103B. Study 104 was unsuccessful in demonstrating efficacy in patients with CF homozygous for the F508del mutation in the CFTR gene.

8. Safety

Database and Patient Demographics

The VX-770 safety data base, while small compared to that for more common conditions, is relatively robust for a subpopulation (those with G551D mutation) of an orphan disease (CF) in which there would be expected to be approximately 1500 patients in the indicated population in the United States. For the VX-770 clinical program, the relevant safety population consists of patients with CF with a G551D mutation in the CFTR gene who participated in the 2 one-year double-blind, placebo-controlled clinical studies used to support the safety and efficacy of VX-770 in the indicated population and an additional 16-week double-blind, placebo-controlled study in patients with CF with a different mutation in the CFTR (homozygous for the F508 deletion mutation in the CFTR gene). Study 101 was a proof-of-concept and dose-ranging study in 39 CF patients with the G551D mutation and provides some safety information for patients exposed to higher doses of VX-770 (250 mg every 12 hours for 4 weeks).

Additional studies conducted for the program consisted primarily of single-dose PK and PD studies in healthy volunteers including studies which evaluated food effect and drug interaction. Small studies in subjects with hepatic impairment and a thorough QT study were also conducted and are discussed in the summary of clinical pharmacology above.

Overall, then, the pooled safety set includes a total of 353 patients with CF (G551D- or F508-CFTR deletion mutation) who received either placebo or VX-770 in one of the 3 double-blind, placebo-controlled clinical studies from 16 to 48 weeks' duration. The pooled safety set includes 221 patients with CF in placebo-controlled studies who received VX-770 at a dose of 150mg every 12 hours and 132 patients who received placebo treatment. Of these patients, 213 patients were in the indicated population (carried at least one G551D mutation in the CFTR gene) of which 109 received VX-770 and 104 received placebo treatment. The other 112 patients with CF were enrolled in the 16-week study in CF patients homozygous for the F508 deletion CFTR allele (study 104). With regard to overall exposure to VX-770, of the 221 patients exposed to VX-770 at the proposed indicated dose, 188 (85%) were exposed for ≥ 16 weeks, 106 (48%) were exposed for ≥ 24 weeks, and 74 (34%) were exposed for \geq one year (48 weeks). If data from an open-label extension of studies 102 and 103 are included, approximately 101 patients with CF and a copy of the G551D mutation in the CFTR have been exposed to VX-770 for \geq one year. While exposure data do not meet the expectations outlined in the ICH E1A Guidance document, given the small population of patients in the United States in the indicated population, the exposure data are adequate.

In patients with CF, safety assessments included adverse events (including CF-related AEs such as exacerbations), clinical laboratories (including hematology, blood chemistry, UA, and pregnancy), vital signs, physical examinations, 12-lead electrocardiograms, and 24 Holter monitoring.

The demographics of the overall safety patient populations are notable for a study population that was overwhelmingly Caucasian (97%). Male and female enrollment was well-balanced, both overall and between VX-770 and active treatment groups. The median age of 21 years for the overall population was relatively young as would be expected. Thirty nine per cent of the population was between 6-17 years of age and 14% 6-11 years. The overall age range in the study population was 6 to 53 years.

Within each of the efficacy studies the demographic characteristics between treatment groups were similar with regard to CF severity as determined by baseline pulmonary function and use of common concomitant medications used by patients with CF (e.g., DNase and inhaled antibiotics). Patients enrolled in the adult and adolescent study (102) has somewhat worse pulmonary function (mean FEV1 64% predicted) than the younger 6-11 year-old study population enrolled in study 103B (mean FEV1 84% predicted).

Overall, few patients discontinued prematurely, with approximately 92-93% of patients completing the studies. A total of 11 patients discontinued due to adverse events (7 in the placebo group and 4 in the VX-770 group). Events reported in patients who discontinued who were treated with VX-770 include arthritis, myopathy, asthenia, fatigue, headache, and hepatic enzymes increased (all one patient).

Deaths

There were no deaths reported in the VX-770 clinical trials.

Serious Adverse Events

The more commonly observed SAEs reflected the relatively frequent occurrence of exacerbations of CF-related lung disease that is observed in this patient population. Exacerbations of CF lung disease, termed “CF Lung” SAEs by the Applicant occurred more commonly in placebo-treated patients (27%) compared to 10% in the VX-770 group. This difference in favor of the active treatment group also supports the efficacy of VX-770. In general, with the exception of several notable AEs discussed below, other SAEs also reflect common co-morbidities observed in the CF patient population. SAEs which occurred more frequently in VX-770-treated patients included abdominal pain, increased hepatic enzymes, and hypoglycemia which occurred in 2 patients each (1%).

Notable Adverse Events

There were several notable reports of events of interest that occurred in patients treated with VX-770:

IgA Nephropathy: A 20 year-old woman with a past medical history of hematuria and rhabdomyolysis enrolled in study 102 was hospitalized on Day 72 of VX-770 treatment for an

episode of hematuria. During the hospitalization study drug was continued. She presented with another SAE of hematuria on Day 100, and was again admitted to the hospital. Subsequently, she was seen by a nephrologist, who gave a presumptive diagnosis of IgA nephropathy based on history, physical, and laboratory findings. The patient completed the study. As the patient had a previous history of hematuria prior to beginning treatment with VX-770, it is doubtful the subsequent diagnosis of IgA nephropathy would be related to VX-770.

Anaphylactic Shock: A 12 year-old enrolled in study 102 experienced a SAE of CF exacerbation (CF lung) on Day 39 of treatment with VX-770. He continued to worsen, and was hospitalized on Day 44. Study drug was placed on hold that day, because of need for treatment with restricted medications. Closely following the patient's first infusion with the antibiotic levofloxacin, he experienced rash, pruritis, difficulty breathing, and circulatory issues, and was transferred to the ICU, where he received treatment with epinephrine, IV diphenhydramine, IV dexamethasone, and IV bolus of normal saline. Study drug continued to be held, and patient was discontinued from study treatment on Day 67, due to long-term requirement for treatment with prohibited medications. This event is strongly temporally related to administration of the quinolone antibiotic levofloxacin, known to be associated with serious allergic reactions.

Myopathy: A 15 year-old male patient enrolled in study 104 was noted to have muscle complaints beginning on Day 2 of study treatment with VX-770. He was hospitalized on Day 5 and treatment with VX-770 was discontinued. The patient continued to have intermittent episodes of elevated enzymes and myopathy throughout the follow-up period. Subsequent genetic testing demonstrated homozygous mutations of the AMPD1 gene, resulting in a diagnosis of myoadenylate deaminase deficiency. Given the subsequent diagnosis of a second genetic disease, the myopathy would not be related to VX-770.

Spontaneous Abortion: A 32 year-old woman in study 102 was noted on Day 151 of VX-770 to have a positive pregnancy test estimated to be within 2 weeks of conception. Study drug was discontinued that day. On Study Day 188, 38 days after VX-770 discontinuation, the woman was noted to have spontaneously aborted. The relationship between exposure to VX-770 and spontaneous abortion cannot be completely discounted. Evidence contrary to a link include that the event occurred over a month after study drug discontinuation and the lack of teratogenicity or effects on peri- and post-natal development in nonclinical studies.

Depression/ Suicidal Ideation: On Day 43 of VX-770 treatment, an 18 year-old man enrolled in study 104 with prior history of depression reportedly fell asleep while driving at 4 am leading to a single-vehicle car accident. The patient was evaluated in an emergency department, and discharged after a normal head CT. Three days later (Day 46), the patient was hospitalized for one week, for depression and suicidal ideation. Study drug was never discontinued and he completed the study. The relationship between VX-770 and the SAE is unlikely given the prior history of depression and the events leading up to the psychiatric hospital admission.

Common Adverse Events

For the safety pool, the most common adverse event for both treatment groups occurred in system classes which would be expected to have events for this patient population including respiratory, infectious, gastrointestinal, and laboratory investigations.

The most common adverse events observed in the overall double-blind, placebo-controlled clinical study data base in 353 patients with CF were headache (17%), upper respiratory tract infection (16%), nasal congestion (16%), nausea (10%), rash (10%), rhinitis (6%), dizziness (5%), arthralgia (5%), and bacteria in sputum (5%). The incidence of common adverse reactions in the indicated population of patients with CF and a G551D mutation in the CFTR are very similar. Table 4 below describes the incidence of adverse reactions (defined as adverse events which occurred in $\geq 8\%$ of VX-770 treated patients with a G551D mutation in the CFTR gene and greater than placebo) for the 2, 48-week clinical studies in the indicated population.

Table 4: Incidence of Adverse Drug Reactions in $\geq 8\%$ of VX-770-Treated Patients with a G551D Mutation in the CFTR Gene and Greater than Placebo in 2 Placebo Controlled Clinical Trials of 48 Weeks Duration

Adverse Reaction (Preferred Term)	Incidence: Pooled 48-week Trials	
	VX-770 N=109 n (%)	Placebo N=104 n (%)
Headache	26 (24)	17 (16)
Oropharyngeal pain	24 (22)	19 (18)
Upper respiratory tract infection	24 (22)	14 (14)
Nasal congestion	22 (20)	16 (15)
Abdominal pain	17 (16)	13 (13)
Nasopharyngitis	16 (15)	12 (12)
Diarrhea	14 (13)	10 (10)
Rash	14 (13)	7 (7)
Nausea	13 (12)	11 (11)
Dizziness	10 (9)	1 (1)

Of the common adverse reactions listed above, based on the nominal difference in number of events reported between VX-770 and placebo-treated patients, rash and dizziness stand out as possibly more strongly associated with use of VX-770. The events were not severe and none required study drug interruption or discontinuation. These events were also noted in pooled data from studies in healthy volunteers.

Vital Signs and Clinical Laboratory Assessments

No clinically significant mean or median changes in systolic or diastolic blood pressure, heart rate, respiratory rate, body temperature, or oxygen saturation were observed in patients during treatment with VX-770 versus placebo.

ECGs and Holter monitoring were also conducted in the clinical studies. Standard 12-lead ECG data noted that greater than 61-62% of both placebo and VX-770 treatment groups had abnormal but not clinically significant findings with about 2% having potentially-clinically significant findings at baseline. These incidences were less at the last scheduled study visit suggesting that there were no obviously apparent VX-770-specific ECG abnormalities. Summary statistics of heart rate, PR interval, RR interval, QT, QTcB, QTcF, QRS Axis, and QRS duration were similar between treatment groups.

Based on the finding of PVCs on ECGs in nonclinical studies in dogs receiving high doses of VX-770, 24-hour ECG monitoring was included in the clinical program. The 24-hour ECG data from the pooled safety set at baseline and throughout the treatment periods showed similar findings to the 12-lead ECGs, with any potentially clinically significant effect at slightly decreased rates in the VX-770-treated groups (5%) compared to placebo (7%). Across all 3 studies, 1 subject treated with VX-770 had a shift from normal baseline to a potentially clinically significantly abnormal finding. This subject had findings of sinus tachycardia, frequent sinus arrhythmia, rare ventricular ectopy, rare supraventricular ectopy, and 1 episode of supraventricular tachycardia on the 24-hour ambulatory ECG at week 24. The 24-hour ambulatory ECG for this subject at the next scheduled visit was normal. Very few cardiac SOC adverse events (total of 7) were reported in the clinical program. Three patients treated with VX-770 reported palpitations as an AE compared to none in the placebo group while placebo patients reported complete atrioventricular block and left ventricular dysfunction (one each).

A thorough QT study was also conducted to assess the impact of supratherapeutic doses of VX-770 (450 mg every 12 hours) on the QT interval. No effect of VX-770 on the QT interval was observed.

Specific Safety Issues

Elevations in Transaminases: As a result of pre-clinical studies demonstrating dose-related hepatic toxicities in rodents (albeit with an adequate margin of safety), assessments for liver injury were an potential safety signal of interest to the Applicant. Mild to moderate liver dysfunction is common in patients with CF with some patients progressing to liver failure usually due to liver cirrhosis. As a result, in the placebo-controlled safety and efficacy studies of VX-770, a degree of abnormal liver function was allowed with liver-related exclusion criterion at screening defined as $>3 \times$ upper limit of normal (ULN) of 3 or more of the following values: AST, ALT, GGT, alkaline phosphatase, and total bilirubin.

During an interim review of blinded safety data for studies 102 and 104, 3 patients were identified as having marked elevations in transaminases levels, with AST and/or ALT levels $> 8 \times$ ULN. As a result, Vertex increased the monitoring of LFTs to every 2 weeks for all study participants, in order to more closely monitor for potential liver toxicities. Subsequently, during a subsequent pre-planned interim review of blinded study results, no imbalances in severity or frequency of elevated transaminases were noted and monitoring of transaminases was amended to every 4 weeks.

Overall, the majority of patients (84% of the VX-770 and 83% of the placebo-treated patients) had no clinically-significant elevation in either AST or ALT during the total double-blind treatment period (defined as maximum AST or ALT < 2 times the ULN). Transaminase elevations between $\geq 3 \times$ ULN and $< 5 \times$ ULN were common and occurred at similar incidences in both groups: 14 (6%) subjects in the VX-770 group and 11 (8%) subjects in the placebo-treated group. Two per cent of patients in each group were noted to have elevations in AST or ALT ≥ 8 times the ULN.

That being said, there was a small imbalance in transaminase elevations reported as adverse events reported for the 48-week studies 120 and 103B which favored the placebo group with 15 patients (14%) reporting transaminase-related AEs in the placebo group versus 20 patients (18%) in the VX-770-treated group.

Interpretation of adverse events resulting from liver-related laboratory studies obtained in the clinical trial setting is complicated by the presence of CF-related liver dysfunction resulting in underlying relatively high rates of laboratory abnormalities in the CF population as a whole as demonstrated by the rates of elevated transaminases and total bilirubin found in the placebo-treated group. In addition, because many patients in the trials had elevated bilirubin levels at baseline, the application of Hy's Law (in which the finding that substantial elevation in ALT elevation, seen concurrently with bilirubin $>2xULN$, identifies a drug likely to cause severe liver injury at a rate roughly 1/10 the rate of Hy's Law cases) may not be as applicable as in a population without pre-existing cholestatic liver disease. Many patients with CF also frequently receive other medications (e.g., fluoroquinolone antibiotics) that are associated with increases in transaminases themselves. As most patients with elevations of ALT or AST $\geq 5x$ ULN had dosing interrupted, the history of continued dosing with VX-770 in that population is unknown. As a result of these confounding issues and relatively small safety data base due to the small patient population, it is reasonable to include the possibility of increased liver transaminases to the Warning and Precaution section of the label with a recommendation to monitor LFTs in patients receiving VX-770 with interruption of drug in patients for transaminases $\geq 5x$ ULN.

Safety Update

As described at 21 CFR 314.50(d)(5)(vi)(b), the Applicant was required to submit a safety update during the review period of the NDA. Vertex submitted the required update on January 6, 2012, which contained safety data from the open-label extension (listed by Vertex as study 105) of the two Phase 3 studies (102 and 103). The safety data were reviewed and no new safety signals were detected.

Summary of Safety

The safety information for VX-770 is derived primarily from studies 102, 103, and 104. Overall, the size of the safety database is acceptable for this sub-population of an orphan disease. The one-year duration of placebo-controlled Studies 102 and 103, supported by additional data from study 104, is adequate to allow for a determination of safety in the proposed population. Safety assessments were appropriate and included adverse events, physical examinations, vital signs, ECGs, and clinical laboratory testing.

No deaths were reported during the placebo-controlled trials, and SAEs were within what would be expected for a CF population, including CF exacerbations (reported as CF lung), and other respiratory, GI, and metabolic concerns. Review of additional safety data from healthy volunteers demonstrated no concerns, and there were no new safety signals identified from patients enrolled in the open-label extension (study 105).

Two potential safety concerns identified in the nonclinical development program included ECG changes (atrioventricular block and supraventricular premature contractions) in dogs, and dose-related liver findings in both rodent species (rat and mouse). In the clinical program there were no significant cardiac safety findings specific to treatment with VX-770. Regarding potential liver toxicities, while the evidence to implicate VX-770 as the cause of any elevation in transaminases observed by patients treated with VX-770 is scant, any determination is clouded by the relatively high incidence of transaminase elevations in CF patients who received placebo. However, given the small increase in liver adverse events in the VX-770 group, the nonclinical findings of liver toxicity in animals receiving very high doses of ivacaftor, and the CF population in general having increased overall risk for elevated transaminases, monitoring of liver function during initial treatment period with VX-770 is reasonable and will be included in the labeling. Common adverse events occurring more frequently in patients treated with VX-770 included headache, rash, dizziness, and upper respiratory tract infections, none of which pose a serious safety risk.

In summary, the data submitted support the safety of VX-770 in patients with CF and a G551D mutation in the CFTR gene. The safety risks of VX-770 appear relatively small and are more than balanced by the evidence for efficacy described above.

9. Advisory Committee Meeting

A pulmonary allergy drug advisory committee (PADAC) meeting was originally planned for in order to discuss the safety and efficacy of VX-770. However, after our initial review, the Division decided that the efficacy and safety were sufficiently robust that holding up approval to discuss at an AC was not necessary.

10. Pediatrics

The safety and efficacy of VX-770 in patients 6 to 17 years of age with CF who have a G551D mutation in the CFTR gene has been studied in 2 placebo-controlled clinical studies. One study evaluated 161 patients with CF who were 12 years of age or older and another evaluated 52 patients with CF who were 6 to 11 years of age. Both studies demonstrated substantial efficacy without major safety concerns.

While patients with CF are an orphan drug population and not subject to PREA, based on the knowledge that CF is a genetic disease which can manifest at birth, Vertex plans to conduct a clinical program in pediatric patients < 6 years of age.

11. Other Relevant Regulatory Issues

- CDRH consult: Because VX-770 will be indicated for only a subset of patients with CF who possess the G551D mutation in the CFTR and correct identification of the mutation is essential in identifying patients who may derive benefit, the Division consulted CDRH Office of In Vitro Diagnostics (OIVD) to help address the issue of specific mutation identification. OIVD noted there were several FDA-cleared

diagnostic tests which could detect the G551D mutation. Because identification of specific CFTR genotypes in patients diagnosed with CF is now considered standard of care in the CF community, most, if not all patients with CF will know their CFTR genotype. CDRH has recommended that if the genotype is not known, then an FDA-cleared CF-mutation diagnostic test be used to determine the patient's genotype.

- Financial Disclosure: For the trials designated as pivotal by the Applicant (102 and 103) one clinical investigator, (b) (6) had a significant equity interest as defined in 21 CFR 54.2(b). This investigator enrolled (b) (6) patients (b) (6) VX-770, (b) (6) (placebo) in study 102 out of the total enrollment of 161. Based on the few patients enrolled at this site and the robust efficacy demonstrated for both the primary and secondary endpoints, it is unlikely that any financial interest of this investigator could influence the results study 102.
- DSI audits information: At the request of the Division of Pulmonary, Allergy, and Rheumatology Products (DPAAP), the Division of Scientific Investigations (DSI) audited clinical sites that participated in Studies 102 and 103 (Joanne Billings/ University of Minnesota/Site# 011 for study 102 and Ahmet Uluer/ Children's Hospital Boston/Site# 045 for both studies 102 and 103). No irregularities were identified that would impact data integrity. Vertex' facility was also inspected and no significant data handling irregularities were uncovered.
- The Division of Medication Error Prevention and Analysis reviewed the proposed proprietary name "Kalydeco" from a safety and promotional perspective and judged it acceptable as of December 30, 2011.
- The Division of Risk Management and Division of Drug Marketing, Advertising, and Communications were consulted to review proposed patient labeling and edits made as appropriate.

12. Labeling

The Applicant submitted a product label in PLR format for review with the NDA submission. Labeling discussions are ongoing and have revolved around determination of dose modification due to drug-drug interactions and inclusion of clinical information in the CF population which was demonstrated not to benefit from VX-770 (those homozygous for the F508 deletion mutation in the CFTR gene). The establishment of a new class of drug "CFTR Potentiator" was also widely discussed. In addition, after input by the study endpoint and labeling team, the label will be modified to remove the term (b) (4) and replace it with the term "CF symptoms" which includes relevant respiratory symptoms.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action for this NDA is for Approval.

- Risk Benefit Assessment

The potential benefits of VX-770 in CF patients with a copy of the G551D mutation in the CFTR gene are substantial and outweigh any potential safety concerns. VX-770 would be the first treatment for patients with CF that actually addresses the defective ion channel that is the cause of CF. In the clinical studies submitted VX-770 the efficacy of VX-770 in the indicated population was robust with demonstration of clinically meaningful benefit in several aspects of CF, lung function, gastrointestinal function as demonstrated by substantial weight gain, and fewer pulmonary exacerbations of CF. While the longer-term efficacy of VX-770, such as a mortality benefit, are unknown, VX-770, given the efficacy already demonstrated, has the potential to be a life-changing therapy in patients with CF with a G551D mutation in the CFTR gene. The safety risks are relatively small, especially given the severity of the disease. There is a finding of possible increased liver transaminases in patients receiving VX-770 and it will be recommended that transaminases be monitored in patients prescribed VX-770.

1. Recommendation for Postmarketing Risk Management Activities

No additional postmarketing risk management activities are recommended beyond standard pharmacovigilance methods. However, Vertex, in order to further evaluate the safety of long-term use of VX-770 in the post-marketing setting, as a voluntary measure, plans to initiate a long-term observational safety study in patients with CF who receive VX-770 utilizing data collected in existing CF patient registries such as the extensive registry maintained by the CF Foundation in the United States.

2. Recommendation for other Postmarketing Study Commitments

The following postmarketing clinical pharmacology commitment is recommended:

In vitro studies indicate that VX-770 has the potential to inhibit P-gp, by which it can increase the exposure of co-administered drugs which are P-gp substrates. The degree of change in exposure of P-gp substrates is unknown, but it could be high and require adjustments in the dose of the co-administered P-gp substrate drug. Therefore, the Applicant will need to assess the impact of VX-770 administration on exposure of co-administered P-gp substrates in an *in vivo* study with a sensitive P-gp substrate, such as digoxin as a PMR.

3. Recommended Comments to Applicant

No additional comments are recommended to be conveyed.

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/s/

ANTHONY G DURMOWICZ
01/27/2012