CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203188Orig1s000

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Pulmonary, Allergy and Rheumatology Drug Products (HFD-570)

Application #:	**203,188**	**Application Type:**	**NDA**
Sponsor:	Vertex	**Proprietary Name:**	Ivacaftor
Investigator:		**USAN Name:**	VX-770
Category:	CFTR modifier	**Route of Administration:**	oral
Reviewer:	K. Witzmann, MD	**Review Date:**	11/29/2011

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
11/16/2011	11/16/2011	Response to IR	SD-6, e005

RELATED APPLICATIONS

Document Date	Application Type	Comments
10/18/2011	New Submission NDA 203,188	SD-01

REVIEW SUMMARY:

Background: This is a medical Officer brief review regarding a Response to Information Request for NDA 203,188, for VX-770. Vertex Pharmaceuticals submitted their completed NDA package on 10/18/2011, for VX-770, which is proposed to modify CFTR channel gating in subjects with CF and a G551D mutation. During the filing and initial review process, we noted that in the NDA package, a Contracted Research Organization, (b) (4) was listed as having been contracted to assist with data management. An Information Request dated November 10, 2011 was sent to the Sponsor, asking for them to clarify the role and responsibility of this CRO with regard to data collection and management.

This submission was a clarification from the Sponsor tha (b) (4) did not function as a CRO, but instead provided staff and services to create study documentation and provide training to staff. They clarified that Vertex maintained all data management for the covered trials.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY A WITZMANN
11/29/2011

MEDICAL OFFICER REVIEW

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Application #:	**203,188**	**Application Type:**	**NDA**
Sponsor:	Vertex	**Proprietary Name:**	ivacaftor
Investigator:		**USAN Name:**	VX-770
Category:	CFTR modifier	**Route of Administration:**	oral
Reviewer:	K. Witzmann, MD	**Review Date:**	11-22-2011

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
10-18-2011	10-18-2011	New NDA	SD-3, e002

REVIEW SUMMARY:

Vertex Pharmaceuticals is developing a small molecule drug, VX-770, (ivacaftor) as the first potential therapy for patients with a specific CFTR mutation (G551D) as the cause of cystic fibrosis. The drug's mechanism of action is to enhance 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). Vertex has submitted their complete NDA application, and this brief review addresses its fileability.

The indication being sought is "use for the treatment of cystic fibrosis in patients age 6 and older with a G551D-*CFTR* mutation." Attached are slides depicting a brief overview of the submission, including items that will require further evaluation in the formal review process, as well as the clinical filing check list. Based on this brief evaluation, there are a number of potential draft comments to the Sponsor with regard to their draft labeling. These comments affect the following sections of the draft labeling: Indications and Usage, Adverse Reactions (sections 6.1 and 6.2), Special Populations (section 8.9), Clinical Pharmacology (section 12.2), and Clinical Studies (section 14.1 and 14.2). These specific draft comments will be included in this review in detail, after the slide set and before the filing checklist.

Overall, the package meets the criteria set forth in CFR, and the package is fileable.

RECOMMENDED REGULATORY ACTION:

NDA Submission: ___X___ **Fileable** _____ **Not Fileable**

Medical Reviewer: K. Witzmann, MD DPARP

Medical Team Leader: A. Durmowicz, MD, DPARP

NDA 203,188
VX-770 (ivacaftor)
Vertex Pharmaceuticals
Filing Meeting

Kim Witzmann, MD
Medical Officer
Clinical Review
November 9, 2011

Regulatory History

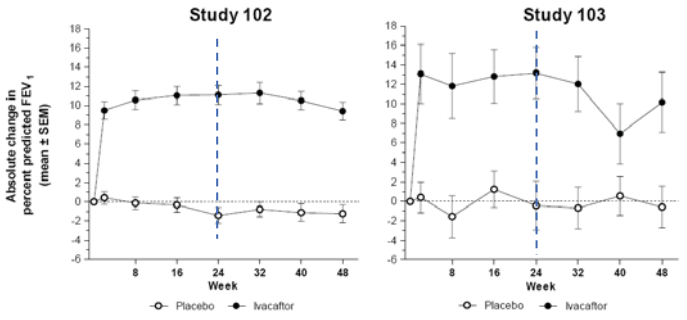
- 3/13/2006 Opening IND submitted
- 5/04/2006 Fast Track Designation granted
- 12/20/2006 Orphan Designation granted
- 6/28/2008 EOP1 Meeting
  - » "clinical relevance of sweat chloride as a biomarker in CF hasn't been shown"
  - » Study 103- small N, "a positive trend with strength overall is likely enough for approval"
  - » Recommend controlled safety data for 1 year
- 4/13/2009 EOP2 Comment sent (no Meeting held)
  - » "Positive results from 102, positive trend from 103 and 48-week safety data from 104 would be adequate for filing"
- 6/17/2011 Clinical Pre-NDA Meeting
  - » 48-week data at NDA submission
  - » CDRH involvement for potential genetic testing [six 510(k)-cleared tests all with G551D]

Clinical Development Program – P2/3

Trial	Design	Population	n	Treatment Arms	Duration	Key Objectives
101	R, DB, PC, Xover	≥ 18yo CF *G551D*	20 + 19	25/75mg BID vs. P/P 75/150mg vs. P/P 150mg BID vs. 250mg BID vs. P BID	14 days each dose 28days	Dose-ranging proof-of-concept
104 Part A	R, DB, PC, PG	≥ 12yo CF *ΔF508/ ΔF508*	140	150mg BID vs. Placebo (P)	16 weeks	Safety
102	R, DB, PC, PG	≥ 12yo CF *G551D*	161	150mg BID vs. Placebo	24 weeks 48 weeks	Efficacy Safety
103 Part B	R, DB, PC, PG	6- 11yo CF *G551D*	52	150mg BID vs. Placebo	24 weeks 48 weeks	Efficacy Safety
104 Part B Closed early	OL	≥ 12yo CF *ΔF508/ ΔF508*	38	150mg BID	96 weeks	Long-term Safety
105 Ongoing	OL	≥6yo CF *G551D* From 102/103	144 + XXX	150mg BID	96 weeks	Long-term Safety

Primary Efficacy= Week 24

Figure 1 **Studies 102 and 103: Absolute Change in Percent Predicted FEV_1 From Baseline Through Week 48, Full Analysis Set**



	Treatment Difference	*P* value	Treatment Difference	*P* value
Through Week 24	10.6 percentage points	<0.0001	12.5 percentage points	<0.0001
Through Week 48	10.5 percentage points	<0.0001	10.0 percentage points	0.0006

Source: Module 5.3.5.1/VX08-770-102/Figure 14.2.1.1, Table 14.2.1.2.1.1, and Table 14.2.1.2.1.2, and VX08-770-103/Figure 14.2.1.1, Table 14.2.1.2.1.1, and Table 14.2.1.2.1.2
SEM: standard error of the mean
Note: The graph represents summary statistics, and the table represents model-based statistics.

Ref: Module 2.7.3 Summary of Clinical Efficacy; Section 3.2.1, Fig 1, page 51

Secondary Efficacy-Key Endpoints

	For Study 102		For Study 103 (Children Ages 6 to 11) Respiratory Domain Score (points)	
Change from Baseline in CFQ-R Respiratory Domain Score (points)[b]				
Through Week 24 (Key Secondary Endpoint)	8.1 (4.7, 11.4)	<0.0001	6.1 (-1.4, 13.5)	0.1092
Through Week 48	8.6 (5.3, 11.9)	<0.0001	5.1 (-1.6, 11.8)	0.1354
Change from Baseline in Sweat Chloride (mmol/L)				
Through Week 24 (Key Secondary Endpoint)	-47.9 (-51.3, -44.5)	<0.0001	-54.3 (-61.8, -46.8)	<0.0001
Through Week 48	-48.1 (-51.5, -44.7)	<0.0001	-53.5 (-60.9, -46.0)	<0.0001
Time to First Pulmonary Exacerbation				
Through Week 24	0.40 (0.23, 0.71)[c]	0.0016		
Through Week 48 (Key Secondary Endpoint)	0.46 (0.28, 0.73)[c]	0.0012	(TTE is 3ry endpoint in study 103)	
Change from Baseline in Weight (kg)				
At Week 24	2.8 (1.8, 3.7)	<0.0001	1.9 (0.9, 2.9)	0.0004
At Week 48 (Key Secondary Endpoint)	2.7 (1.3, 4.1)	0.0001	2.8 (1.3, 4.2)	0.0002

Sources: Module 5.3.5.1/VX08-770-102/Table 14.2.1.2.1.1, Table 14.2.1.2.1.2, Table 14.2.3.2.1.1, Table 14.2.3.2.1.2, Table 14.2.2.2.1.1, Table 14.2.2.2.1.2, Figure 14.2.7.1.2.1, Figure 14.2.7.1.1.1, Table 14.2.4.2.1.1, and Table 14.2.4.2.1.2

[a] Treatment difference is ivacaftor to placebo (least squares [LS] mean absolute change)
[b] Data pooled from CFQ-R versions for adolescents/adults and for 12 to 13 years of age
[c] Hazard ratio (CI)

Source: Module 5.3.5.1/VX08-770-103/Table 14.2.1.2.1.1, Table 14.2.1.2.1.2, Table 14.2.3.2.1.1, Table 14.2.3.2.1.2, Table 14.2.2.2.1.1, Table 14.2.2.2.1.2, Figure 14.2.4.1, Table 14.2.4.2.1.1, Table 14.2.4.2.1.2

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Ref: Module 2.7.3, Summary of Clinical Efficacy; section 2.1.1, Table 3, page 25. and Section 2.1.2, Table 7, page 33.

Safety-Exposure

Table 7 Number of Subjects Exposed to Ivacaftor, Any Dose and Duration

Study Type (Population)	Subjects Exposed to Ivacaftor
Pooled Studies	
Pooled Phase 1 (10 studies in healthy subjects: Studies 001 [excluding Part D] through 003, 005 through 007, 009 through 012)	258
Pooled Phase 2b/3 studies (Studies 102, 103 Part B, 104, and 105 in subjects with CF)	293
Non-Pooled Studies	
Non-pooled Phase 1 (Study 008 in healthy subjects)	76
Non-pooled Phase 1 (Study 009-005 in healthy subjects)	18
Non-pooled Phase 1 (Study 013 in 12 hepatic impaired subjects and 12 healthy subjects)	24[a]
Non-pooled Phase 1 (Study 001, Part D in subjects with CF)	4
Non-pooled Phase 2a (Study 101 in subjects with CF)	31[b]
Non-pooled Phase 3 (Study 103 Part A in subjects with CF)	9[c]
Total Exposure: Subjects With CF	**324**[b,c,d]
Total Exposure: Healthy Subjects	**364**[a]
Total Exposure: All Subjects	**700**[a]

Source: Module 5.3.5.3/VX-770 ISS/Table 1.1.1 and Table 2.1.1.1; Appendix 1 (Section 11.1)

- Study 102 (N=161)
  - PI (78) → (68)
  - VX (83) → (77)
- Study 103 (N=52)
  - PI (26) → (22)
  - VX (26) → (26)

Total 48 Wks

104

Ref: Module 2.7.4 Summary of Clinical Safety; Table 7, pg 34 and Table 8, pg 37.

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Deaths, SAE, W/D due to AE

- **No Deaths**
- **W/D for AE: 7 Pl vs. 6 VX-770** (1 arthritis, 1 myopathy, 1 H/A, 1 increased hepatic enzymes; 2 in LT safety, myalgia leg pain)
- **SAE:**

Table 21 Incidence of SAEs in At Least 2 Subjects in Any Treatment Group by System Organ Class and Preferred Term: Pooled Phase 2b/3 Studies, Safety Set

System Organ Class Preferred Term	Placebo-Controlled Studies (102, 103 Part D, 104 Part A) Placebo (N = 132) n (%)	 Ivacaftor (N = 221) n (%)	Uncontrolled Extension Studies (104 Part D and 105) Placebo/ Ivacaftor (N = 72) n (%)	 Ivacaftor/ Ivacaftor (N = 110) n (%)	Overall Phase 2b/3 Studies All Ivacaftor (N = 293) n (%)
Subjects with Any SAE	**46 (34.8)**	**39 (17.6)**	**5 (6.9)**	**21 (19.1)**	**55 (18.8)**
Congenital, familial and genetic disorders	**35 (26.5)**	**23 (10.4)**	**2 (2.8)**	**17 (15.5)**	**36 (12.3)**
Cystic fibrosis lung	35 (26.5)	23 (10.4)	2 (2.8)	17 (15.5)	36 (12.3)
Respiratory, thoracic, and mediastinal disorders	**7 (5.3)**	**7 (3.2)**	**1 (1.4)**	**2 (1.8)**	**10 (3.4)**
Haemoptysis	4 (3.0)	2 (0.9)	1 (1.4)	2 (1.8)	5 (1.7)
Gastrointestinal disorders	**3 (2.3)**	**4 (1.8)**	**1 (1.4)**	**0**	**5 (1.7)**
Abdominal pain	0	2 (0.9)	0	0	2 (0.7)
Infections and infestations	**4 (3.0)**	**4 (1.8)**	**0**	**3 (2.7)**	**7 (2.4)**
Pneumonia	0	1 (0.5)	0	1 (0.9)	2 (0.7)
Investigations	**1 (0.8)**	**3 (1.4)**	**0**	**0**	**3 (1.0)**
Hepatic enzyme increased	0	2 (0.9)	0	0	2 (0.7)
Metabolism and nutrition disorders	**0**	**2 (0.9)**	**0**	**0**	**2 (0.7)**
Hypoglycaemia	0	2 (0.9)	0	0	2 (0.7)

Source: Module 5.3.5.3/VX-770 ISS SAP/Table 2.1.3.8

Ref: Module 2.7.4 Summary of Clinical Safety; Table 21, pg 59.

Overall AE

Table 1: Incidence of Adverse Drug Reactions in at Least 5% of KALYDECO-Treated Patients with the *G551D* in the *CFTR* Gene in the Phase 3 Trials with an Incidence of at Least 3% Compared to Placebo

Adverse Reaction (Preferred Term)	Incidence: Pooled Phase 3 Studies KALYDECO N=109 n (%)	 Placebo N=104 n (%)
Upper respiratory tract infection events*	69 (63.3)	52 (50.0)
Headache	26 (23.9)	17 (16.3)
Abdominal pain	17 (15.6)	13 (12.5)
Rash	14 (12.8)	7 (6.7)
Diarrhea	14 (12.8)	10 (9.6)
Dizziness	10 (9.2)	1 (1.0)
Bacteria in sputum	8 (7.3)	4 (3.8)

* Upper respiratory tract infection (URTI) events includes the following grouped list of terms: URTI, nasal congestion, pharyngeal erythema, oropharyngeal pain, rhinitis, sinus congestion, and nasopharyngitis.

Ref: Module 1.14 (b) (4)

Filing Meeting: FILEABLE

- Clinical Filing Checklist completed, no omissions noted
- DSI Audit
  - To discuss for this NME
- Pediatric Development Plan:
  Orphan status, not required

Planning for VX-770

Issues:

Consults
Efficacy
Safety
Label

Consults

1. QTc Study- (Partha)
2. Patient Labeling Team
3. DDMAC
4. CDRH- diagnostic test information required in the label?
5. SEALD- Is (b) (4) respiratory domain qualified?
6. DSI- Site selection for Clinical Inspection?

DSI: Clinical Study Sites

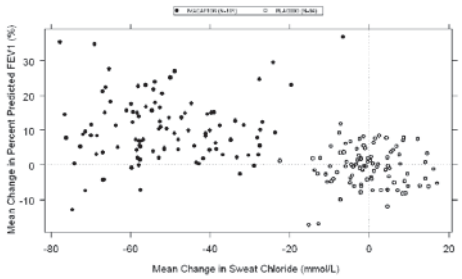
- Largest N=7, reasonable AE and SAE listings, protocol violations, etc.
- Study 102: 62% US/ 26%Eu/ 12%Au, 103: 52% US/ 21% Eu/ 27% Au
- Given High-profile, could we *NOT* inspect clinical sites?

Site #	Site	Study	N	Δ FEV1	reason
045	Children's Hosp Boston	102 103	5 2	7% --8%	+3% VX, -4% Pl -6% VX, +3% Pl Largest N
011	U of MN	102 103	5 1	+22% 1%	+17%VX (3), -5%P one Pl
014	CHOP	102	4	32%	One VX +30%, 3 Pl no Δ
019	Women/Children Buffalo	102	4	+24%	+21% VX (2)
022	LI Jewish/ Schneider's	102	3	+31%	+20% VX (2), -10% Pl
028	Riley Children's Indianapolis	103	2	+28%	+33% VX, +5% Pl
401	Belfast City Ireland	102	4	+30%	+22% VX (2), -9% Pl (b) (6)

Efficacy

- Overall, FEV1 increased 10% in VX group, all secondary endpoints supportive
- 25% of patients had a response less than 5%- examine
- Demographics vs. Efficacy
- Does best FEV1 correlate with best weight gain?
- Genotype correlation with benefit?

Figure 8 **Studies 102 and 103 (Pooled): By-Subject Change in Percent Predicted FEV_1 Versus Change in Sweat Chloride Concentrations From Baseline Through Week 48, Full Analysis Set**



ISE Fig 8, p59.

Safety

- Fewer CF exacerbations on VX than in placebo group
- Potential Liver concern during pivotal studies
  - 3 subjects with elevated transaminases >8x ULN
  - One VX and 2 placebo
  - Transaminase monitoring changed to Q2 weeks, review of blinded data showed low frequency of elevated transaminases, planned Interim reviews of Studies 102 and 104A did not show imbalances of groups

Table 27 Incidence of Subjects with ALT Abnormalities for Subjects With a Medical History of Elevated Liver Function Tests: Pooled Placebo-Controlled Phase 2b/3 Studies, Safety Set

	Placebo-Controlled Studies (102, 103 Part B, 104 Part A)					
	Placebo (N = 132)			Ivacaftor (N = 221)		
	History of Elevated LFTs n (%)	No History of Elevated LFTs n (%)	All n (%)	History of Elevated LFTs n (%)	No History of Elevated LFTs n (%)	All n (%)
Baseline						
N	22	110	132	34	187	221
No elevation	13 (59.1)	85 (77.3)	98 (74.2)	14 (41.2)	147 (78.6)	161 (72.9)
>1 × ULN	9 (40.9)	25 (22.7)	34 (25.8)	20 (58.8)	40 (21.4)	60 (27.1)
≥2 × ULN	1 (4.5)	3 (2.7)	4 (3.0)	6 (17.6)	4 (2.1)	10 (4.5)
≥3 × ULN	0	0	0	3 (8.8)	0	3 (1.4)
≥5 × ULN	0	0	0	1 (2.9)	0	1 (0.5)
≥8 × ULN	0	0	0	0	0	0
Maximum on-treatment						
N	22	109[a]	131[a]	34	187	221
No elevation	7 (31.8)	53 (48.6)	60 (45.8)	4 (11.8)	105 (56.1)	109 (49.3)
>1 × ULN	15 (68.2)	56 (51.4)	71 (54.2)	30 (88.2)	82 (43.9)	112 (50.7)
≥2 × ULN	6 (27.3)	10 (9.2)	16 (12.2)	13 (38.2)	17 (9.1)	30 (13.6)
≥3 × ULN	2 (9.1)	6 (5.5)	8 (6.1)	7 (20.6)	5 (2.7)	12 (5.4)
≥5 × ULN	1 (4.5)	2 (1.8)	3 (2.3)	3 (8.8)	1 (0.5)	4 (1.8)
≥8 × ULN	1 (4.5)	1 (0.9)	2 (1.5)	2 (5.9)	0	2 (0.9)

Source: Module 5.3.5.3/VX-770 ISS/Table 2.2.4.14 2.7.4 Summary of Clinical Safety Table 27 pg 69.

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(b) (4)

Mid-Cycle Deliverables

- Draft of Advisory Committee Clinical Package
- Draft Primary review
- Preliminary labeling review

COMMENTS TO THE SPONSOR WITH REGARD TO DRAFT LABELING

We have the following initial comments on the labeling submitted as part of the NDA October 18, 2011. These are based on information required in labeling as noted in 21 CFR 201.56 and the Guidance for Industry, Clinical Studies Section of Labeling for Human Prescription Drug and Biological Product - Content and Format, January 2006. We ask that you make the changes listed below and resubmit a revised package insert.

Indications and Usage

- Spell out the words for “CFTR” when used in the label for the first time.
- Insert a “Limitations of Use” subheading to note that Kalydeco has been shown to be effective only patients with cystic fibrosis who have a G551D mutation in the CFTR gene and that it is not effective in patients with cystic fibrosis who are homozygous for the F508 mutation in the CFTR.
- Insert a statement indicating that an FDA-approved test should be used to identify the presence of the G551D mutation.

Adverse Reactions

Section 6.1
Clinical Trials Experience:

- The safety data represented in Table 1 should include the "Adverse Reactions Reported in ≥5% of Patients Treated with Kalydeco 150 mg Twice Daily and Greater than Placebo in Placebo-controlled Trials of 48 Weeks Duration".

- The composite term "upper respiratory tract infection events" used in Table 1 should be "ungrouped" to include the appropriate preferred term, e.g., nasal congestion, rhinitis, nasopharyngitis, etc.

- After Table 1, include a section listing by system-organ-class adverse reactions that occurred in the Kalydeco group at a frequency of 1-5% where rates exceeded that in placebo group.

(b) (4)

Special Populations

Section 8.9
Use of Kalydeco in Patients with Other Mutations in the CFTR Gene

- (b) (4) Study 104 convincingly demonstrated that cystic fibrosis patients who are homozygous for the F508 deletion do not benefit from Kalydeco. Correct the language in Section 8.9 accordingly.

Clinical Pharmacology

Section 12.2
Pharmacodynamics

- As change in sweat chloride is a pharmacodynamic endpoint, the data demonstrating the effect of Kalydeco on sweat chloride should be described in the Pharmacodynamic section (b) (4)

(b) (4)

Clinical Studies

Section 14

- In this section studies should be described with regard to mutation in the CFTR gene rather than by specific study. For instance, Section 14.1 would describe "Studies in Patients with a G551D Mutation in the CFTR Gene. Section 14.2 should subsequently be titled as "Study in Patients Homozygous for the F508 Deletion in the CFTR Gene. The efficacy results currently described in Section 14.2 should be incorporated in Section 14.1.

- (b) (4) A statement stating changes in BMI were consistent with those for weight gain would suffice.

- Figure 5 adds no additional efficacy information not presented in Figure 1 and should be deleted.

NDA Number: 203,188 **Applicant: Vertex** **Stamp Date: 10-18-2011**

Drug Name: VX-770 (ivacaftor) **NDA Type: 505(b)(1)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				**505(b)(1)**
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: **101** Study Title: **Ph 2a, R, DB, PC study of VX-770 to evaluate safety, PK, and biomarkers of CFTR activity in CF subjects with genotype G551D** Sample Size: **N=39** Arms: **2** Location in submission: **Mod 5.3.4.2** Study Number: **103 Part A** Study Title: **Ph 3, 2-part, R, DB, PC, PG study to**	X			

	Content Parameter	Yes	No	NA	Comment
	evaluate PK, efficacy and safety of VX-770 in subjects 6-11yo with CF and the G551D mutation Sample Size: **N=12** Arms: **1** Location in submission: **Mod 5.3.5.1**				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: **102** **Module 5.3.5.1** Indication: **Male and female subjects with CF, 12 years of age and older, who have the G551D-CFTR mutation in at least 1 allele** Pivotal Study #2: **103 Part B** **Module 5.3.5.1** Indication: **Subjects with CF 6-11yo who have a G551D-CFTR mutation on at least 1 allele**	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Primary endpoint conforms to FDA comment, no formal agreements in place
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			Orphan disease, limited population
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	Orphan indication, ICH not applicable, but adequate data at 48 weeks+ submitted

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	Content Parameter	Yes	No	NA	Comment
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	NME in expected new drug class
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			No deaths occurred in development program, but narratives for all SAE included
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Orphan (not required)
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			Majority of studies performed in US; Orphan disease
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report	X			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
	Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?				
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

See preliminary labeling comments to the Applicant above.

K. Witzmann, MD — November 17, 2011
Reviewing Medical Officer — Date

A. Durmowicz, MD — November 23, 2011
Clinical Team Leader — Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY A WITZMANN
11/23/2011

ANTHONY G DURMOWICZ
11/23/2011

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203,188
Priority or Standard	Priority
Submit Date(s)	October 18, 2011
Received Date(s)	October 18, 2011
PDUFA Goal Date	April 18, 2012
Division / Office	DPARP/ ODE II
Reviewer Name(s)	Kimberly A. Witzmann, MD
Review Completion Date	January 17, 2012
Established Name	VX-770; ivacaftor
(Proposed) Trade Name	Kalydeco
Therapeutic Class	CFTR Potentiator (pending final review)
Applicant	Vertex Pharmaceuticals
Formulation(s)	Film-coated tablet
Dosing Regimen	150mg every 12 hours
Indication(s)	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
Intended Population(s)	CF patients age 6 years and older who have a G551D mutation in the CFTR gene

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommended regulatory action, from a clinical perspective, is **Approval** of VX-770 (ivacaftor) 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, at a chronic dose of 150mg orally every 12 hours, taken with a fat-containing food.

1.2 Risk Benefit Assessment

The risk-benefit profile supports the approval of VX-770, as noted above. For this program, efficacy was demonstrated in two randomized, placebo-controlled, double-blinded clinical trials of 48 weeks' duration, in which treatment with VX-770 improved lung function (as measured by absolute change in percent predicted FEV1 from baseline to week 24) by 10 and 12% in studies in adolescents/ adults, and in children aged 6-11 years, respectively. Secondary endpoints, including weight gain and time to first exacerbation, were supportive of efficacy. VX-770 was well-tolerated, and demonstrated no major safety signals in clinical trials. No deaths were reported, SAEs were generally those associated with CF (exacerbations, pneumonia, GI issues), and number of discontinuations was low. Common AE included headache, upper respiratory tract infection, nasal congestion, nausea, rash, rhinitis, dizziness, arthralgia, and bacteria in sputum, which were generally well-tolerated. Laboratory assessments suggest the possibility that VX-770 may be associated with an increase in liver transaminases, but the increase was only slightly over those who received placebo treatment in the clinical trials. Transaminases are recommended to be monitored in patients receiving VX-770. There are a number of drug-drug interactions for VX-770; these will be addressed in labeling. Overall, there is a robust clinical benefit for VX-770, with no major safety signals identified.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Given the favorable risk-benefit determination and safety profile of VX-770, no formal postmarket risk evaluation and mitigation strategies are warranted. The continued evaluation of safety can be assessed with standard pharmacovigilence, as required by regulation. However, the Applicant plans to further evaluate the safety of long-term VX-

770 use in the post-market setting as a voluntary measure, by initiating a long-term observational study which will utilize data collected in existing CF patient registries.

The Applicant is also planning studies to evaluate the effects of VX-770 in pediatric patients less than 6 years of age with a G551D mutation, as well as in patients with other gating mutations, and those who have a mutation in CFTR with residual CFTR function.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations from the Clinical team for any post-marketing commitments or requirements.

2 Introduction and Regulatory Background

2.1 Product Information

Information

The chemical name for VX-770 (also called ivacaftor) is N-(2, 4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxymide. The proposed trade name is Kalydeco®. VX-770 is a new molecular entity, which is an orally-bioavailable small molecule that targets the underlying defect in a subgroup of patients with cystic fibrosis. Its proposed mechanism of action is to act on the CFTR protein to increase the channel-open probability (gating) to increase chloride transport (see Brief Clinical Background section below for more details). The proposed indication for VX-770 is 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 proposed chronic dosing regimen is 150mg every 12 hours, to be taken with a fat-containing food.

VX-770 is formulated as a waxed, light blue film-coated tablet containing 150mg of VX-770 drug substance. Each tablet contains the following excipients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet film coat contains carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, and titanium dioxide. The printing ink contains ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

The to-be-marketed formulation is the same as those used in Phase 2B/3 trials, except tablets were packaged as blister dose cards for the clinical trials, but will be marketed in high-density polyethylene 60-tablet bottles.

Brief Clinical Background

Cystic fibrosis (CF) is an autosomal recessive genetic disease that affects approximately 30,000 children and adults in the United States[1], and approximately 36,000 children and adults in Europe[2]. Approximately one in 3,500 children in the United States is born with CF each year, and CF affects all ethnic and racial groups, although is most common in Caucasians. There is no cure for cystic fibrosis, and despite progress in the treatment of the disease, the predicted median age of survival for a person with CF is the mid-30's[1].

In 1989, researchers discovered the gene that caused CF[3], which codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The CFTR protein is an epithelial chloride ion channel, which aids in the regulation of salt and water absorption and secretion throughout the body. Lack of properly functioning CFTR is responsible for the clinical sequelae of CF, including malabsorption of nutrients, and the inability to mobilize tenacious respiratory secretions, leading to recurrent infections and lung damage. While CF affects most organ systems in the body, the majority of morbidity and mortality from cystic fibrosis results from its effects in the lungs[4]. The lack of normally functioning CFTR causes abnormal chloride secretion and water reabsorption, leading to dehydration of the airway surface liquid and impaired mucociliary clearance. Over time, the CF lung is exposed to a vicious cycle of infection, inflammation, and damage, which causes progressive and irreversible airways obstruction, bronchiectasis, and ultimately respiratory failure[5, 6].

The mutations in the CFTR gene result in reductions in quantity, quality, or both, of the CFTR proteins. These mutations have been classified into groups by their mechanism of action. Class 2 mutations (such as ΔF508) cause improper folding and processing of the protein, which leads to degradation in the endoplasmic reticulum and failure of the protein to reach the cell membrane. Class 3 mutations (such as G551D) create proteins that reach the cell surface, but do not respond normally to activation signals[7], and are termed "gating mutations."

Agents that increase the chloride ion transport properties of the channel in the presence of cyclic AMP-dependent protein kinase A activation have been termed "potentiators" in the literature. VX-770 is one such drug; currently, there are no drugs marketed that alter CFTR function. By increasing the chloride channel opening, these agents could lead to more normally hydrated airway secretions, which could break the cycle of obstruction, infection, inflammation, and damage that ultimately leads to respiratory failure for patients with CF.

In the United States, approximately 90% of patients carry at least one ΔF508 allele[1], with 60-70% of patients being homozygous for ΔF508. Worldwide, approximately 4% of patients carry the G551D mutation[1, 8]. Vertex has conducted a development program to evaluate the use of VX-770 in these two populations.

2.2 Tables of Currently Available Treatments for Proposed Indications

VX-770 is the only drug proposed to treat the underlying defect identified in a subpopulation of patients with cystic fibrosis, namely those with at least one copy of the G551D- CFTR mutation. There are no other drugs available to treat cystic fibrosis, but a number of drugs are used to treat the symptoms and sequelae of the disease. Listed below in the table are drugs commonly used for the treatment of cystic fibrosis and its complications, including those with both FDA-approved indications and those with common off-label usage. This list is not exhaustive, but is rather meant to address the most common categories of medications typically utilized by patients with CF.

Table 1: Drugs Commonly Used for the Treatment of Cystic Fibrosis

Active Ingredient	Trade Name	FDA-approved for CF Indication?
Inhaled Antibiotics for the Treatment of Pseudomonas aeruginosa		
Tobramycin (nebulized)	TOBI	Yes
Aztreonam (nebulized)	Cayston	Yes
Polymyxin E (IV form given via nebulizer)	Colistin	No
Inhaled Treatments used as Mucolytics		
Dornase alpha (DNase)	Pulmozyme	Yes
Hypertonic Saline (7%)	----	No
Oral Pancreatic Enzyme Supplementation		
Pancrease, pancrelipase	Creon, Pancreaze, Zenpep, Pancrelipase™	Yes
Inhaled Bronchodilators		
Albuterol sulfate	Pro-Air, Ventolin, Proventil, Albuterol™, etc.	Approved as bronchodilator
Levalbuterol hydrochloride	Xopenex	Approved as bronchodilator
Anti-Inflammatory Agents		
Oral azithromycin	Zithromax	No
Oral high-dose Ibuprofen	Motrin, Advil, etc.	No
[Source: Approved labeling data from Drugs@FDA,.gov]		

2.3 Availability of Proposed Active Ingredient in the United States

VX-770 is a new molecular entity, and is not currently marketed in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

VX-770 is a new molecular entity with no related drugs, so there are no issues to note.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Prior to submission of this NDA, VX-770 has been the subject of multiple regulatory proceedings, (as IND 74,633), summarized below:

- Opening IND Submission (March 13, 2006)
  - Initial safety review noted that preclinical data did not support doses over 500mg
  - Teleconference held with Applicant (April 12, 2006) to discuss modification of protocol
  - The modified protocol with doses <500mg was allowed to proceed
- Fast Track designation granted (May 4, 2006)
- Orphan drug product designation granted (December 20th, 2006) for the treatment of patients with cystic fibrosis
- End-of-Phase-1 Meeting (June 28, 2008) Key points discussed included:
  - Clinical relevance of sweat chloride as a biomarker in CF has not been demonstrated
  - Controlled data for 1 year would better support durability of treatment effect
  - Safety data for 1 year was recommended
  - Study 103 (small pediatric study) showing a positive trend to support Study 102 in adolescents and adults would likely be adequate for approval, given the small number of patients
- FDA sent End-of-Phase-2 pre-meeting comments to Applicant (April 13th, 2009)
  - Meeting was later cancelled
  - Comments 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
- Clinical Pre-NDA meeting held with Applicant (June 17, 2011), discussion included:
  - The need for 48-week data at the time of NDA submission
  - That the Center for Devices and Radiologic Health (CDRH) would need to be involved with regard to potential genetic testing issues
  - Early submission of CMC portion of NDA discussed

- CDRH sent a Pre-IDE Memorandum to the Applicant (July 29, 2011), with regard to potential development of CF mutation screening test
    - Since there are six 510(k)-cleared genetic mutation screening tests on the market, as well as gene sequence testing, CDRH informed the Applicant that it would not be necessary for them to develop their own test if they did not wish to do so
- The Applicant began submitting portions of the NDA (July 27, 2011)
- NDA submission was completed (October 18, 2011)

2.6 Other Relevant Background Information

Not applicable

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The original NDA dated October 18, 2011, was submitted in electronic common technical document (eCTD) format, well-organized, and easily navigated by this reviewer. There were no issues with respect to submission quality and/or integrity.

The Division has requested an audit by the Office of Scientific Investigation (OSI) for this NDA, since VX-770 is new molecular entity proposed for an indication for which there are no FDA-approved therapies. Due to the rarity of this orphan disease, and that only 4% of the CF population carries a G551D mutation, there were a large number of US and international clinical trial sites, with few subjects enrolled at each site. Two sites were recommended for audit based on relatively high enrollment, and demonstration of outcomes that were in favor of VX-770. Preliminary report of the DSI inspections notes that there were no deficiencies found at the clinical sites operated by Drs. Billings and Uluer, and that both were in compliance with Good Clinical Practices (GCP), and required no action (NAI). In addition, because VX-770 is a new molecular entity, the Vertex company site was also inspected, to assess the Applicant's oversight of the clinical trials; this inspection was found to be in compliance with regulations. Overall, the OSI inspections concluded that no regulatory violations were noted, and based on inspectional findings, the study data collected appear generally reliable in support of the requested indication. Please refer to Dr. Anthony Orencia's Clinical Inspection Summary for further details.

3.2 Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices is located in each clinical study report, within the electronic submission.

3.3 Financial Disclosures

The Applicant has submitted a Debarment statement to Module 1.3.3 of this NDA submission, certifying that no debarred individuals were used in the conduct of the trials included in this NDA.

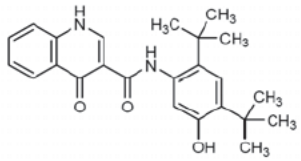
The Applicant has submitted the following financial interest form, in accordance with 21CFR part 54:

- [redacted] (b) (6) (trial VX08-770-102) Category 2: Significant payments. [redacted] (b) (6) was noted to have received financial compensation for an educational symposium, advisory board participation, European regulatory dossier review, and for consultation at the European regulatory meeting. [redacted] (b) (6) enrolled [redacted] (b) (4) subjects [redacted] (b) (4) in each treatment group) out of the total 167 patients, into Study 102. Even though this site had a greater than 20% treatment effect in primary efficacy between placebo and VX-770-treated patients, the small patient number relative to the total population of Study 102 means that [redacted] (b) (6) financial interest could not have significantly affected the results of Study 102.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The chemical name for VX-770 (also called ivacaftor) is N-(2, 4-Di-tert-butyl-5-hydroxyphenyl)-1, 4-dihydro-4-oxoquinoline-3-carboxymide. The molecular formula of VX-770 is $C_{24}H_{28}N_2O_3$ and its molecular weight is 392.49 grams per mole. VX-770 has the following structural formula:



VX-770 is a white to off-white powder that is practically insoluble in water. VX-770 is formulated as a waxed, light blue capsule-shaped, film-coated tablet for oral administration containing 150mg of VX-770 drug substance. Each tablet contains the following excipients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet film coat contains carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, and titanium dioxide. The printing ink contains ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

The CMC reviewer has identified two primary issues with the drug substance.

- A number of compounds were identified as observed, potential, or theoretical (b) (4) impurities that possessed structural alerts for genotoxicity. This issue was evaluated by Dr. Timothy Robison, Ph.D., D.A.B.T., in consultation to CMC. Dr. Robison has determined that the potentia (b) (4) impurities, heavy metals, and residual solvents found in the drug substance, (b) (4), and/or drug product are considered qualified from a toxicologic perspective.
- (b) (4) In order to address this issue, discussion of drug product dissolution procedures and specifications are ongoing.

The recommendation from the CMC Review Team is Approval, pending agreement with regard to the methodology and specifications for determining dissolution of the final drug product. Further details can be found in Dr. Arthur Shaw's CMC Review and Dr. Sandra Suarez' Biopharmacology Review.

4.2 Clinical Microbiology

Not applicable

4.3 Preclinical Pharmacology/Toxicology

The recommendation from the Nonclinical Review is for Approval. Please refer to Dr. Marcie Wood's full Non-clinical Review for additional details to any of these sections, except as noted.

Safety Pharmacology

Safety pharmacology studies were conducted to assess the neurological, cardiovascular, pulmonary, and gastrointestinal effects of VX-770. Treatment-related findings were limited to inhibition of hERG current in vitro and a decrease in gastrointestinal motility in rats that received single oral doses of VX-770.

General Toxicology

General toxicology studies were conducted in the mouse, rat, and dog up to 3-months, 6-months, and 12-months. Target organs identified by general toxicity studies included the liver in mice and rats (hepatocellular necrosis), and the gastrointestinal tract in dogs (clinical signs of abnormal feces and vomiting). Supraventricular premature complex (SVPC) was also observed in dogs in the 12-month toxicity study. Gastrointestinal clinical signs and ECG findings were considered to be clinically monitorable, and were not used in safety factor determinations for clinical doses.

Genetic Toxicology

VX-770 was negative in a bacterial reverse mutation assay, a Chinese hamster ovary chromosomal aberration assay, and in an in vivo mouse micronucleus assay.

Reproductive and Developmental Toxicity

A battery of reproductive and developmental toxicity studies of VX-770 were completed in rats and rabbits. These studies evaluated the effect of VX-770 on fertility in rats, teratogenicity in rats and rabbits, and peri- and post-natal development in rats. Results showed that VX-770 decreased fertility indices in male and female rats at doses of 200 mg/kg/day, but that the dose that caused any fertility effect was essentially the lethal dose in the parent animal, giving the finding of impaired fertility at the highest dose no clinical relevance. Results from teratogenicity studies demonstrated that the drug was non-teratogenic in rats and rabbits. VX-770 had no effects on peri- and post-natal development in rats. The NOAEL of VX-770 for reproductive toxicity was 100 and 100 mg/kg/day in rat and rabbits, respectively. Please refer to the full non-clinical Reproductive Toxicology Review of Dr. Luqi Pei for more detailed information.

Carcinogenicity

2-year mouse and 2-year rat carcinogenicity studies were carried out under GLP, and with agreement by the FDA. The Executive Carcinogenicity Advisory Committee (ECAC) concurred that both mouse and rat carcinogenicity studies were acceptable and that there were no test article-related tumor findings in either study. The ECAC also concurred that coverage for parent and metabolites was acceptable.

4.4 Clinical Pharmacology

The Clinical Pharmacology recommendation is for Approval. Refer to sections 7.2.5 and 7.5.5 of this review, and Dr Lokesh Jain's Clinical Pharmacology Review, for additional clinical pharmacology information.

4.4.1 Mechanism of Action

VX-770 is a potentiator of the CFTR protein. The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. VX-770 appears to increase the probability of CFTR channel opening (or gating) to enhance chloride transport.

4.4.2 Pharmacodynamics

Sweat Chloride Evaluation

In clinical trials in patients with the G551D mutation in the CFTR gene, VX-770 led to statistically significant reductions in sweat chloride concentration. In two randomized, double-blind, placebo-controlled clinical trials (one in patients 12years and older, and the other in patients 6-11 years of age), the mean change in sweat chloride from baseline through week 24 was -48 (95% CI -51, -45) and -54 (95% CI -62, -47), respectively. These changes persisted through 48 weeks. The clinical significance of this finding is unknown.

ECG Evaluation (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 supratherapeutic 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 supratherapeutic 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 $\Delta\Delta$QTcF for the active comparator moxifloxacin was greater than 5 ms.

In summary, treatment with VX-770 at the therapeutic dose (150 mg every12 hours) or at a supratherapeutic dose (450 mg every12 hours) had no significant QTc prolongation effect, on the QTcF and QTcB intervals.

4.4.3 Pharmacokinetics

The pharmacokinetics of VX-770 is similar between healthy adult volunteers and patients with CF.

After oral administration of a single 150 mg dose to healthy volunteers in fed state, peak plasma concentrations (Tmax) occurred at approximately 4 hours, and the mean (±SD) for AUC and Cmax were 8814 ± 4363 ng*hr/mL and 673 ± 245 ng/mL, respectively.

After every 12 hour dosing, steady-state plasma concentrations of VX-770 were reached by days 3 to 5, with accumulation ratio ranging from 2.2 to 2.9.

Absorption
The exposure of VX-770 increased approximately 2- to 4-fold when given with food containing fat. Therefore, VX-770 should be administered with fat-containing food. The median (range) Tmax is approximately 4.0 (3.0; 6.0) hours in the fed state.

Distribution
VX-770 is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin. VX-770 does not bind to human red blood cells.

The mean apparent volume of distribution (Vz/F) of VX-770 after a single dose of 275 mg of VX-770 in the fed state was similar for healthy volunteers and patients with CF.

Metabolism
VX-770 is extensively metabolized in humans. In vitro and clinical studies indicate that VX-770 is primarily metabolized by CYP3A. M1 and M6 are the two major metabolites of VX-770 in humans. M1 has approximately one-sixth the potency of VX-770 and is considered pharmacologically active. M6 has less than one-fiftieth the potency of VX-770 and is not considered pharmacologically active.

Section 7.5.5 Drug-Drug Interactions, of this review contains more detailed information on metabolism and drug-drug interactions; please refer there for more details.

Elimination
Following oral administration, the majority of VX-770 (87.8%) is eliminated in the feces after metabolic conversion. The major metabolites M1 and M6 accounted for approximately 65% of the total dose eliminated with 22% as M1 and 43% as M6. There was negligible urinary excretion of VX-770 as unchanged parent. The apparent terminal half-life was approximately 12 hours following a single dose. The mean (SD) apparent

clearance (CL/F) of VX-770 was similar for healthy volunteers and patients with CF: CL/F was 12.1 (5.0) L/hr in healthy volunteers and 12.4 (5.9) L/hr in patients with CF.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant's Clinical Development program for VX-770 was comprised of 22 clinical studies, which include fifteen clinical pharmacology studies in healthy volunteers, two studies in patients with cystic fibrosis to evaluate exploratory biomarkers, and five Phase 2/3 studies which form the primary basis for evaluation of the clinical efficacy and safety of VX-770 in patients with cystic fibrosis. These studies are briefly described in the tables below.

Reviewer's Comment:
The Applicant notes throughout their package that their program consists of 23 studies, but only 22 are listed in Module 5.2, under development for this IND. When we queried the Applicant, they noted that they included a single-patient IND using VX-770 drug product in their total count, but did not include further reference to it in their NDA submission, because the individual Clinical Investigator (and not Vertex) is responsible for control of that data.

Table 2: Late-Phase Studies Relevant to Clinical Regulatory Decision-Making

Study #/ Years conducted	Study Type/ Design	Study Duration	CF Mutation	Pt Age (years)	Baseline FEV1	n	Treatment Arms	Countries
Dose-Ranging and Proof of Concept								
101 2007-2008	Dose-ranging, PK, PD R, DB, PC, X-over Proof-of-concept	2 weeks 4 weeks	***G551D***	≥ 18	≥ 40%	39	Part 1[a] VX-770: 25, 75, 150, 250mg, Placebo Part 2[a] VX-770: 150, 250mg, Placebo	North America, Germany
103[b] Part A 2009	Open-label, PK Dose-finding	1 day	**G551D**	6-11	40- 105%	12[b]	100mg single dose VX-770	N. America, Europe, Australia
Phase 3 and Supportive								
102 2009-2011	Efficacy Safety R, DB, PC, PG	24/48 weeks[c]	***G551D***	≥ 12	40- 90%	161	150mg BID vs. Placebo	N. America, Europe, Australia
103 Part B 2009-2011	Efficacy Safety R, DB, PC, PG	24/48 weeks[c]	***G551D***	6- 11	40- 105%	52	150mg BID vs. Placebo	N. America, Europe, Australia
104 Part A 2009-2010	Proof-of-concept Safety R, DB, PC, PG	16 weeks	***ΔF508/ ΔF508***	≥ 12	[redacted]	140	150mg BID vs. Placebo	North America
104 Part B 2009-2011	Long-term Safety[d] Open-label	40 weeks	***ΔF508/ ΔF508***	≥ 12	[redacted]	38	150mg BID	North America
105 Ongoing 2011-	Long-term Safety Open-label	96 weeks	***G551D*** From 102/103	≥6	≥ 40%	144[e] +	150mg BID	N. America, Europe, Australia

a= Study 101 Part 1 was crossover for 2 weeks of treatment in each arm; Part 2 was 4 weeks of R, DB, PC treatment
b= Study 103 Part A consisted of single dose PK, with subsequent modeling, to determine dose for Part B; Part A randomized 12 patients, but dose given to 9
c= Studies 102 and 103 Part B include Primary efficacy at 24 weeks, but Key secondary at Week 48; studies were blinded through week 48
d= Study 104 Part B enrolled "responders" from part A, which later showed no clinical efficacy; originally planned for 96 weeks, Part B was terminated for futility after Week 40
e= Study 105 has enrolled 144 Patients from Study 102, and is currently enrolling Patients from Study 103

Table 3: Additional Studies in the VX-770 Clinical Development Program

Study #	Phase	Design	Objective	Population	# Exposed VX-770/Pl.
Healthy Patients- Clinical Pharmacology					
001	1	R, DB, PC Escalation	Safety FIH	healthy	84 51/33
002	1	R, OL, 3-p X-over	BA, PK, food	healthy	18 18/0
003	1	OL single dose	PK, elimination, safety	healthy	7 7/0
005	1	R, DB, PC, X-over, multi	PK with oral contraceptives	healthy	30 (34??) 30/0
006	1	OL, X-over, single dose	M1, M6, PK with ketoconazole	healthy	24 24/0
007	1	R, OL, X-over, single dose	BA, PK, food	healthy	36 36/0
008	1	A: R, DB, PC B: R, DB, P and active C	Safety, PK, tolerance hi dose, **QTc**	healthy	78 76/2
009	1	OL, X-over, single dose	M1, M6, PK with rifampin	healthy	24 24/0
010	1	OL, X-over, multi-dose	PK midazolam, rosiglitasone, fluconazole	healthy	24 24/0
011	1	OL, X-over, multi-dose	M1, M6, PK with desipramine	healthy	24 24/0
012	1	R, OL, X-over, single dose	BA, Food effect	healthy	20 20/0
013	1	OL, single dose	PK- **hepatic impairment**	healthy	24 24/0
809-005 *	1	R, DB, PC, multi-dose	Safety, PK of VX-770+VX-809	healthy	24 18/6
Other Studies					
004	1	OL, multi-dose	Palatability of formulations	healthy	4
014	1	OL, single dose	Palatability of formulations	healthy	5, ongoing
106	2	R, DB, PC, X-over, multi dose	Lung clearance index Biomarker	≥ 6yo CF G551D FEV1> 90%	ongoing
107	2	Non-R, PC, single blind multi-dose	^{3}Helium-MRI ventilation Biomarker	≥ 12yo CF G551D	ongoing

*= Study 809-005 is a DDI study conducted unde (b) (4) for VX-809
[Source: Module 5.2, Tabular Summary of all Clinical Studies]

5.2 Review Strategy

The clinical development program for VX-770 was relatively small, as would be expected for a program designed for a small subset of an orphan patient population. Dose ranging exploration was limited to studies 101 and 103 Part A. The twice-daily dosing regimen was based on results of pharmacokinetic studies that showed a terminal half-life of 12 hours. The initial proof-of-concept data was collected in Study 101. Although the Applicant has identified Studies 102 and 103 as pivotal for supporting the efficacy and safety of VX-770 in a population of patients with CF and at least one copy of the G551D mutation ≥ 6 years of age, Study 104 is also relevant in that it demonstrates the lack of efficacy in the CF population who are homozygous for the ΔF508 deletion in CFTR, and also adds additional support for the safety of VX-770 in the CF population. Study 105 is the open-label extension for CF patients who have completed the 48 week treatment periods in Studies 102 and 103 Part B, and provides additional unblinded long-term safety data for the indicated population.

As studies 101, 102, 103, and 104 are each important for assessing the safety and efficacy of VX-770 in patients with cystic fibrosis, all will be reviewed individually below. Study 105 will be very briefly described, since it adds additional unblinded safety data to support the program, and will be addressed further in the Summary of Safety, Section 7.

To orient the reader, the review has been organized in the following manner. The protocols for trials 101, 102, 103, and 104 are discussed in detail in section 5.3, "Discussion of Individual Studies/ Clinical Trials." Dose selection based on the results of Studies 101 and 103 Part A, and efficacy results for each trial (patient disposition, demographics, primary and secondary outcomes) are presented in section 6, "Review of Efficacy." Safety results from Studies 102, 103, 104, and the open-label long-term safety extension Study 105, including extent of exposure, deaths, serious adverse events, and adverse events, are presented in Section 7, "Review of Safety."

5.3 Discussion of Individual Studies/Clinical Trials

STUDY 101

Study Title:
A Phase 2a, Randomized, Double-blind, Placebo-Controlled Study of VX-770 to Evaluate the Safety, Pharmacokinetics, and Biomarkers of CFTR Activity in Cystic Fibrosis (CF) Patients with Genotype G551D

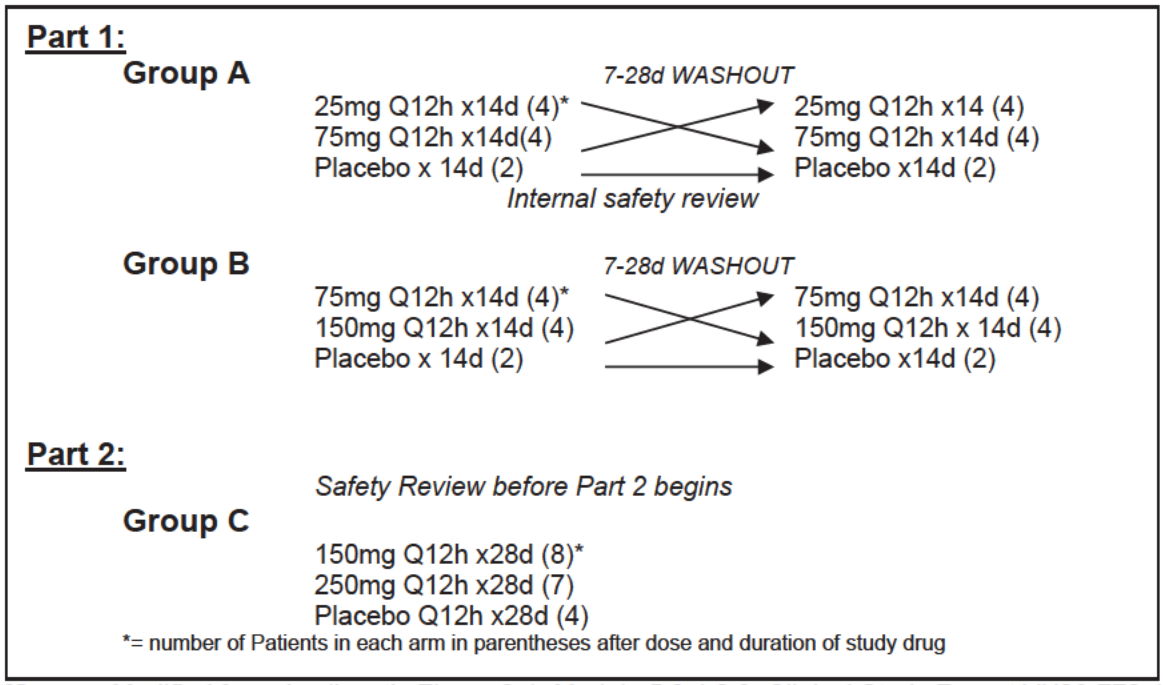
Study Dates:
May 10, 2007 through August 22, 2008.

Study Sites:
This study was conducted at 15 sites in North America and Germany.

Description of Study

This was the Applicant's Phase 2a, randomized, double-blind, placebo-controlled, 28-day dose-finding and proof-of-concept study in 39 patients with cystic fibrosis and at least one copy of the G551D mutation, aged >18years. This study will be discussed further in section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations, and in the Clinical Pharmacology Review as pertains to the pharmacokinetic data. The study design is shown in the figure below.

Figure 1: Study 101 Design



[Source: Modified from Applicant's Figure 9-1, Module 5.3.4.2.3, Clinical Study Report VX06-770-101]

Study Schedule

The study schedule for Study 101 Part 1 (both for Groups A and B) included a 21 day screening period, randomization on Day 1, and a first 14-day treatment period with assessments taken on Days 1, 7, and 14. After the first treatment period, there was a 7-28 day washout period, followed by a second 14-day treatment on the crossover dose (with assessments on Days 1, 7, and 14), and a subsequent follow-up Visit 5 to 9 days after last dose of study drug. Part 2 (Group C) began with a 21-day screening period, during which the timing of any inhaled antibiotic use by patients was taken into consideration, so that the 28-day inhaled tobramycin treatment would be given on the

same 28 days as VX-770 study treatment. The patients were randomized on Day 1, and assessments were collected on Days 1, 3, 9, 14, 21, and 28, with a Follow-up Visit 5-9 days after the last dose of study drug.

Screening assessments were the same for both Parts 1 and 2, and included informed consent, history and physical, weight, vital signs, genotype confirmation, sweat chloride, nasal potential difference (NPD) and other CF-related labs (aldosterone, immunoreactive trypsinogen {IRT}), baseline safety clinical labs and ECGs, and respiratory studies (pulse oximetry and spirometry).

The Part 1 treatment periods consisted of similar assessments as the screening period, except that IRT was not collected, and nasal potential difference was performed on Days 1 and 14. In addition, a patient symptom questionnaire and PK assessments were collected on assessment days (Days 1, 7, and 14). The washout period between treatments included a telephone contact, if longer than 10 days.

The Part 2 treatment period consisted of similar assessments on Days 1, 3, 14, 21, and 28, except that nasal potential difference was collected on days 1, 14, and 28, a phone assessment was added on Day 9, and that the symptom questionnaire was replaced by the Cystic Fibrosis Questionnaire revised (CFQ-R). The CFQ-R is a disease-specific health-related quality of life measure for cystic fibrosis. It consists of generic and CF-specific scales (grouped into 3 modules and 9 domains) that measure quality of life, health perception, and symptoms over a 2-week recall period. It is available in age-appropriate formats, including a child age 6-11 interview format, a self-reported child age 12-13, an adolescent/adult form for ages >14 years, and a parent proxy format. The respiratory domain of CFQ-R has also been utilized independently to evaluate symptoms and perceptions of respiratory health and quality of life.

Reviewer's Comment:
Neither the CFQ-R as a whole, nor the CFQ-R respiratory domain, has completed full evaluation across all CF patient populations of all psychometric properties (reliability, construct validity, sensitivity, and interpretability) in order to be considered "validated" from a regulatory perspective.

The follow-up visit assessments for Part 1 and 2 consisted of physical exam, weight, vital signs, pulse oximetry, and clinical labs. In addition to these, Part 1 added the symptom questionnaire, and Part 2 added PK evaluations at follow-up. Patients who prematurely discontinued for any reason completed a follow-up assessment 7 days after last dose of study drug.

Population

Study 101 planned to enroll 20 patients in Part 1 and 18 for Part 2 (total N=38). There were 41 patients randomized, and 39 received at least one dose of study drug, with 39 completing treatment as well.

For Part 1, eleven study sites were active (10 in the US and 1 in Canada), and 9 sites enrolled at least one patient. For Part 2, 14 sites were active (12 in the US, 1 in Canada, 1 in Germany) with 11 sites enrolling at least one patient. All patients were Caucasian, half were male, and most (32 of 39) had ΔF508 identified as their second CFTR allele.

Summary of Notable Inclusion/Exclusion Criteria
The pertinent inclusion criteria for Study 101 are as follows, and similar to subsequent VX-770 studies:

- ≥ 18 years of age
- Confirmed diagnosis of CF (as defined by the CF Foundation consensus statement published in 1998), with G551D mutation in at least one CFTR-allele
- Part 1 patients could not have R117H or 2789+5G—>A as their second mutation; Part 2 patients could have any second mutation
- FEV1 ≥ 40% predicted, with no upper limit noted

Notable exclusion criteria include any acute or confounding chronic illness or medical history, abnormal laboratory or ECG findings, recent use of intranasal medications (due to NPD measurements), and pertinent concomitant medication exclusions.

Treatments

In Part 1, three dose levels of 25, 75, and 150mg administered every 12 hours for 14 days, were studied to find the therapeutic range, based upon concentrations that increased gating activity of CFTR channel *in vitro*, and upon PK data from an earlier study in healthy human volunteers. Part 2 doses of 150 and 250mg administered every 12 hours for 28 days were selected based on tolerability, PK/PD modeling from data obtained in Part 1, changes in nasal potential difference and sweat chloride after administration of VX-770 in Part 1, and from safety evaluations.

All medications for routine CF care were permitted (with the exception of cytochrome P450 modifiers), and use of cycled inhaled antibiotic was timed to coincide with study drug dosing from Day 1 through Day 28 in Part 2. No dose-modifications were allowed in the study. Study drug dosing was 30 minutes after the start of a standard high-fat, high-calorie CF meal or snack, which was the same as that for Studies 102, 103, 104, and 105.

Patient Discontinuation/ Withdrawal Criteria

Patients were discontinued at any time if the patient, Investigator, or Applicant determined it was not in the patient's best interest to continue. In addition, need for use of a prohibited medication or increase in safety labs or additional findings (i.e., rash) would also disqualify a patient from further study.

Study Objectives

The primary objective was to assess the safety and tolerability of VX-770, as described by AE, SAE, clinical laboratory testing, vital signs, physical examination findings, and ECG results. Secondary objectives included assessment of pharmacodynamic parameters (change from baseline in nasal potential difference (NPD) and sweat chloride), pharmacokinetic (PK) parameters, and efficacy as determined by evaluations of forced expiratory volume in 1 second (FEV1), and CFQ-R.

Conduct of the Trial

The study protocol was amended twice. Version 2 of the protocol added changes to help better define the patient population and clarify laboratory and PK assessments. Version 3 was the planned amendment which defined the doses used for Part 2 of the study, and this amendment also clarified some safety evaluations, and streamlined study assessments. There were four minor deviations from the statistical analysis plan (SAP) reported, and a number of ad hoc analyses added. A key point to note is that, after database lock and unblinding, the Applicant noted that the volumes of sweat collected were not definitively measured, but rather estimated based on visual comparison of a set of tubes with known volumes for comparison. This method was within the standard operating procedure of the lab at the time, but resulted in collection and use of sweat volumes exceeding the 100 microliter maximum capacity of the proprietary Macroduct collection system used. Because the original SAP used the ion concentration from the arm with the highest volume for analyses, data was re-analyzed using an average from both arms instead, to correct for sweat volume impact on outcomes. The original estimation method could potentially underestimate chloride values, but would likely have affected both treatment and placebo patients. (Two patients in Part 1 each had one sample with a total sweat volume over 100 microliters; 5 patients for Part 2 had such, including 1 patient with 1 sample volume >100 microliters, 2 patients with 2 sample volumes >100, 1 with 4 samples >100, and 1 with 7 samples >100 microliters). Taking an average of the two values from each time point for all patients mitigated any potential outlier values, and since this was done for all samples, is reasonable. Overall, this likely did not influence final outcomes significantly, since sample volumes >100 microliters were noted in only 16 samples out of a total of 508 sample collections for both parts of this study.

Reviewer's Comments:
Study 101 was designed much like subsequent pivotal studies, with very similar inclusion/exclusion criteria, withdrawal criteria, and schedules of assessments. One difference is that, for patients in study 101, the spirometry was evaluated with Hankinson reference values, whereas studies 102, 103, and 104 utilized Knudson reference values. Because the reference values are valid for the population, and the Applicant did not change reference values during the conduct of an individual study, this does not affect interpretation of results. Another noted difference which does not affect interpretation of data is that in this earlier study, the entire Cystic Fibrosis Questionnaire-Revised (CFQ-R) was evaluated as an endpoint, but subsequent studies focused on the CFQ-R respiratory domain as an assessment of respiratory symptoms (all studies collected the full CFQ-R data).

STUDY 102

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

Study Dates: June 10, 2009, through January 11, 2011

Study Sites: 161 patients were enrolled at 65 sites in North America, Europe, and Australia.

Description of Study 102

Study 102 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group trial designed to assess the safety and efficacy of treatment with VX-770 compared to placebo in patients with cystic fibrosis and at least one copy of the G551D mutation in patients 12 years of age and older. Patients were randomized in a 1:1 fashion to either placebo or 150 mg VX-770 every 12 hours, for a total treatment period of 48 weeks, with the primary efficacy endpoint measured at week 24. The medication was delivered orally as one tablet by mouth every 12 hours, taken 30 minutes after the start of a high-fat meal or snack. Patients received study drug from randomization until week 48 at the final study visit, or alternately, they enrolled into study 105, the open-label extension, where they received 150mg Q12 hours of 150mg VX-770 for an additional 40+ weeks.

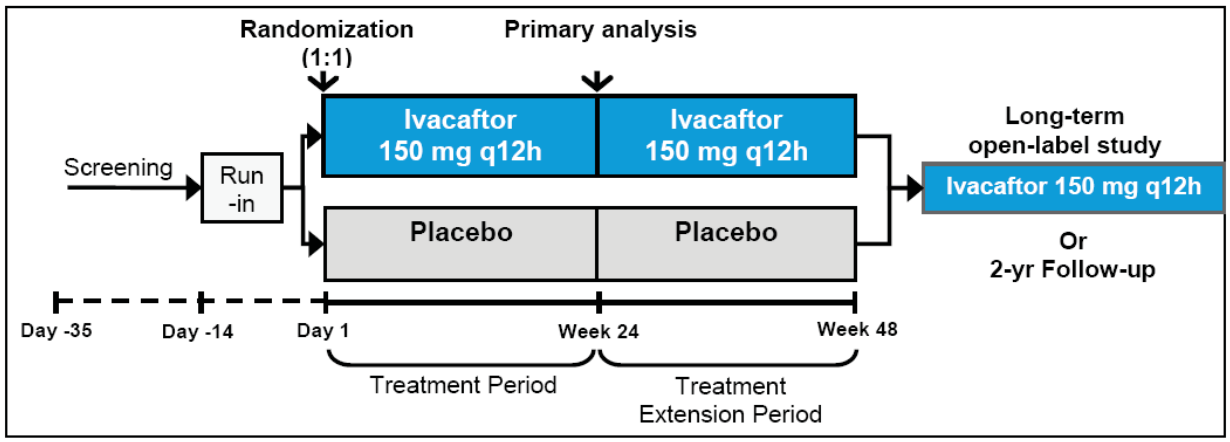
Study Schedule

The study schedule for Study 102 is presented below; Study 103, discussed next in this section of the review, was of similar design. All new patients began in a screening period, from Day -35 to -15. During this time, it was confirmed that patients had maintained a stable medication regimen for 4 weeks before screening through week 48, which included continuation of a stable inhaled daily antibiotic, or continuation of a cycled inhaled antibiotic, given that Day 1 and Visit weeks 8, 16, 24, 32, 40, and 48 all occurred at the end of an "off" cycle, but no less than 14 days after the last dose of the "on" cycle. The run-In period extended from Day-14 to Day -1, and documented patient stability and adherence with the current medical regimen. The treatment period was defined as Day -1 to week 24 visit, and the Applicant defined the second part of double-blinded treatment during Week 24-48 as the treatment extension period. There was a final follow-up visit for patients who did not roll over to Study 105.

Reviewer's Comment:
The Applicant has labeled the first 24 weeks of double-blinded treatment as the "Treatment Period," and the second 24-week block of double-blinded treatment as the "Treatment Extension Period." This terminology is somewhat confusing, since conventionally, "extension" studies are typically open-label assessments with unblinded treatment regimens. Because some of this study's key efficacy endpoints extend to Week 48, and because Study 105 is noted as the open-label, long-term extension safety study, this review will describe the entire double-blinded period from Day 1 through week 48 as the "treatment" period, and refer to Study 105 as the subsequent "extension" study, in order to conform with conventional terminology, and to mitigate reader confusion.

The schematic for Study 102 (and subsequent Study 103 part B) is shown below.

Figure 2: Schematic of Study 102 and 103B Design



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

[Source: Module 2.5 Clinical Overview, section 1.4.2, Fig 1, p 14.]

Screening assessments included comprehensive history, demographics, CF genotype, review of prior and concomitant medications/ treatments, physical exam, vital signs, pulse oximetry, ECG, spirometry, report of adverse events, and clinical laboratories. Patients who met all the eligibility criteria and none of the exclusion criteria and for whom there was documented informed consent/assent as applicable, continued into the run-in period of study.

The run-in period was used to establish that patients on chronic cycled inhaled antibiotics were at the proper place in their treatment cycle relative to randomization at Day-1. Assessments performed at this visit included history, medication and treatment review, pre-bronchodilator spirometry, completion of the CFQ-R form, and any outcomes since the screening visit.

The double-blinded treatment period began at randomization on Day 1, and continued through week 48. Patients were randomized in a 1:1 fashion to either placebo or VX-770. Patients for Study 102 were stratified for age (<18 vs. ≥18 year) and FEV1 (<70 vs. ≥70 % predicted). Patients continued their blinded study drug, with regularly scheduled evaluations, through week 48. During the entire treatment period, patients were monitored every 4 weeks, either by telephone contact or with a clinic visit [see schedule of assessments table below].

Table 4: Study 102 and 103B Schedule of Assessments

Event/Assessment	Screening Period (3 weeks)	Run-in Period (2 wks)	Double-blinded 48-Week Treatment Period			
	Day -35 to Day -15	Day -14 to Day -1 ± 2 days	Day 1	Day 15 ± 1 day	Weeks 4, 12, 20, 28, 36, 44 ± 5 days	Weeks 8, 16, 24, 32, 40, 48 ± 5 days
Clinic Visit	X	X	X	X		X
Telephone contact					X	
Pregnancy test[a]	X		X			
Hematology	X		X	X		X
Coagulation studies	X		X	X		X
Chemistry	X		X	X		X
Urinalysis	X		X	X		X
Weight and height	X	X	X	X		X
Physical Exam	X	X	X	X		X
Vital signs	X	X	X	X		X
Pulse oximetry	X	X	X	X		X
ECG	X		X	X		X
Spirometry[b]	X	X	X	X		X
Sweat chloride[c]			X	X		X
CFQ-R[d]		X	X	X		X
EQ-5D[e]		X	X	X		X
Adverse Events	X	X	X	X	X	X
Medication/ treatment	X	X	X	X	X	X

a= for females of child-bearing potential
b= pre-bronchodilator and pre-morning dose of study drug
c= performed within a 2-hour window relative to morning dose of study drug
d= completed prior to any assessments; ≥ 14yo use adult/adolescent form, 12 &13 yo use child form, 6-11yo study coordinator interviews with child form, and all <14 yo also include parent form
e= only for Study 102, since EQ-5D is not validated for <12 yo

[Source: Module 5.3.5.1.3, Clinical Study Report Body 102, Section 9.5.1, Schedule of Assessments, and Clinical Study Report Body 103, section 9.5.1, Schedule of Assessments]

All patients who completed through week 48 either enrolled into Study 105, the open-label extension, or they completed a follow-up visit, consisting of clinical laboratory testing, serum pregnancy testing if applicable, abbreviated physical exam, ECG, and adverse event (AE) assessments.

Patients who prematurely discontinued for any reason completed an early termination visit as soon as the decision was made to terminate, consisting of the following: collection of returned study drug, sweat chloride testing, serum pregnancy testing if applicable, clinical laboratory assessments, physical exam with vital signs, weight, height, and pulse oximetry, patient/parent reported outcome forms, ECG, pre-bronchodilator spirometry, and assessment of adverse events. Patients also had a follow-up visit 4 weeks after discontinuation (described above), and if they received more than 4 weeks of study drug, also had long-term follow-up visits every 3 to 4 months from the follow-up visit, which included spirometry, abbreviated exam with vital signs, weight, and height, and assessment of adverse events since the previous visit.

Population

For Study 102, the planned enrollment was a minimum of 80 patients ≥ 12 years of age with CF and at least one copy of the G551D-CFTR mutation, randomized 1:1 to VX-770 or placebo. The actual enrollment was double the planned number, and included 83 patients randomized to VX-770, and 78 to placebo.

Summary of Inclusion Criteria

- Male or female patient age ≥ 12 years, with confirmed diagnosis of cystic fibrosis
- G551D on at least one allele (any other disease-causing mutation for other)
- FEV1 40-90% predicted of normal for age/gender/ht at screening (Knudson reference standards)
- Females of child-bearing potential with negative serum pregnancy at screen and negative urine pregnancy at Day 1
- All patients agree to contraceptive regimen as applicable
- Hematologic, serum chemistry, coagulation and urinalysis results without significant abnormalities per investigator
- Appropriate consent/assent

Definition of "Confirmed Diagnosis of CF"

A sweat chloride ≥ 60mmol/L by quantitative pilocarpine iontophoresis
OR sweat sodium ≥ 60mmol/L at least once (later removed from protocol)
OR 2 identified CF-causing genetic mutations
AND chronic sinopulmonary or gastrointestinal/nutritional abnormalities

Summary of Exclusion Criteria

Disease-Related exclusions

- History of illness that would confound results or increase risk for patient
- Acute respiratory illness or infection within 6 weeks of Day 1
- Colonization with organisms associated with a more rapid decline in pulmonary status (e.g., *B. cenocepacia, B. dolosa, M. abcessus*) at screening
- Change of systemic antibiotics due to change in pulmonary symptoms within 6 weeks of Day 1
- Current use of inhaled hypertonic saline (a washout period of 6 weeks' duration prior to Day 1 is acceptable)

Medical Exclusions

- Pregnant, breastfeeding, or refusal to follow specific contraception plan
- History of solid-organ or hematologic transplant
- History of alcohol, medication or illicit drug abuse within 1 year of study
- Any "non-CF-related" illness within 6 weeks of Day 1
- Concomitant use of inhibitors or inducers of cytochrome P450 3A4

Abnormal Laboratory Exclusions

- Hemoglobin less than 10mg/dL
- Abnormal liver function (≥ 3x ULN)
- Abnormal renal function (methodology and definition adjusted for age)
- History of prolonged QT/QTc interval

Concomitant Medication Exclusions

- Current use of nebulized hypertonic saline
- Any recent changes (<6 weeks from Day 1) to CF regimen, including high-dose ibuprofen, dornase alpha, inhaled antibiotics, oral macrolides, inhaled corticosteroid, inhaled beta-agonists

Reviewer's comment:
The inclusion/exclusion criteria as outlined are appropriate.

Treatments

Study treatments
Patients were randomized in a 1:1 ratio to receive either 150mg of VX-770 or placebo orally every 12 hours, taken 30 minutes after the start of a high-fat meal, for 48 weeks.

Dose modification
Modification of the study drug dose was prohibited, but study drug could be interrupted to allow for use of prohibited medications for up to 4 weeks during the second half of the treatment period, from weeks 25 through 48 (during what the Applicant called the "treatment extension period").

Permitted Medications
Patients were expected to remain on their stable CF medication regimen from 4 weeks before the screening period (Day -35 to Day -15) through the end of the study (week 48), with "stable CF regimen" defined as "current medication regimen that Patients have been following for at least 4 weeks prior to screening." Chronic inhaled antibiotics were permitted to continue. Cycled inhaled antibiotics were also allowed, but Day 1 visit had to be planned to occur at the end of an off-cycle (no less than 14 days after last dose). Acute treatments for exacerbations were allowed per physician judgment.

Prohibited Medications
Inhaled hypertonic saline, while not FDA-approved as a treatment for CF, is commonly used by CF patients as a mucolytic/expectorant, and was the only CF-specific treatment excluded from this trial. Patients were allowed to wash out from inhaled saline therapy in order to enroll in the trial. Any other investigational study drugs were not permissible within 6 weeks prior to Day 1, and any drugs or dietary supplements that induced or

inhibited Cytochrome P450 enzymes were prohibited, including herbal St. John's Wort, and dietary or supplemental grapefruit.

Patient Discontinuation/Withdrawal Criteria

A patient could discontinue at any time, for any reason, throughout the trial. A patient could be discontinued at any time from the study at the Investigator's or Applicant's discretion, if continued participation was felt to be not in the patient's best interest. In addition, the Applicant had additional specific withdrawal criteria, listed below:

- If patient develops a condition that requires treatment with a prohibited medication
- If they develop a life-threatening adverse reaction, or a serious adverse reaction that places them at an immediate risk
- If a female patient becomes pregnant, or if a male patient's partner becomes pregnant (non-compliance with contraception requirements)
- If patient is non-compliant with study protocol, medication, or procedures
- If LFT's increase 3x over highest baseline, or if absolute increase 5xULN
- If they experience a prolonged QTcF interval (>450 msec)
- If treatment becomes unblinded to any participant or provider in study
- If study closes early
- If a patient experienced a SAE which was not life-threatening nor was there immediate risk, the patient may be removed (case-by-case basis)

Follow-up after Premature Discontinuation
Patients who discontinued would undergo an early termination visit. If the patient had been on study treatment less than 4 weeks, there was a follow-up visit held 4 weeks after the termination visit. If patients received more than 4 weeks of study drug, they would undergo follow-up visits 4 weeks after the final study dose, as well as continued follow-up visits every three months for the remainder of the planned 48-week treatment and extension periods.

Replacement Plans
No patients were to be replaced if discontinued after randomization.

Efficacy Analyses

For Study 102, all efficacy parameters were based on the full analysis set, defined as all randomized patients who received at least 1 dose of study drug (i.e., VX-770 or placebo). The primary efficacy parameter was the adjusted mean absolute change from baseline in percent predicted FEV1 through week 24. Baseline is defined as the most recent measurement prior to intake of the first dose of study drug. The primary efficacy analysis utilized a mixed effects model for repeated measurements. With a mixed effects model as the primary analysis model, no imputation of missing data was done. However, sensitivity analyses assessing the impact of missing data on efficacy

evaluations were performed. [Source: Module 5.3.5.1.3, Clinical Study Report Body 102, Section 9.7.3.5]

Spirometry measurements were conducted in a uniform fashion across time and study sites in accordance with procedural guidelines described in the protocols, and performed according to the American Thoracic Society Guidelines, utilizing Knudson reference standards. All spirometry was to be collected pre-bronchodilator, if possible, defined as no SABA within 4 hours and no LABA within 12 hours. If patient forgot to hold his SABA or LABA at the screening visit, then post- bronchodilator values were recorded at screening, but all other visits collected pre-bronchodilator values. If Day 1 spirometry was measured pre-bronchodilator, but at another visit the patient forgot to withhold SABA/LABA, then the post-bronchodilator values were collected for that visit only. If patient used bronchodilator on Day 1, the Day 1 visit and all subsequent visits collected post-bronchodilator values. [Source: Module 5.3.5.1.3, Clinical Study Report Body 102, Section 9.7.3.5.1].

Key secondary endpoints were identified as absolute change from baseline in percent predicted FEV1 through week 48, absolute change in sweat chloride from baseline to week 24, absolute change in pooled (Child version for 12-13 year-olds, and adult version for ≥14 years) CFQ-R respiratory domain score from baseline to week 24, absolute change in weight from baseline to week 48, and time to first pulmonary exacerbation through week 48.

Reviewer's Comment:
While the full CFQ-R was completed by participants, the CFQ-R respiratory domain was predefined as the key secondary outcome measurement to be evaluated. The respiratory domain, as its name implies, focuses on respiratory health perception, quality of life, and clinically-relevant respiratory symptoms, such as cough, wheezing, and sputum production.

Additional endpoints included absolute change in sweat chloride from baseline to week 48, change in CFQ-R respiratory domain at week 48, absolute change in weight to week 24, and time to exacerbation through week 24. Additional spirometric and clinical endpoints were also evaluated, including rate of decline in FEV1, change in oxygen saturation, number of hospitalizations for exacerbations, number of outpatient sick visits, and courses of outpatient antibiotic needed to treat sinopulmonary infections. Study 102 included an endpoint of change in the EQ-5D score; this PRO tool is a general measure of health-related quality of life, and is only validated in Patients over age 12. Analyses of these endpoints were performed after 24 and 48 weeks of treatment.

Event data, such as hospitalizations, exacerbations, courses of IV antibiotics, and outpatient sick visits were analyzed in 3 ways: count (e.g., number of hospitalizations, number of exacerbations, number of courses of IV antibiotics, and number of outpatient

visits); duration (e.g., days of hospitalization and exacerbations), and time to first event (e.g., time to first exacerbation, time to first hospitalization, time to the first use of IV antibiotics, and time to first outpatient visit). [Source: Module 5.3.5.1.3, Clinical Study Report Body 102, Sections 9.7.3.5.2 and 9.7.3.5.3]

Protocol Amendments/Conduct

Study 102 had four protocol revisions (three after study initiation), and two administrative letters were issued by the time of database lock. These amendments were clarifying or administrative in nature, or increased the safety monitoring of the program. These changes were not likely to have impacted the analysis of data. A brief summary of significant changes is included in the table below.

Table 5: Conduct for Study 102

Conduct	Date	Major Changes Made
Amendment 1 (Before enrollment)	04-17-2009	• Addition of 24-week extension period for a total blinded treatment duration of 48 weeks • Additional key secondary endpoints at week 48 added, additional 2ry and 3ry endpoints added • Addition of ambulatory (24-hr) ECG monitoring added • Definition of pulmonary exacerbation amended • Exclusion #12: changed time in which patient cannot have "non-CF-related" illness
Amendment 2	09-10-2009	• Inclusion #1: removed language for sweat sodium level from definition • Inclusion # 5: amended timing of urine pregnancy testing • Exclusion #2: decreased length of time for Patients to have had exacerbation or change in medications • Exclusion #7: Added that QTcF>450 msec will exclude a patient from enrollment • Exclusion #13: decreased length of time needed for washout from hypertonic saline • Exclusion #15: added exclusion for previous inclusion in Vertex study
Admin Letter	01-2010	• Clarification of timing of ECG collection and monitoring times
Amendment 3	04-12-2010	• Liver function testing changed to every 2 weeks, and language added to repeat elevated labs within 48-72 hours • Criteria for study drug interruption and discontinuation were added
Amendment 4	07-09-2010	• Added another point to liver function abnormalities

		leading to discontinuation • SAE language changed to state that all SAEs collected, but only reported if attributed to study drug • Additional clarification of intended analyses of endpoints were provided
Admin letter	09-2010	• SAE language amended to state all collected, and all reported • Typographical error in withdrawal criterion for liver function abnormalities was corrected
SAP vs. protocol differences		• Removed the genotype subgroup analysis from primary endpoint (G551D/severe mutation vs. non-severe mutation) since most Patients were "severe" • Changed language of subgroup analysis "FEV1 severity at screening" to "FEV1 severity at baseline" • Changed secondary endpoint from "rate of change in weight through weeks 24 and 48" to "Change from baseline in weight at weeks 24 and 48" to allow for clinical interpretation

[Ref: Module 5.3.5.1.3, Clinical Study Report Body 102, Section 9.8]

STUDY 103

Studies 102 and 103 were of almost identical design, with both studies evaluating CF patients with at least one copy of the G551D mutation, except that Study 103 was performed in pediatric CF patients aged 6-11 years. In addition, Study 103 was divided into two parts; Part A evaluated the PK in children to confirm the dose to be used in Part B, which comprised the major efficacy and safety determination portion of the study. Part A will be discussed in more detail in section 6.1.8 of this document, "Clinical Information related to dosing." The dose ultimately chosen for Part B was the same as that for the adult (>12yo) population, at 150mg every 12 hours, taken 30 minutes after the start of a high-fat meal. Both Studies 102 and 103 Part B had the same primary efficacy endpoint of absolute change from baseline in percent predicted FEV1 through week 24, with secondary efficacy and safety endpoints through weeks 24 and 48.

Study Title:
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 Patients with Cystic Fibrosis and the G551D Mutation

Study Dates: Part A began on August 5, 2009, and completed November 2, 2009. Part B began March 12, 2010, and completed April 28, 2011.

Study Sites: Part A included 8 US sites which enrolled 12 patients, and Part B included 24 sites in North America, Europe, and Australia which enrolled 52 patients.

Description of Study 103

PART A
Part A was designed to evaluate a single dose of VX-770 and was used to confirm the dose for Part B. Part A was conducted in the same study population described below as the subsequent safety and efficacy portion of study 103 (Part B). It included a screening period (Days -28 to -2), an evaluation period (Days 1 to 2), and a follow-up visit (Day 8 ± 2 days after the dose of VX-770). In Part A, enrollment was planned for a minimum of 8 Patients (at least 3 of the 8 Patients must have been 6 to 8 years of age). All Patients received a single, open-label dose of VX-770, 100 mg administered orally 30 minutes after the start of a high-fat, high calorie meal or snack on Day 1 of the evaluation period. Blood PK samples were collected pre-dose and at 2, 4, 6, 8, 12, and 24 hours post-dose to determine the plasma concentrations of VX-770 and metabolites M1 and M6. The PK data from Part A were analyzed to determine the dose to carry forward into Part B. All Patients completing Part A were offered the opportunity to participate in Part B.

PART B
In 103 Part B, patients were randomized in a 1:1 fashion to either placebo or 150 mg VX-770 every 12 hours, for a total treatment period of 48 weeks, with the primary efficacy endpoint measured at week 24. The medication was delivered orally as one tablet every 12 hours, taken 30 minutes after the start of a high-fat meal or snack. Patients received study drug from randomization until week 48 at the final study visit, or alternately, they enrolled into study 105, the open-label extension, where they received 150mg Q12 hours of 150mg VX-770 for an additional 40+ weeks.

Reviewer's Comment:
Since Study 103 Part B was the efficacy portion of this trial, it will be described in further detail below. The subsequent sections refer to Part B of Study 103 unless otherwise specified.

Study Schedule

The study Schedules for both Study 102 (previously described above) and 103 Part B are roughly the same, with the caveat that any of the Patients who completed Part A of 103 could proceed directly to the run-in period of Part B without repeating a screening period. All new patients began in a screening period, from Day -35 to -15. During this time, it was confirmed that patients had maintained a stable medication regimen for 4 weeks before screening through week 48, which included continuation of a stable inhaled daily antibiotic, or continuation of a cycled inhaled antibiotic, given that Day 1 and visit weeks 8, 16, 24, 32, 40, and 48 all occurred at the end of an "off" cycle, but no

less than 14 days after the last dose of the "on" cycle. The run-in period extended from Day-14 to Day -1, and documented patient stability and adherence with the current medical regimen. The double-blind treatment period of 103 Part B extended from Day 1 through week 48. There was a final follow-up visit for patients who did not roll over to Study 105.

Reviewer's Comment:
Please refer to the earlier reviewer's comment with regard to terminology of the treatment period.

The schematic for Study 103 part B is shown in the combined Figure 2: Schematic of Study 102 and 103B Design, under the section above for Study 102 description.

Screening and run-in assessments were the same as for Study 102, outlined above.

The treatment period was the same as that for Study 102, except patients for Study 103 were stratified based on FEV1 percent predicted criteria of <70%, 70 to 90%, or >90 to 105% predicted; they were not further stratified by age. Patients were monitored every 4 weeks throughout the 48-week treatment period, either by telephone contact or clinic visit. Please refer to Table 4: Study 102 and 103B Schedule of Assessments, under Study 102 above.

All patients who completed through week 48 either enrolled into Study 105, the open-label extension, or they completed a follow-up Visit, consisting of clinical laboratory testing, serum pregnancy testing if applicable, abbreviated physical exam, ECG, and adverse event assessments.

Patients who prematurely discontinued for any reason completed an early termination visit, with the same parameters as for Study 102, described above.

Population

For Part A, enrollment was planned for a minimum of 8 patients; 12 patients were enrolled, and 9 received at least 1 dose of VX-770.

For Part B, the planned enrollment was a minimum of 30 patients 6-11 years of age with CF and at least one copy of the G551D-CFTR mutation, randomized 1:1 to VX-770 or placebo. The actual enrollment included a total of 52 patients, 26 in each treatment group.

Summary of Notable Inclusion and Exclusion Criteria
Inclusion criteria (for both parts A and B) were almost identical to that for Study 102. There were only a few notable differences in inclusions, due to age of the population, listed below. Exclusion criteria were the same as for Study 102.

- Male or female patient aged 6 to 11years, with confirmed diagnosis of CF (same definition of "confirmed" as for Study 102) and G551D mutation on at least one allele (with any other disease-causing mutation for the second allele)
- FEV1 40-105% predicted of normal for age/gender/ht at screening (Knudson reference standards)
- Appropriate consent/assent
- Able to swallow tablets, and weight >15kg

Reviewer's comment:
The inclusion/exclusion criteria as outlined are appropriate.

Treatments

Study treatments
Patients were randomized in a 1:1 ratio to receive either 150mg of VX-770 or placebo orally every 12 hours, taken 30 minutes after the start of a high-fat meal, for up to 48 weeks.

Dose modification, Permitted and Prohibited Medications
Modification of the 150mg study drug dose a determined in Part A was prohibited, but study drug could be interrupted to allow for use of prohibited medications for up to 4 weeks during the second half of the treatment period, from Weeks 25 through 48 (during what the Applicant called the "Treatment Extension Period"). Permitted and prohibited medications were the same as for Study 102, outlined above.

Patient Discontinuation/Withdrawal Criteria

A patient could discontinue at any time, for any reason, throughout the trial. A patient could be discontinued at any time from the study at the Investigator's or Applicant's discretion, if continued participation was felt to be not in the patient's best interest. Specific additional withdrawal criteria are the same as for Study 102, as are the planned follow-up after premature discontinuation plans. As in Study 102, no Patients were replaced if discontinued after randomization.

Efficacy Analyses

For study 103 part B, all efficacy parameters were based on the full analysis set, defined as all randomized Patients who received at least 1 dose of study drug (i.e., VX-

770 or placebo). The primary efficacy parameter was the adjusted mean absolute change from baseline in percent predicted FEV1 through week 24. Baseline is defined as the most recent measurement prior to intake of the first dose of study drug. [Source: Module 5.3.5.1.3, Clinical Study Report Body 103, section 9.7.3.5] The primary efficacy analysis utilized a mixed effects model for repeated measurements. With a mixed effects model as the primary analysis model, no imputation of missing data was done. However, sensitivity analyses assessing the impact of missing data on efficacy evaluations were performed.

Spirometry measurements were conducted in a uniform fashion across time and study sites in accordance with procedural guidelines described in the protocols, and performed according to the American Thoracic Society Guidelines, utilizing Knudson reference standards for both studies. All spirometry was to be collected pre-bronchodilator, if possible, defined as no SABA within 4 hours and no LABA within 12 hours. If patient forgot to hold his SABA or LABA at the Screening visit, then post-bronchodilator values were recorded at screening, but all other visits collected pre-bronchodilator values. If Day 1 spirometry was measured pre-bronchodilator, but at another visit the patient forgot to withhold SABA/LABA, then the post-bronchodilator values were collected for that visit only. If patient used bronchodilator on Day 1, the Day 1 visit and all subsequent visits collected post-bronchodilator values. [Source: Module 5.3.5.1.3, Clinical Study Report Body 103, section 9.7.3.5.1]

Key secondary endpoints were identified as absolute change from baseline in percent predicted FEV1 through week 48, absolute change in sweat chloride from baseline to week 24, absolute change in CFQ-R respiratory domain score from baseline to week 24, and absolute change in weight from baseline at Week 24.

Additional spirometric and clinical endpoints were also evaluated after 24 and 48 weeks of treatment. Event data, such as hospitalizations, exacerbations, courses of IV antibiotics, and outpatient sick visits were analyzed in 3 ways: count (e.g., number of hospitalizations, number of exacerbations, number of courses of IV antibiotics, and number of outpatient visits); duration (e.g., days of hospitalization and exacerbations), and time to first event (e.g., time to first exacerbation, time to first hospitalization, time to the first use of IV antibiotics, and time to first outpatient visit). Statistical analyses were modified if there were less than 5 Patients in the treatment group. [Source: Module 5.3.5.1.3, Clinical Study Report Body 103, Sections 9.7.3.5.2 and 9.7.3.5.3]

Protocol Amendments/Conduct

Study 103 had 6 protocol amendments, and 5 administrative letters before database lock. These amendments were clarifying or administrative in nature, or increased the safety monitoring of the program. These changes were not likely to have impacted the analysis of data. A brief summary of significant changes is included in the table below.

Table 6: Conduct of Study 103

Conduct	Date	Major Changes Made
Amendment 1 (Before enrollment)	04-24-2009	• Addition of 24-week extension period for a total blinded treatment duration of 48 weeks • Additional key secondary endpoints at week 48 added, additional 2ry and 3ry endpoints added • Addition of ambulatory (24-hr) ECG monitoring added • Definition of pulmonary exacerbation amended • Exclusion #12: changed time in which patient cannot have "non-CF-related" illness
Amendment 2	08-31-2009	• Inclusion #3: increased upper limit of FEV1 to 105% predicted (to adjust for Knudson standards) • All other changes the same as for Amendment #2 for Study 102 (below)
Amendment 3	02-05-2010	• Dose changed for Part B from 100mg to 150mg every 12 hours (based on results of Part A) • Clarified timing of assessments for part B • Updated description of Part B patients to note that "at least 20 of 30 Patients will have FEV1≤ 90% predicted"
Amendment 4	04-12-2010	• Liver function testing changed to every 2 weeks, and language added to repeat elevated labs within 48-72 hours • Criteria for study drug interruption and discontinuation were added
Amendment 5	07-09-2010	• Added another point to liver function abnormalities leading to discontinuation • SAE language changed to state that all SAEs collected, but only reported if attributed to study drug • Additional clarification of intended analyses of endpoints were provided
Amendment 6	11-13-2010	• LFT monitoring changed to every 4 weeks through Week 48 • SAE language amended to state all collected, and all reported • Changed secondary endpoint from "rate of change in weight through weeks 24 and 48" to "Change from baseline in weight at weeks 24 and 48" to allow for clinical interpretation • Removed the genotype subgroup analysis from primary endpoint (G551D/severe mutation vs. non-severe mutation) since most Patients were "severe" • Changed language of subgroup analysis "FEV1 severity at screening" to "FEV1 severity at baseline" • Modifications to SAP made to assess for missing

		data
SAP vs. protocol differences		• Database was locked after all patients completed the week 24 visit while the double-blind extension period from week 25 through week 48 continued • Some statistical parameters were modified

[Ref: Module 5.3.5.1.3, Clinical Study Report Body 103, section 9.8]

STUDY 104

Study Title:
A Phase 2, Randomized, Double-blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of VX-770 in Patients Aged 12 Years and Older with Cystic Fibrosis Who Are Homozygous for the *F508del-CFTR* Mutation

Study Dates:
September 21, 2009 through July 20, 2010 for Part A, through June 2011, for Part B

Study Sites:
This study was conducted at 34 sites in the United States.

Description of Study

This was a randomized, double-blind, placebo-controlled, parallel-group multi-center study (Part A) with an open-label extension (Part B) of orally-administered VX-770, in patients with CF who were ΔF508-homozygous. Part A was designed to evaluate the safety and efficacy of 16 weeks' treatment with orally-administered VX-770 to patients greater than 12 years of age, and Part B was designed to evaluate the safety and efficacy of long-term treatment with VX-770 in the same population.

Reviewer's Comments:
Study 104 was performed for two reasons: to increase the safety database for VX-770 and to demonstrate whether the drug had any clinical activity in the ΔF508 CFTR-mutation, since ΔF508 is the most common CFTR mutation, and because it creates a non-gating defect. The Applicant had in vitro cell line data which suggested that cells demonstrating ΔF508 mutations responded to VX-770, but the physiology of abnormal CFTR-proteins suggested that VX-770's mechanism of action would not provide benefit to Patients with a Class 2 CFTR-mutation such as ΔF508, so this trial further tested that theory. This study provides strong evidence that VX-770 does not offer any clinical benefit to Patients with the most common CFTR-allele mutation, ΔF508, in the absence of a G551D mutation.

Study Schedule

The study Schedule for Study 104 Part A, the double-blind, placebo-controlled treatment period, closely resembles that of both Study 102 and 103 Part B, with the notable exception that 104 Part A lasted for 16 weeks only. The treatment period was defined as Day -1 to week 16 visit. There was a final follow-up visit for Patients who did not "respond," and continue on into Part B, the open-label long-term extension.

Screening assessments were the same as for Studies 102 and 103, and included comprehensive history, demographics, CF genotype, review of prior and concomitant medications/ treatments, physical exam, vital signs, pulse oximetry, ECG, spirometry, report of adverse events, and clinical laboratories. Patients who met all the eligibility criteria and none of the exclusion criteria and for whom there was documented informed consent/assent as applicable, continued into the run-in period of study.

The run-in period was used to establish that Patients on chronic cycled inhaled antibiotics were at the proper place in their treatment cycle relative to randomization at Day-1. Assessments performed at this visit included history, medication and treatment review, pre-bronchodilator spirometry, completion of the CFQ-R form, and any outcomes since the screening visit.

The treatment period included patient randomization at Day1, and continued through week 16. Patients were randomized in a 1:4 fashion to either placebo or VX-770. The schedule of assessments for Study 104 Part A is almost identical to those for studies 102/103B, except does not continue past Week 16.

At the end of week 16, Patients completed a follow-up visit 4 weeks $\pm$ 7 days after last dose of study drug. Alternately, those who met "responder" criteria could be re-consented, and continue into the open-label long-term safety extension (Part B).

Patients designated as "responders" from Part A could be continued into Part B, originally planned to continue for 96 additional weeks (through week 112 of dosing). The criteria for "responders" to participate in Part B of the trial include proper consent and assent (if appropriate), completion of Part A, and must have either an increase from baseline in FEV1 (b) (4) predicted at one or more time points from Day 15 through week 16, or a decrease from baseline in sweat chloride concentration of (b) (4) /L at both Day 15 and week 8 visits. Of the 140 Patients enrolled in Part A, 38 met this definition and enrolled in the open-label extension.

Patients who prematurely discontinued for any reason completed an early termination visit as soon as the decision was made to terminate, consisting of the following: collection of returned study drug, sweat chloride testing, serum pregnancy testing if applicable, clinical laboratory assessments, physical exam with vital signs, weight, height, and pulse oximetry, patient/parent reported outcome forms, ECG, pre-

bronchodilator spirometry, and assessment of adverse events. Patients who prematurely discontinued in Part B had an early termination visit as soon as could be scheduled, and were required to complete the extension period follow-up visit.

Reviewer's Comment:
The Part B extension study was discontinued for futility in June 2011, after all Patients had reached week 40, and results from Part A showed no benefit; full analysis up to week 40 is available.

Population

Study 104 planned to enroll 120 Patients in Part A; no formal number was given for Part B enrollment. 140 Patients actually enrolled in Part A and were randomized 1:4 to placebo or VX-770 at 150mg orally Q12 hours for 16 weeks. Thirty-eight patients subsequently met "responder" criteria and continued into the open-label extension period (Part B).

Summary of Inclusion Criteria
The inclusion criteria for Study 104 are very similar to that for Studies 102 /103B, with the following exceptions:

- population is ≥ 12 years of age (the same as Study 102)
- Patients are homozygous for the ΔF508- CFTR mutation
- FEV1 (b) (4) predicted, with no upper limit noted

Definition of "Confirmed Diagnosis of CF"
This definition is the same for Study 104 as for 102/103B.

Summary of Exclusion Criteria
Exclusion criteria are the same for Study 104 as they are for 102/103B, including disease-related, medical, abnormal laboratory values, and concomitant medication exclusions.

Treatments

Study Treatments
Part A, the double-blinded treatment period, consisted of administration of placebo: VX-770 in a 1:4 ratio, at a dose of 150mg orally every 12 hours for 16 weeks. The open-label extension period (Part B) consisted of unblinded treatment with VX-770 at 150mg Q12 hours, initially planned for a duration of 96 weeks, but it was discontinued early in June 2011 for futility, after all Patients had completed treatment up to 40 weeks.

Permitted and prohibited medications were the same as for Studies 102/103B, and no dose-modifications were allowed in the study. Dosing 30 minutes after the start of a

standard high-fat, high-calorie CF meal or snack was the same as that for Studies 102/103B.

Patient Discontinuation/ Withdrawal Criteria

Discontinuation criteria for Study 104 are very similar to those for 102/103B. Study 104 criteria list two separate withdrawal criteria for elevated transaminases; these were merged into one criterion during the conduct of studies 102/103B.

Follow-up after premature discontinuation was very similar to the other studies, and Patients who discontinued prematurely were not replaced in Study 104.

Study Objectives

The primary efficacy endpoint for Study 104 Part A was similar to that for studies 102/103B, with the exception of duration; study 104 assessed the absolute change from baseline in percent predicted FEV1 through week 16. Outcomes for Study 104 are discussed further in this review in section 6.1.10 Additional Efficacy Analyses.

Conduct of the Trial

The study protocol was amended 4 times before the data cut, and twice more by the time the final clinical study report was completed. Version 7.0, dated September 10, 2010, was the final protocol version. These amendments were clarifying or administrative in nature, or increased the safety monitoring of the program. Two of these amendments were made to unlock the database, to correct information used in safety analysis for a few subjects. The re-coding of a hospitalization was changed to a more conservative assessment of SAE, so overall, these amendments did not adversely impact interpretation of study data.

Table 7: Conduct for Study 104

Conduct	Date	Major Changes Made
Amendment 1	05-06-2009	• Exclusion #12: Time period for "non-CF-related illness" changed • Removal of stratification by age and FEV1 • Definition of CF pulmonary exacerbation modified to be consistent with other Vertex studies
Amendment 2	10-09-2009	• Amended protocol to divide into Parts A and B, Part B added to protocol, and clarification language added throughout • Inclusion #1: removed language for sweat sodium level from definition • Inclusion # 5: amended timing of urine pregnancy testing • Exclusion #2: decreased length of time for Patients

		to have had exacerbation or change in medications • Exclusion #7: Added that QTcF>450 msec will exclude a patient from enrollment • Exclusion #13: decreased length of time needed for washout from hypertonic saline • Exclusion #15: added exclusion for previous inclusion in Vertex study • Updated and clarified withdrawal criteria
Amendment 3	04-08-2010	• Liver function testing changed to every 2 weeks, and language added to repeat elevated labs within 48-72 hours • Criteria for study drug interruption and discontinuation were added
Amendment 4	07-02-2010	• Added another point to liver function abnormalities leading to discontinuation • SAE language changed to state that all SAEs collected, but only reported if attributed to study drug
Amendment 5	09-10-2010	• SAE language amended to state all collected, and all reported • Part B two secondary endpoints added, which had been omitted from previous protocol
Amendment 6	09-10-2010	• Liver function testing for part B amended to every 4 weeks
Data unlock	08-23-2010	• Incorrect data entry information for 2 patients was re-entered to correct
Data unlock	02-14-2011	• Data query noted incorrect data for 2 patients, re-entered to correct (one event changed from "planned hospitalization," to "unplanned" SAE • Updated SAE information from August 2010 through February 2011 • 2 AE re-coded to be more specific

[Source: Module 5.3.5.1.3, Study 104 Clinical Study Report Body, Section 9.8.1]

STUDY 105

Study Title:
An Open-Label, Rollover Study to Evaluate the Long-Term Safety and Efficacy of VX-770 in Patients with Cystic Fibrosis

Study Dates:

The first Informed Consent was signed on July 08, 2010; the Study is ongoing. The Interim Analysis date was April 12, 2011, which was the date the last patient completed the Week 12 Visit.

Study Sites:
This study is ongoing at 60 sites in the United States, Canada, Europe, and Australia.

Description of Study

Study 105 is the open-label extension study for patients enrolled in either study 102 or 103, which continues to follow patients for long-term safety and efficacy. Patients with CF with G551D-CFTR on at least one allele and are at least 6 years of age are rolled over into Study 105 after signing a separate informed consent and assent if applicable. They receive 150mg of VX-770 orally every 12 hours, for an additional 96 weeks (or until the drug is commercially available). Patients are allowed to use hypertonic saline while enrolled in Study 105; this was a prohibited medication for Studies 102 and 103. Patients are evaluated on Day 1, Day 15, and roughly every 12 weeks thereafter. The primary objective was to collect additional safety information as evidenced by incidence of AEs, clinical laboratory values, ECGs, vital signs, and physical exams. Other endpoints included changes in spirometry, number of pulmonary exacerbations, rate of change in weight, changes in patient-reported outcomes (PROs), number of hospitalizations, outpatient sick visits, treatment with antibiotics for sinopulmonary infections, and long-term evaluation of PK parameters of VX-770 and metabolites M1 and M6. Ongoing results from Study 105 will be discussed further in the Safety discussion of this document, found in Section 7.

6 Review of Efficacy

Efficacy Summary

Support for the efficacy of the 150mg every 12 hour dose of VX-770 for the treatment of cystic fibrosis in patients aged 6 and older with at least one copy of the G551D CFTR mutation is derived from Studies 102 and 103 Part B. Both trials were randomized, placebo-controlled, double-blinded 48-week period studies in patients with CF and at least one copy in the G551D CFTR mutation. Study 102 evaluated patients 12 years and older, whereas Study 103 included patients aged 6-11 years old.

Overall, these studies were of adequate design, and met the criteria for “adequate and well-controlled studies,” as defined in 21 CFR 314.126. They evaluated an appropriate patient population which was well-balanced at baseline between placebo and VX-770-treated groups. The choices of patient population, control groups, and the primary endpoint were relevant and clinically-meaningful to this patient population, and allowed

for a clear assessment of benefit. The analysis of the primary endpoint, absolute change in percent predicted FEV1 through week 24, demonstrated a clinically and statistically meaningful treatment effect, and the effect was substantiated by continued durability through 48 weeks. The key secondary endpoints of change in weight, time-to-exacerbation, and patient-reported respiratory symptoms such as cough, wheezing, etc. (as measured by CFQ-R respiratory domain) all supported the primary efficacy endpoint, as did the pharmacodynamic endpoint of change in sweat chloride concentrations.

Both trials individually demonstrated a significant improvement in the primary endpoint, and were supported by key secondary endpoints. The data from these trials were also combined with a similar conclusion. VX-770 150mg dosed every 12 hours demonstrated a statistically significant improvement in absolute change in percent predicted FEV1compared to placebo at week 24 with a 10.6% improvement in adult and adolescent patients in Study 102, and a 12.5% improvement in children 6 to 11 years old in Study 103; these improvements were maintained at week 48 in both studies as well .

The efficacy of VX-770 in the population of patients 12 years of age and older who were homozygous for the ΔF508-CFTR mutation was also studied in a single 16-week, randomized, double-blind, placebo-controlled trial (study 104). At the end of the placebo-controlled treatment period, there was no clinically- or statistically-significant difference noted between the VX-770- and placebo-treated groups. This provides strong evidence that VX-770 does not provide clinical benefit in this additional (more common) patient population.

6.1 Indication

The Applicant's proposed indication for VX-770 is use for the treatment of cystic fibrosis in patients age 6 and older with a G551D-*CFTR* mutation.

6.1.1 Methods

This is a small program of two Phase 3 adequate and well-controlled clinical trials (Studies 102 and 103B) which form the basis for efficacy determination in Patients with cystic fibrosis and at least one G551D-CFTR mutation. The pre-specified design and statistical analyses of these studies had been discussed with the Applicant in meetings and communications, (as outlined in section 2.5 Summary of Presubmission Regulatory Activity Related to Submission) and the Division informally agreed with the Applicant's proposal for the primary efficacy endpoint and statistical analysis thereof, their planned approach to handle missing data, and the method to control the type I error for the analyses of the primary and key secondary endpoints. Detailed analyses of these results are described in the sections below.

The studies were of fairly robust design, with no significant flaws identified. The Agency has no issue with the way in which the pre-specified analyses were conducted. Please refer to section 5.3 of this document, "Discussion of Individual Studies," for full details of study descriptions.

Applicant's Pre-specified analysis Methods

The Applicant pre-specified that they would utilize a mixed-effects model for repeated measures (MMRM) for the primary efficacy analysis method, which assumes a stable treatment effect over time. The MMRM was used to analyze the effects of VX-770 on FEV1, sweat chloride concentration, and CFQ-R respiratory domain at 24 and 48 weeks. Because weight was expected to increase over the treatment period, a linear mixed-model (LMM) was used for this data.

The Applicant pre-specified sequential testing for primary and key secondary endpoints, to control of the Type I error rate. For study 102, the primary efficacy endpoint was tested at a significance level of 0.05. After significance was determined for the primary endpoint, changes from baseline through Week 24 in CFQ-R respiratory domain and in sweat chloride were tested at a significance of 0.05. Finally, if positive results were obtained, time-to-first-exacerbation through Week 48 and change from baseline in weight at Week 48 were tested. For Study 103 Part B, the primary endpoint was similarly tested at significance level of 0.05, followed by testing the changes from baseline at Week 24 in weight and in sweat chloride levels at 0.05, and finally testing change from baseline in CFQ-R respiratory domain score through Week 24. Multiple sensitivity analyses were pre-specified, and performed to determine the robustness of these analyses.

Both the FDA and the Applicant have primarily used the Full Analysis Set (FAS) data for efficacy analysis, defined as all randomized Patients who received at least one dose of study drug.

6.1.2 Demographics

A total of 213 patients were randomized in the two Phase 3 trials, with 161 patients from study 102, and 52 from the efficacy portion of Study 103 (Part B). Within each study, demographic characteristics were comparable between treatment groups, with respect to age, sex, and race/ethnicity, as described in Table 8: Demographics of the Full Analysis Set. Study 103 had more males receiving placebo and more females receiving VX-770; this does not appear to have any clinical significance, but is rather a function of small patient numbers. For both studies, the vast majority of patients were Caucasian, which is not unexpected for a genetic disease most common in the Caucasian population, with a genetic allele mutation (G551D) that is typically found in North

Western Europeans, and very prevalent in the Northern Irish CF population. Study 102 had a median age of 24 years, which also is not unexpected for a life-shortening disease being studied. The range of ages was reasonable, with the oldest patients in VX-770 and placebo groups both 53 years of age.

Table 8: Demographics of the Full Analysis Set

	Study 102		Study 103 Part B		
Demographic Parameter	Placebo N=78	VX-770 N=83	Placebo N=26	VX-770 N=26	Overall N=213
Geographic region[a]					
US and Canada[b]					127 (60%)
EU/ Australia					86 (40%)
Age (years)					
Mean (SD)	24.7(9.2)	26.2 (9.9)	8.9 (1.9)	8.9 (2.0)	
Median	23	25	8.5	9	
Min, max	12, 53	12, 53	6, 12	6, 12	
Age group (years), n (%)					
Study 103: 6-8 years			13 (50)	12 (46)	
Study 103: 9-11			12 (46)	11 (42)	
Study 103: >11			1 (4)	3 (12)	
Study 102: 12 <18	17 (22)	19 (23)			
Study 102: >18	61 (78)	64 (77)			
Sex, n (%)					
M	38 (49)	39 (47)	16 (62)	9. (35)	
F	40 (51)	44 (53)	10 (38)	17 (65)	
Race					
White	77 (99)	81 (98)	23 (88)	22 (84)	
Other	0	0	1 (4)	2 (8)	
Can't ask[c]	1 (1)	2 (2)	2 (8)	2 (8)	
Ethnicity					
Hispanic or Latino	0	0	0	1 (4)	
Non-Hispanic or Latino	77 (99)	81 (98)	24 (92)	23 (88)	
Can't ask[c]	1 (1)	2 (2)	2 (8)	2 (8)	

a=Source: Module 2.5, Clinical overview, Section 4.1.2; Module 5.3.5.1, Clinical Study Report-102, Table 14.1.3 and Module 5.3.5.1, Clinical Study Report-103B, Table 14.1.3.
b= Applicant divided Patients by continent, so their listing of North America included the US sites as well as those in Canada. The 3 Canadian sites for study 102 and one in Study 103 contributed only 11 Patients total from the 127 total Patients listed above.
c= Not allowed to ask ethnicity or race questions per local regulation

Source: Module 2.7.3, Summary of Clinical Efficacy, Section 3.1.2, Table 10.

Baseline characteristics for all patients who were randomized and received at least one dose of study drug (FAS) are listed below in Table 9: Baseline Characteristics of the Full Analysis Set (FAS). When examining baseline lung function, patients in study 102 were well matched by treatment group; Study 103 had slightly more patients with worse lung function in the VX-770 group than in the placebo group, but numbers were small.

Mean and median baseline weights for both studies were well matched across treatment groups, as were other medical diagnoses for this group of CF patients. Older children and adults from Study 102 reported having more diagnoses in their medical history than younger patients in Study 103, as would be expected.

Table 9: Baseline Characteristics of the Full Analysis Set (FAS)

	Study 102		Study 103 Part B	
Baseline Characteristic	Placebo N=78	VX-770 N=83	Placebo N=26	VX-770 N=26
% Predicted FEV1, n (%)				
Study 102: <70%	45 (58)	49 (59)		
Study 102: ≥ 70%	33 (42)	34 (41)		
Study 103: <70%			8 (31)	4 (15)
Study 103: ≥70 to ≤ 90%			6 (23)	12 (46)
Study 103: >90%			12 (46)	10 (39)
Weight (kg)				
Mean (SD)	61.2 (13.9)	61.7 (14.3)	30.0 (7.2)	31.8 (9.95)
Median	58.7	58.8	29.7	28.2
Min, Max	31.9, 109.9	30.2, 107.2	17.8, 46.3	18.8, 62.6
Genotype				
G551D/ ΔF508	58 (74)	64 (77)	20 (77)	22 (85)
G551D/ not ΔF508	20 (26)	19 (23)	6 (23)	4 (15)
Prior Medical History				
CF Lung Disease	78 (100)	83 (100)	26 (100)	26 (100)
Pancreatic Insufficiency	75 (96)	74 (89)	25 (96)	25 (96)
Symptomatic Sinus Dz.	35 (45)	47 (57)	5 (19)	6 (23)
Gastroesophageal Reflux	29 (37)	32 (39)	7 (27)	6 (23)
Asthma	26 (33)	18 (22)	3 (12)	4 (15)
CF-Related Diabetes	13 (17)	17 (21)	0	1 (4)
Elevated Liver Enzymes[a]	7 (9)	12 (15)	2 (8)	2 (8)
Liver disease[b]	8 (10)	8 (10)	1 (4)	2 (8)

a= For these studies, screening levels of AST, ALT, GGT, alk phos, or Tbili ≥3xULN was an exclusion criterion
b= non-cirrhotic liver disease

Sources: Module 2.7.3, Summary of Clinical Efficacy, Section 2.1.1, Table 2, Section 2.1.2, Table 6, Section 3.1.2, Tables 10, 11, and Section 3.3, Table 16; Module 5.3.5.1, Clinical Study Report 102, Table 14.1.4.1, and Clinical Study Report 103, Table 14.1.4.1

All patients enrolled in these studies had at least one G551D mutation on CFTR, and the identification of their second allele was not different than expected; roughly 77% of these patients across all studies carried ΔF508 as their second allele mutation (for reference, approximately 87% of all patients with cystic fibrosis in the United States carry at least one allele for the ΔF508 mutation[1]). There were too few other mutations (no more than five patients in any second allele group, other than ΔF508), and many were singly-identified second alleles only noted in one treatment group, so further sub-analysis is not useful.

The Applicant has submitted to this NDA a comprehensive list of any prior medications used in >15% of patients in any group. This reviewer has selected pertinent medications commonly used within the standard of care for patients with cystic fibrosis to highlight, as a representation of the overall patient population studied. Use of baseline prior medications was compared across treatment groups, and was fairly well balanced between groups; see Table 10: Select Baseline Prior Medications (FAS), below. In addition, average percentages of certain treatments conform to general knowledge of CF management in the United States, suggesting that the VX-770 patient study population is very representative of the overall US cystic fibrosis population. For example, data from the Cystic Fibrosis Foundation Patient Registry: Annual Data Report 2009[1] notes that 90% of US CF patients use pancreatic supplements, and 78% use dornase alpha. These numbers are in line with the percentages seen in the table below.

Table 10: Select Baseline Prior Medications (FAS)

	Study 102		Study 103 Part B	
Prior Medications	Placebo N=78	VX-770 N=83	Placebo N=26	VX-770 N=26
Any prior medication	78 (100)	83 (100)	26 (100)	26 (100)
Pancrelipase	72 (92)	73 (88)	25 (96)	25 (96)
Albuterol	42 (54)	35 (42)	11 (42)	11 (42)
Dornase alpha	57 (73)	54 (65)	22 (85)	18 (69)
Azithromycin[a]	50 (64)	51 (61)	12 (46)	12 (46)
Tobramycin[a]	35 (45)	28 (34)	5 (19)	5 (19)
Colistin	5 (6)	9 (11)	6 (23)	3 (12)
Ursodeoxycholic acid	9 (12)	7 (8)	4 (15)	3 (12)
Hypertonic solutions[b]	12 (15)	8 (10)	4 (15)	0
Supplemental nutrition	5 (6)	5 (6)	6 (23)	2 (8)

a= chronic use is standard of care for Patients with chronic pseudomonal infection
b= hypertonic saline use was discontinued in the screening period, and an exclusion through Week 48

Sources: Module 2.7.3, Summary of Clinical Efficacy, Section 3.1.2, Table 12.; Module 5.3.5.1, Study Report 102, Table14.1.5.1 and Clinical Study Report 103, Table 14.1.5.1

That being said, two of the baseline medication uses are somewhat different from what would generally be expected. The first is the percentage of patients using nebulized hypertonic saline. In the US, approximately 45% of patients over the age of 6 years use inhaled hypertonic saline as an expectorant/ mucolytic[1], but only 10-15% of the study populations report doing so. A possible reason for this difference is that hypertonic saline was an exclusion criterion for these studies, and patients were allowed to wash out use of hypertonic saline during the screening period. So this relatively low percentage could merely reflect that patients had already discontinued its use in anticipation of trial enrollment.

The second difference is that the number of patients utilizing inhaled cycled antibiotic (TOBI® and colistin) is lower than expected. This number is more difficult to ascertain because cycled antibiotic regimen is only used for patients who are found to be chronically infected with *Pseudomonas aeruginosa*, and microbacterial status was not a major parameter for this drug program. However, chronic oral azithromycin is used in the same *Pseudomonas*-infected population, so numbers for these two treatment modalities would be expected to be similar. Overall in the US, 30% of children aged 6 to 10, 50% of children aged 11-17, and 70 to 80% of adults 18 years and older are chronically infected with *Pseudomonas aeruginosa*, and 69% of these eligible patients use TOBI[1]. Similar percentages exist for other countries[14]. In Study 102, 60% of patients used azithromycin (similar to the overall percentage of CF patients expected to use chronic anti-pseudomonal therapy), whereas only 40% of patients were treated with inhaled TOBI and 8% with inhaled colistin. This is lower than what would be expected. In Study 103, small overall numbers and a younger population less likely to be infected with *Pseudomonas* could account for lower use of inhaled antibiotics; although 46% of patients received oral azithromycin, 19% received inhaled TOBI and 18% received colistin.

However, since prior medications were identified as those used within 30 days prior to the screening period, if patients had delayed timing of a new cycle of inhaled antibiotic treatment to meet enrollment criteria, their inhaled antibiotic use might not be adequately captured in report forms.

Overall, the baseline demographics, patient characteristics, and prior medication use demonstrate that the patient population for the VX-770 development program, while small, demonstrated a fairly representative group of US and world-wide CF patients for which the drug is intended.

6.1.3 Patient Disposition

There were a total of 213 patients evaluated for efficacy in two Phase 3 trials for VX-770; 104 patients in placebo groups, and 109 patients in VX-770 groups. Disposition information is provided in Table 11: Disposition of Phase 3 Patients (FAS). Overall, 91% of patients who enrolled in the Phase 3 program completed 48 weeks of study drug treatment.

Table 11: Disposition of Phase 3 Patients (FAS)

Disposition Category	Study 102		Study 103		Overall
	Placebo n (%)	VX-770 n (%)	Placebo n (%)	VX-770 n (%)	n (%)
Randomized Set	83	84	26	26	219
Safety Set	78	83	26	26	213
Full Analysis Set (FAS)	78	83	26	26	213
Week 24 Completers	71 (91)	80 (96)	23 (89)	26 (100)	200 (94)
Did not complete to Wk 24	7 (9)	3 (4)	3 (12)	0	3 (6)
Week 48 completers	68 (87)	77(93)	22 (85)	26 (100)	193 (91)
Did not complete to Wk 48	10 (13)	6 (7)	4 (15)	0	20 (9)
Reasons:					
Adverse Event	4 (5)	1 (1)	1 (4)	0	6 (3)
Noncompliance	0	2 (2)	0	0	2 (1)
Physician decision	1 (1)	0	0	0	1 (<1)
Pregnancy	0	1 (1)	0	0	1 (<1)
Required prohibited med	2 (3)	1 (1)	1 (4)	0	4 (2)
Withdrew consent	1 (1)	1 (1)	1 (4)	0	3 (1)
Other[a]	2 (3)	0	1 (4)	0	3 (1)

a= one patient in each study discontinued due to inelig ble genotype (enrolled in error), second patient from study 102 discontinued due to difficulty of blood collection.

Sources: Module 5.3.5.1, Clinical Study Report 102, Section 10.1, Table 10-1; Module 5.3.5.1, Clinical Study Report 103, Section 10.1.2, Table 10-1; Module 2.7.3, Summary of Clinical Efficacy, Section 3.1.1, Table 9.

Six patients in Study 102 (1 patient in the VX-770 group and 5 patients in the placebo group) discontinued the study before receiving their first dose of study drug; there were no patients in Study 103 who were randomized but did not receive at least one dose of study treatment. The FAS and the safety set were identical.

The dropout rate for both studies was fairly low, with only 9% of the total patients not completing to week 48. Roughly twice as many dropouts were in the placebo groups (n=14) as in the VX-770 groups (n=6). Specific reasons for dropouts are listed in the table above. More patients discontinued due to an adverse event in the placebo groups than in the VX-770 treated groups (5 vs. 1). There were no discontinuations due to lack of effect in these two studies. It is also noted that more patients in the placebo groups versus VX-770 groups required a prohibited medication, but the numbers were very small, so not much can be inferred further from these observations.

Protocol Violations

For both studies, the majority of the reported protocol deviations could be categorized in one of the following ways: incomplete study assessments, patient visits that were out of the protocol-specified visit window, study drug administration issues, PK blood collection difficulties, minor, non-reportable completion errors of the ICF form, and use of prohibited medications. Most of the protocol deviations were considered minor by the Applicant, and not to have had substantial impact on efficacy or patient safety. This

reviewer concurs. More significant protocol violations that led to patients being excluded from the Per Protocol Set (PPS) include 10 patients for missing FEV1 or drug compliance <80% and one with inclusion/exclusion violation (no G551D mutation) from Study 102. Four patients from Study 103 were excluded from the PPS for violations including missing FEV1 data, <80% drug compliance, prohibited use of hypertonic saline, and one patient had an inclusion/exclusion violation (no G551D mutation). [Source: Module 5.3.5.1, Clinical Study Report Body 102, Sections 10.2 and 11.1; Module 5.3.5.1, Clinical Study Report Body 103, Sections 10.2.2 and 11.1]

Compliance and Exposure Rates

Treatment compliance and overall drug exposure data is shown below in Table 12: Study Drug Exposure and Overall Compliance (FAS). For this table, the overall study drug compliance is the ratio of the number of tablets taken, to the number of tablets administered during each patient's time on-study. The number of tablets consumed was determined by pill counting; both protocols read that the study team will "review returned study drug (empty/full blister cards)". [Source: Module 5.3.5.1.17, section 16.2.2, Protocol VX088-770-102, section 13.3.4.2, and Module 5.3.5.1.4, Section 16.1.1, Protocol VX08-770-103, Section 13.6.4.2] Over 80% of patients in these trials had ≥90% compliance with study medications, and no patients had less than 50% compliance for the time they were on study treatment.

Table 12: Study Drug Exposure and Overall Compliance (FAS)

		Study 102		Study 103		Overall
Summary	**Category or statistic**	**Placebo N=78**	**VX-770 N=83**	**Placebo N=26**	**VX-770 N=26**	**N=213**
Compliance with Study Drug						
On-Study Study Drug Compliance[a] %	**N**	78	83	26	26	
	Mean (SD)	96 (7)	93 (9)	96 (7)	94 (8)	
	Median	99	97	99	98	
	Min, max	63, 100	59, 100	68, 100	71, 100	
Overall On-Study Study Drug Compliance n (%)	**<50%**	0	0	0	0	0
	50% to <75%	2 (3)	5 (6)	1 (4)	2 (8)	5%
	75% to <90%	7 (9)	16 (19)	3 (11)	3 (11)	14%
	≥ 90%	69 (88)	62 (75)	22 (85)	21 (81)	81%
Exposure to Study Drug						
Days Exposed through Week 48	**Mean (SD)**	312 (79)	328 (50)	299 (97)	337 (5)	
	Median	337	337	337	337	
	Min, max	7, 386	54, 365	13, 342	328, 346	
Exposure Grouping n (%)	**<4 weeks**	2 (3)	0	2 (8)	0	2%
	≥4 to <24 wk	5 (6)	3 (4)	1 (4)	0	4%
	≥24 to <40 wk	2 (3)	1 (1)	1 (4)	0	2%
	≥40 to <48 wk	18 (23)	15 (18)	6 (23)	10 (39)	23%
	≥ 48 weeks	51 (65)	64 (77)	16 (61)	16 (61)	69%

a= On-Study Compliance defined as "Ratio of # of tablets consumed to the expected # of tablets administered during the patient's time on-study during treatment and extension periods" [as defined in Section 9.7.2.6]

Sources: Module 5.3.5.1, Clinical study Report 102, Section 11.3, Table 11-6 and Table 14.1.7.1; Module 5.3.5.1, Clinical Study Report 103B, Section 11.3.2, Table 11-5 and Table 14.1.7.2; Module 2.7.3 Summary of Clinical Efficacy, Section 3.1.5

6.1.4 Analysis of Primary Endpoint(s)

Basis for Choice of Endpoint

The primary efficacy parameter for these studies was the absolute change from baseline in percent predicted FEV1 through week 24. The Applicant's choice of FEV1 as the primary efficacy endpoint was appropriate for a disease in which the major cause of early death is respiratory failure. Pulmonary function is monitored very closely in patients with cystic fibrosis, and progressively declines over the lifetime, at a rate as high as 1-4% of total function per year, so improvement in FEV1 would be considered clinically meaningful. In addition, cystic fibrosis lung disease as measured by FEV1 is correlated not only with pulmonary outcomes, but with longer term overall morbidity and

mortality[7, 9]. The majority of death in the CF population is due to pulmonary causes[7], so improvement in FEV1 is a useful and clinically-meaningful endpoint.

Change in FEV1 has been used as the primary basis for demonstration of clinical benefit and subsequent regulatory approval for a wide variety of respiratory products. Spirometry testing has standardized methods, and physicians and CF clinicians utilize spirometric assessments to determine overall lung health chronically, as well as acute worsening (pulmonary exacerbation), to guide overall patient management decisions, such as when to give antibiotics, when to hospitalize, when to place a patient on a lung transplant list. When performed according to accepted standard practices[11], individual patient data can be evaluated by the clinician for repeatability among values, and reproducibility over time.

Choice of Control Population

The Applicant chose to conduct Phase 3 placebo-controlled studies, in addition to regularly prescribed medications/ standard-of-care management. The Applicant's choice of a placebo control group is appropriate, since there are no other drugs with a similar mechanism of action, to serve as an active comparator for VX-770.

Regulatory Adequacy of Trials

These Phase 3 clinical trials met the regulatory criteria for trial design of "Adequate & Well-controlled," as defined under 21 CFR 314.126, as listed below. These studies:

1. Had a clear statement of objectives, summary of methods proposed and methods used
2. Used a study design of placebo concurrent-control, which allows for a quantitative assessment of drug effect
3. Had methods of selection of patients that provided adequate assurance that patients have the disease being studied
4. Utilized a method of assigning patients to treatment and control groups which minimized bias and intended to assure comparability with respect to pertinent variables (age, sex, severity of disease, use of therapies other than test drug), and included additional stratification of key patient characteristics
5. Contained adequate measures to minimize bias, including adequate blinding and randomization procedures, prospective statistical analysis plans, and clearly identified endpoints with hierarchical analysis
6. Identified methods of assessment of response that are well-defined and reliable, and the protocol and study reports explain variables measured, methods of observation, and criteria to assess responses

7. Provided an analysis of results adequate to assess effect of the drug, including adequate comparability of test and control groups with respect to variables and effects of interim analyses

Overall, this development program had clear study designs that provided reasonable assessment of benefit, by utilizing FEV1 as their primary efficacy parameter.

Summary of Primary Efficacy Endpoint

Studies 102 and 103 Part B demonstrated positive results for their primary efficacy endpoint, as demonstrated below in Table 13: Summary of Primary Efficacy. The primary endpoint was absolute change in percent predicted FEV1 through Week 24 of treatment. Both studies showed a robust clinically and statistically significant treatment effect at Week 24, which was sustained at Week 48. The Applicant notes that results of all sensitivity analyses for the primary endpoint were consistent with the results of the primary analyses; please see Dr. David Hoberman's Statistical Review for further detail.

Table 13: Summary of Primary Efficacy

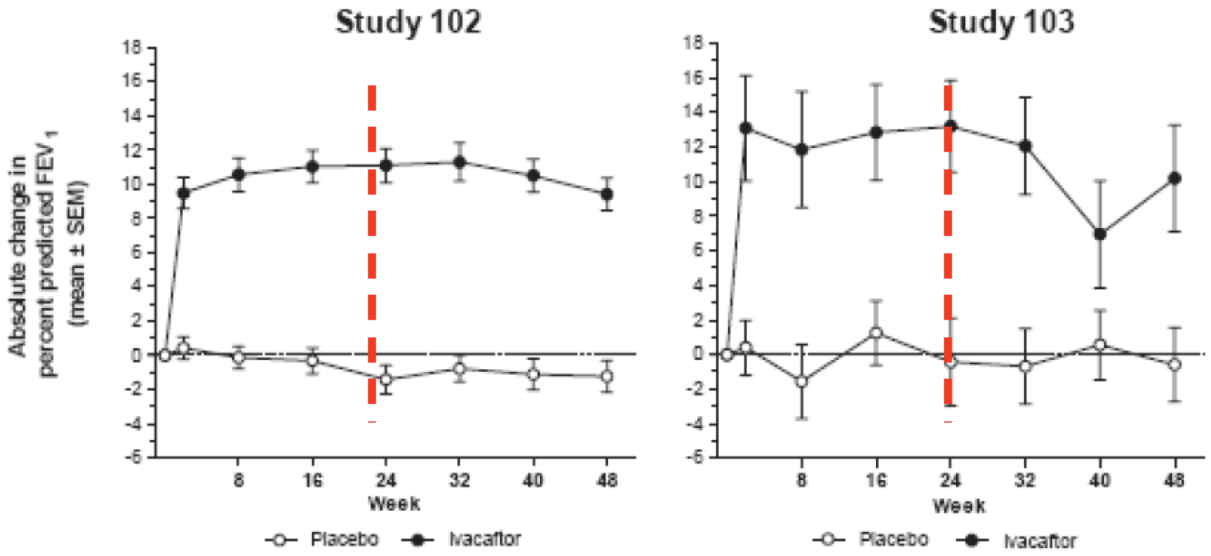
Description		Study 102 N=83		Study 103 N=26	
		Tx. Δ[a]	P value	Tx. Δ[a]	P value
Primary Endpoint	Absolute change from baseline in percent predicted FEV1 through Week 24	**10.6%**	**<0.0001**	**12.5%**	**<0.0001**

a: Treatment Difference= effect of VX-770 minus effect of placebo

[Source: Module 2.5, Clinical Overview, Sections 4.2 and 4.3, Tables 4 and 5]

In both studies, improvements in percent predicted FEV1 in the treatment groups were apparent by Day 15, the first on-treatment time point. Differences between VX-770 and placebo groups were maintained such at subsequent visits throughout the total 48 week treatment period, and achieved statistical significance at the specified 24 and 48 week time points; this is best viewed in Figure 3: Absolute Change in % Predicted FEV1, (FAS) below.

Figure 3: Absolute Change in % Predicted FEV1, (FAS)



Red dashed line= Primary Efficacy endpoint; absolute change in % predicted FEV1 through Week 24
[Source: Modified from Applicant's, Module 2.7.3, Summary of Clinical Efficacy, Section 3.2.1, Figure 1]

6.1.5 Analysis of Secondary Endpoints

For both studies 102 and 103 Part B, the Applicant had a pre-identified analysis plan for evaluation of key secondary endpoints, with a hierarchical evaluation, as described in section 6.1.1 of this review. Key secondary efficacy endpoints for Studies 102 and 103 are listed below, in Table 14: Summary of Key Secondary Endpoints. Overall, these endpoints all met statistical significance, with the exception of change in CFQ-R for study 103. The further clinical relevance of each endpoint will be described in separate sections, below. Since the hierarchy of analysis for key secondary endpoints was different for the two studies, this review will present each of these key secondary outcomes in a slightly different order than as listed in the table below.

Table 14: Summary of Key Secondary Endpoints

Description		Study 102		Study 103	
		Tx. Δ[a]	P value	Tx. Δ[a]	P value
Key Secondary Endpoints	Absolute change from baseline in CFQ-R respiratory domain through Week 24[b,c]	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 (Week 24[d])	2.7kg	<0.0001	1.9kg[d]	0.0004
	Time-to-first Pulmonary Exacerbation through Week 48 (hazard ratio)	0.46	0.0012	----[e]	----[e]

a: Treatment Difference= effect of VX-770 minus effect of placebo
b: Patients in Study 102 completed Adolescent/Adult, or if age was 12 to <14yo at baseline, self-completed the CFQ-Child form; Study 103 utilized the CFQ-Child-Interviewer format
c: The Minimal Clinically-important Difference for CFQ-R respiratory domain is 4 points
d: Weight change at Week 48 was the key endpoint for Study 102, but Study 103 used Week 24
e: Time-to-first Exacerbation was a tertiary endpoint for Study 103

[Source: Module 2.5, Clinical Overview, Sections 4.2 and 4.3, Tables 4 and 5]

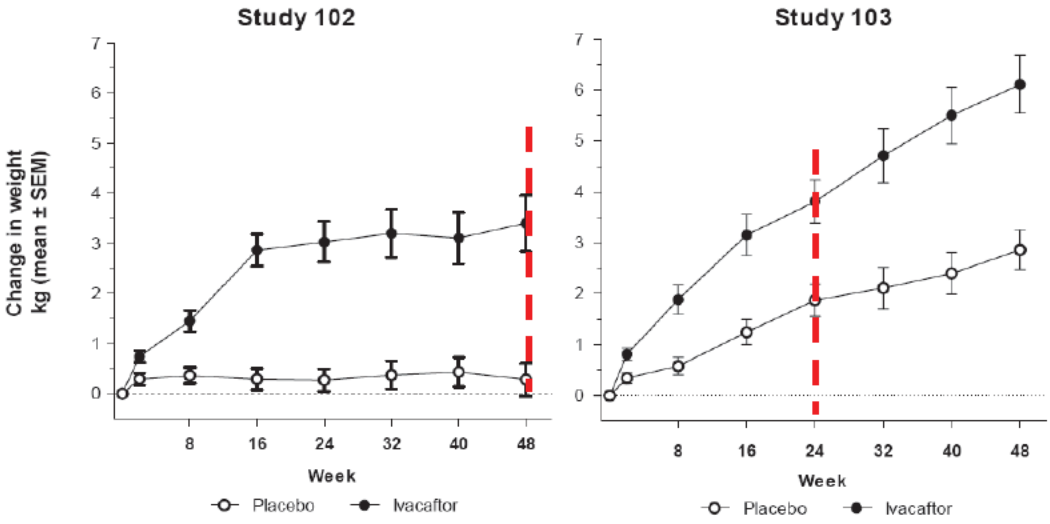
Change in Weight

The endpoint of change in weight was tested in the second tier of hierarchical analysis for Study 103, and in the third tier for study 102. Initially, the key secondary endpoint for weight was identified as, "rate of change in weight through week 48" for Study 102, and "rate of change in weight through week 24" for Study 103. However, because it is somewhat difficult to determine the clinical relevance of "rate of change in weight," both studies put forth amendments in the protocol to change the weight endpoint to "change from baseline in weight." (This was addressed in an Administrative letter dated 9/2010 for Study 102, and as Protocol Amendment 6 dated 11/2011 for study 103; see Section 5.3, Conduct, of this review under each study description for more details).

Both studies demonstrated a clinically and statistically significant change from baseline, at both the 24 and 48-week endpoints. Although Study 102 pre-specified the 48-week endpoint, and Study 103 the 24-week endpoint for their key efficacy, this review will describe the data across both time points.

A treatment difference (VX-770 minus placebo) in mean weight change at week 24 was demonstrated of 2.8kg (P<0.0001) for Study 102, and of 1.9kg (P= 0.0004) Study 103. This was sustained and improved upon by week 48, with a difference of 2.7kg (P=0.0001) for Study 102 and 2.8kg for Study 103; see Figure 4: Change in Weight from Baseline, (FAS), below.

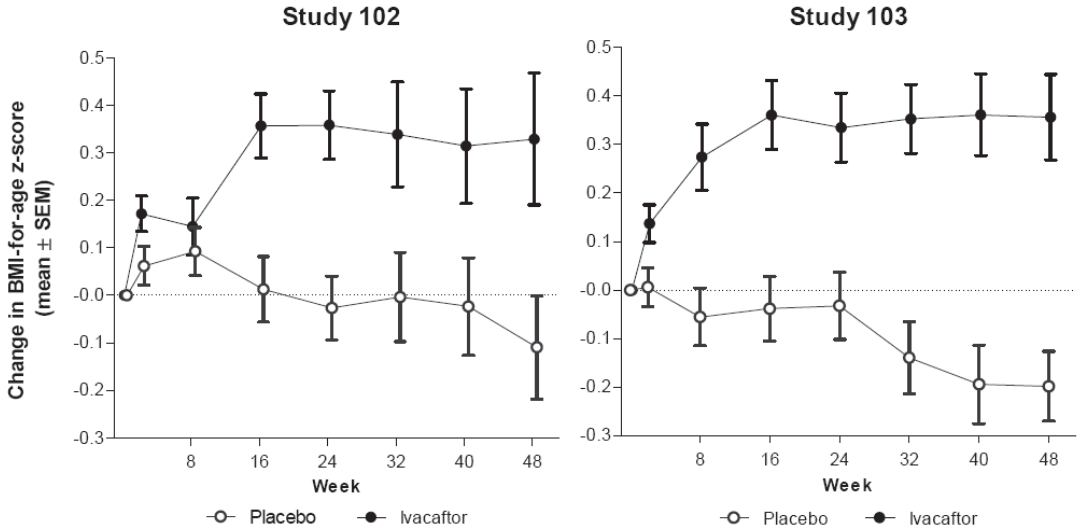
Figure 4: Change in Weight from Baseline, (FAS)



Red dashed line= Key endpoint; Change in weight
[Source: Modified from Applicant's, Module 2.7.3, Summary of Clinical Efficacy, Section 3.2.4, Figure 4]

The clinical ramification of a 2.7 and 2.8kg weight gain in less than one year for patients with CF is considerable. Patients with CF have difficulty gaining weight, due to pancreatic insufficiency leading to malabsorption as well as due to higher metabolic demands[7]. Weights below the 5th percentiles and poor growth for children with CF have been linked with lower lung function, increased morbidity and mortality when compared to CF peers of appropriate weight[12, 13]. So a significant gain in weight linked to the use of VX-770, in addition to all other nutritional standard of care therapies, is robust. Patients for Study 102 were older than 12 years, so age-appropriate increasing weight in the younger of these patients would be expected, but an average across the population of both growing pediatric patients and adults (who presumably would maintain weight) of 2.7kg weight gain is clinically relevant. Patients in Study 103 were younger (6-11 years old), and would be expected to grow during the study period, but again the magnitude of that weight gain is substantial. When adjusted for expected growth by using BMI-for-age *Z*-scores, the data remain both clinically and statistically significant. As demonstrated in Figure 5: Change in BMI-for-age *Z-score* (FAS), for Study 102, both 24 and 48 week data show treatment differences of 0.34 and 0.33 points, with P values of 0.001 and 0.049, respectively. Study 103 notes differences at 24 and 48 weeks of 0.34 and 0.45 points, with p-values of 0.0002 and <0.0001, respectively.

Figure 5: Change in BMI-for-age Z-score (FAS)



[Source: Modified from Applicant's, Module 2.7.3, Summary of Clinical Efficacy, Section 3.2.4, Figure 5]

Change in CFQ-R respiratory domain

The change from baseline in the Cystic Fibrosis Questionnaire- Revised (CFQ-R) respiratory domain score through week 24 was a key secondary endpoint for both studies. As previously described in section 5.3, under Study 101, the CFQ-R is a disease-specific health-related quality of life measure for cystic fibrosis used as a Patient-Reported Outcome (PRO) tool, consisting of generic and CF-specific scales (grouped into 3 modules and 9 domains) that measure quality of life, health perception, and symptoms over a 2-week recall period, and is available in age-appropriate formats. The CFQ-R poses questions "during the past 2 weeks," with regard to quality of life, difficulty with activities, and symptoms. Specific topics include difficulty with physical activities compared to peers, how patients felt emotionally, how much they experienced treatment burden, their perception of health, trouble with school or work, and frequency of respiratory symptoms, difficulty gaining weight, and GI complaints. The respiratory domain focuses specifically on respiratory symptoms including cough, wheeze, congestion, sputum production, difficulty breathing, and nighttime awakening due to cough.

Reviewer's Comment:
It is important to note that the CFQ-R respiratory domain has not been fully validated as a PRO, as described in the FDA's PRO Guidance. In studies to date, this tool has not correlated directly with change in FEV1, so it measures a different parameter of overall

respiratory well-being not solely linked to pulmonary function. When taken into consideration with other parameters of clinical improvement, the change in CFQ-R respiratory domain lends additional support to the clinical benefit profile of VX-770, in that patients find clinically-meaningful improvement in respiratory symptoms(cough, wheezing, sputum production, etc.) that affect quality of life.

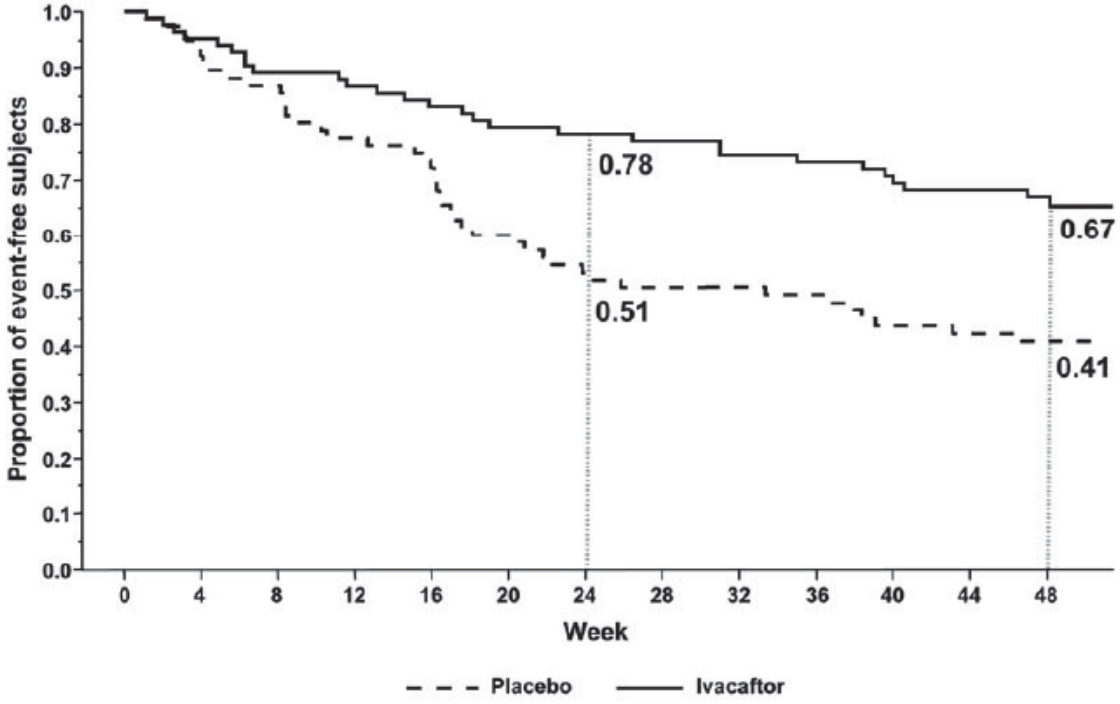
Study 102 used pooled versions of CFQ-R respiratory domain for adolescents/adults and for 12-13 years of age, whereas Study 103 utilized the child version for 6 to 11 years of age, which was administered by the study coordinator in an interview format to the patients. Study 102 demonstrated an improvement in respiratory symptoms as measured by CFQ-R respiratory domain which met statistical significance, as noted in Table 14: Summary of Key Secondary Endpoints, above. Study 103 data note a difference of 6.1 points, but a p-value of 0.1092, which would not be considered statistically significant.

Overall, the symptoms measured with the respiratory domain score of the CFQ-R are clinically relevant to patients and providers, and VX-770 demonstrates an improvement in respiratory symptomatology and well-being not solely linked to pulmonary function. Improvements in these respiratory scores provide additional support for the benefit of VX-770 in the CF population with at least one copy of the G551D allele.

Change in Time-to-Exacerbation

Time-to-first pulmonary exacerbation through Week 48 was a key secondary endpoint for Study 102. It was not identified as a key secondary endpoint for Study 103 for two reasons; the first being that younger children are generally healthier with milder lung disease than older patients with CF, and less likely to have exacerbations, and the second being that key efficacy endpoints were identified at week 24 for this study, and it was thought the window too short to capture a meaningful change. This was the case, as only 7 patients in Study 103 experienced an exacerbation by 24 weeks (3 placebo and 4 VX-770). The definition for pulmonary exacerbation in both studies was the same, and pre-established in the protocols. The definition is based on Fuch's criteria[15] of CF exacerbation from the clinical trials literature, with additional modification to state that treatment for symptoms with antibiotic therapy could be given by parenteral, oral, or inhaled routes, to accommodate for advances to standard-of-care.
For Study 102, the hazard ratio with a 95% confidence interval was 0.46 (*P*=0.0012), which translates to a 55% reduction in risk of pulmonary exacerbation when treated with VX-770 versus placebo, as demonstrated in the figure below.

Figure 6: Time-to-Exacerbation for Study 102 (FAS)

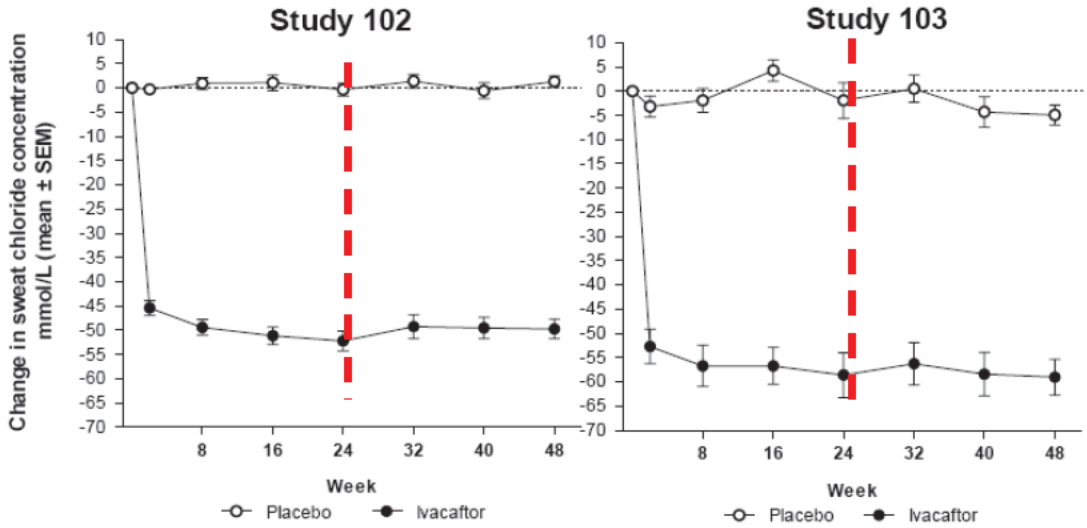


[Source: Module 2.7.3, Summary of Clinical Efficacy, Section 3.2.2, Figure 2]

In addition, the rate of exacerbations was 57% lower for the VX-770- treated group than for placebo (P=0.0003), and the mean duration of an exacerbation was 13.5 days, versus 37 days in the placebo group (P= 0.0007). [Source: Module 2.7.3, Summary of Clinical Efficacy, Section 3.2.2]

Change in Sweat Chloride

The Applicant identified a change in sweat chloride value from baseline through week 24 as a key secondary endpoint for both studies, analyzed in the second tier of the pre-specified statistical hierarchy. Results for both studies provided statistically significant values for this pharmacodynamic endpoint; see Table 14: Summary of Key Secondary Endpoints. Study 102 demonstrated a treatment difference of -48mmol/L (P< 0.0001), and the treatment difference was -54mmol/L for Study 103 (P<0.0001). The effects were sustained out to week 48 and retained statistical significance for both studies. The decrease in sweat chloride concentration was noted in the treatment group at the first measured time point, Day 15, and persisted through the treatment period. [Source: Module 2.7.3, Summary of Clinical Efficacy, Section 3.2.5]



[Source: Modified from Applicant's, Module 2.7.3, Summary of Clinical Efficacy, Section 3.2.5, Figure 7]

The clinical significance of a decrease in sweat chloride concentration is that the diagnosis of cystic fibrosis is made (in part) based on elevations in sweat chloride, as measured by pilocarpine iontophoresis. A sweat chloride value of greater than 60mmol/L is considered positive for CF, whereas a value less than 40 mmol/L for older children and adults (or less than 30 mmol/L for infants) is considered normal. Values in between are considered indeterminate. The baseline median sweat chloride values for these studies were 100 and 104 mmol/L [Source: Module 2.7.3, Summary of Clinical Efficacy, Section 3.1.2, Table 10], so a decrease by 50 mmol/L could place a patient into the borderline diagnostic range, or even into the normal range.

Making any further clinical implications based on a pharmacodynamic endpoint such as sweat chloride, however, is difficult. Sweat chloride change has not been validated as a biomarker, and 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. The Applicant has provided analyses which evaluate 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.

6.1.6 Additional Analyses

6.1.1.1 Applicant's Additional Analyses

The Applicant collected data on additional tertiary and exploratory endpoints for Studies 102 and 103. For Study 102, additional endpoints evaluated through weeks 24 and 48 included the following:

- Rate of decline in FEV1
- Change from baseline in oxygen saturation
- Change in EuroQol Questionnaire (EQ-5D)
- Hospitalizations for pulmonary exacerbation
- Outpatient sick visits to the clinic or hospital for CF unrelated to study protocol
- Courses of IV antibiotics
- Levels of inflammatory mediators in the blood

For Study 103, additional endpoints evaluated through weeks 24 and 48 were the same as for Study 102, except that pulmonary exacerbations were collected as a tertiary endpoint (this was a key secondary outcome for study 102), and EQ-5D was not evaluated, since this questionnaire is not applicable to children under 12 years of age.

In general, results were also supportive of the efficacy of VX-770 in the indicated population.

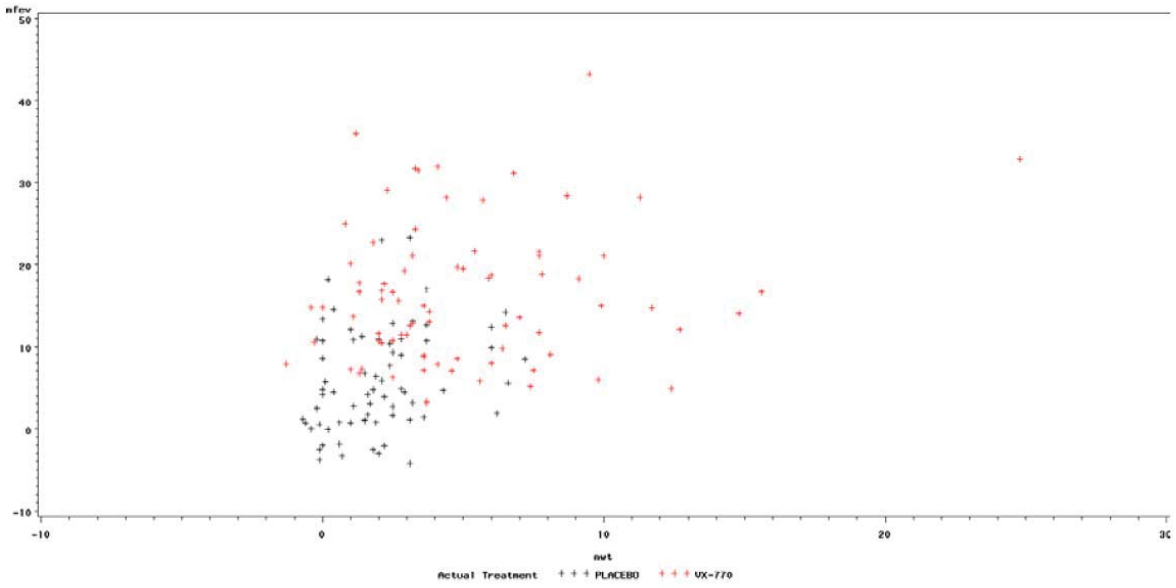
6.1.6.2 Additional FDA Analyses

Correlation of Change in Weight to Change in FEV1

Because Studies 102 and 103 demonstrated a clinical improvement in weight as well as an improvement in FEV1, the FDA wanted to explore if there was a correlation between these two clinically important parameters. The post-hoc analysis performed by FDA biostatistician Dr. Hoberman demonstrates that change in percent predicted FEV1 is correlated with change in weight for each treatment group (r=0.32, p=0.004), but that overall, change in percent predicted FEV1 is not a good predictor of change in weight.

However, investigation of any association between the maximum change in weight and maximum change in percent predicted FEV1 was also performed. It demonstrates little to no correlation in the placebo group, but there is evidence of correlation in the VX-770-treated patients. The graph below displays change in weight on the x-axis and change in FEV1 on the y-axis, with placebo patients denoted with a black plus sign (+), and those who received VX-770 with a red plus sign (+). One can clearly see clustering of the placebo group near the bottom left of the graph, indicating little change in FEV1 or weight, with the VX-770-treated patients clustered at the top right, indicating a larger change in both FEV1 and weight at the 48-Week time point (verify this). These findings further strengthen support for VX-770's efficacy in both pulmonary and non-pulmonary outcomes.

Figure 7: Correlation between Maximum Change in Weight with Maximum Change in Percent Predicted FEV1 (FAS)



[Source: Dr. Hoberman's Biostatistical review, page 22, Figure 13]

Description of Patients with G551D-CFTR who Received VX-770 but Achieved less than 5% Improvement in FEV1

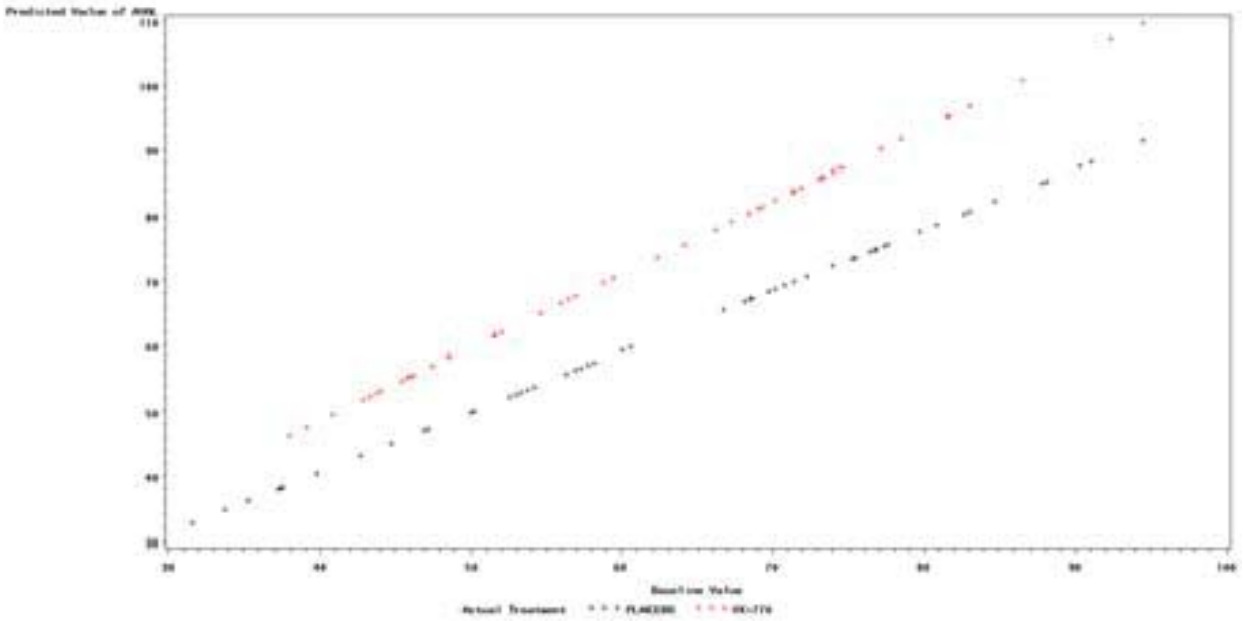
While the overall efficacy data notes a statistically and clinically-significant improvement by 10% percent predicted FEV1 at week 24, there was a group of patients who did not demonstrate such an improvement. In examining data from Study 102, there were a total of 25 patients who received VX-770, but did not achieve a change from baseline of at least 5% in percent predicted FEV1 by week 48. Dr. Hoberman further evaluated the data from this group of "non-responders" to see if any inferences could be made.

> There were 18 from North America, 5 from Europe and 2 from Australia. Examination of baselines and genotype did not reveal any pattern of covariates which may account for 'non-responders'. On the other hand, of those who completed 48 weeks, there were 33 of 78 (43%) ivacaftor patients who achieved a change of at least 5% at 15 days which persisted through 48 weeks. There was 1 of 69 in the placebo group. The respective numbers for persistence through 24 weeks were 43 (54%) in the ivacaftor group and 2 in the placebo group. [Dr. Hoberman's Review, page 16]

So there was a clear relation between treatment with VX-770, and improvement in percent predicted FEV1. In addition, it is important to note that there is no significant relationship between improvement in FEV1 and placebo treatment, further supporting

the treatment effect of VX-770 in its primary objective. Plot of the regression lines by treatment groups, comparing baseline value (x-axis) to change in percent predicted FEV1 at week 48 for completers of Study 102 (y-axis) demonstrates nicely the treatment effect of VX-770 over placebo for the primary outcome, seen below. There is a clear separation between placebo-treated patients (black +, lower line) and those who received VX-770 for 48 weeks (red +, upper line), demonstrating the change in treatment effect between groups at all levels of baseline function.

Figure 8: Regression Lines by Treatment Groups at 48 weeks, Study 102



Source: Dr. Hoberman's Biostatistical review, page 17, Figure 5]

6.1.7 Subpopulations

Standard Subpopulations

The Applicant analyzed the data for both studies 102 and 103 based on sub-populations, to evaluate for treatment effects. Data was divided by geographic region, gender, baseline medications used, and baseline percent predicted FEV1. Study 102 treatment differences all favored VX-770; Study 103 was similar. In general, the treatment comparison between VX-770 and placebo among the subgroups were similar to the overall primary efficacy results.

Subpopulation of age less than or over 18 was also examined, since older patients with CF in general have lower lung function and more co-morbidities than younger CF patients. Dr. Hoberman performed additional analyses on the pediatric patients less than 18 years old in Study 102, versus those 18 or older. He concluded that there is no substantial interaction between age and primary efficacy at week 24, and no evidence of interaction at week 48. So overall, the older CF patients did not have decreased efficacy in relation to their younger counterparts. Please refer to Dr. Hoberman's review, "Section 4: Findings in Special/ Subgroup Populations" for more detail regarding age, and for his additional subpopulation analyses.

Subpopulation by CFTR Genotype

The Phase 3 studies for VX-770 all specified that patients must have the G551D mutation in at least one CFTR allele, but there was no qualification criterion for the second allele. The Applicant evaluated the pooled FAS data from Studies 102 and 103 with regard to genotype. Patients with ΔF508 as their second allele made up 77% of the total population. The frequency of other specific second-allele genotypes was very small, with no more than 4% for any other second genotype, with only 1 to 5 patients in each group. The Applicant noted that for the G551D/ ΔF508 patients, patients who received placebo had a -0.7 percent change in % predicted FEV1, whereas those treated with VX-770 has an 11.1% point difference from baseline through Week 24. They note that the numbers for other allele types were too small to evaluate.

Dr. Hoberman, the FDA biostatistician, performed additional subgroup analysis to determine if there was a difference between patients with the G551D/ ΔF508 genotype versus those with G551D/ other genotype. The data from Study 102 at week 48 are noted below, with p-value of 0.51. Additional subgroup analysis was not performed for Study 103, due to unreliability of an interaction test, given the small sample size.

Figure 9: Change in Primary Endpoint by Genotype, Study 102

Study 102 Genotype of Patients who completed to wk 48, (N=146)	Placebo	VX-770	Difference	95% CI
G551D/ ΔF508	-1.4	8.9	10.3	(7.2, 13.3)
G551D/ other	-0.9	11.2	12.1	(6.8, 17.4)

[Source: Dr. Hoberman's Biostatistical Review, page 32, excerpt from Table 11]

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose-finding portion of the VX-770 program is relatively small, but this is not unexpected, given the orphan nature of the disease and the limited target population. Initial in vitro data suggested that VX-770 needs to be present in adequate concentration in plasma to maintain its effect, so the Applicant chose to use the minimum observed concentration at steady state ($C_{min,ss}$) as the target exposure for the dosing throughout the dose interval. Dosing interval was chosen as 12 hours based on the terminal half-life of VX-770. [Source: Module 2.7.2, Summary of Clinical Pharmacology Studies, Section 1.2 and Module 2.5, Clinical Overview, Section 3.6]

Dose ranging for adults and adolescents consisted of study 101, which assessed doses of 25, 75, 150, and 250 over a 14-28 day dosing period. Dose-ranging for children aged 6-11 years was evaluated in Part A of study 103 with collection of PK data from 12 patients after administration of a single 10mg-dose of VX-770, with subsequent PK modeling to try to achieve comparable PK as that for adults in study 101. Please refer to Section 5.3 of this document, in which both studies are described in more detail.

Results from Study 101 demonstrated that doses of 75 and 150mg every 12 hours for 14 days led to statistically-significant changes in FEV1, nasal potential difference, and sweat chloride concentrations. Doses of 150 and 250mg twice daily for 28 days were evaluated in Part 2 of that study, and led to statistically significant changes in FEV1 and sweat chloride values ($p< 0.05$). See the table below for results.

The 150mg-dose was chosen to carry forward in development based on slight nominal differences between the 75- and 150mg doses. The 250mg dose did not provide any additional benefit over the 150mg dose.

Table 15: Efficacy Results, Study 101

Treatment Group		Mean Change in Percent Predicted FEV1 (%)			Nasal Potential Difference Change from Baseline Zero Chloride + Isoproterenol Response (mV)[a]			Mean Change from Baseline in Sweat Chloride (mmol/L)		
		Value %	95% CI	p-value	Value mV	95% CI	P<0.05[b]	Value mmol/L	Min/max	P<0.05[b]
Part 1 Day 14	Placebo N=8	+0.7	-8.82, +10.16	0.879	-1.74	-6.12, +2.64	–	+4.35	-10.39, +19.09	–
	25mg N=8	+4.9	-2.64, +12.51	0.180	-1.55	-5.62, +2.52	–	-32.88	-42.43, -23.32	■
	75mg N=16	+10	+4.52, +15.56	0.002	-4.72	-7.52, -1.93	■	-40.44	-48.73, -32.15	■
	150mg N=8	+10.5	+3.34, +17.67	0.008	-5.40	-9.26, -1.55	■	-42.30	-52.83, -31.77	■
Part 2 Day 28	Placebo N=4	+7.3	+5.19, +8.19	0.125	+0.25	-2.25, +4.00	–	+4.75	-2.00, +11.00	–
	150mg N=8	+8.71	+2.25, +31.28	0.008	-4.31	-8.25, +0.50	■	-52.75	-66.00, -19.00	■
	250ng N=7	+4.36	0.00, +18.30	0.031	-10.14	-28.50, +2.00	■	-32.36	-47.00, -10.50	■

a= measures CFTR-mediated Chloride transport
b= p-values were evaluated using linear mixed model and or paired analysis model
■= met p-value of <0.05

[Source: Module 5.3.4.2.3, Clinical Study Report, Study 101, Tables 11-3, 11-4, 11-6, 11-7, 11-9, and 11-10]

In Study 103, the initial dose of 100mg every 12 hours was chosen for Part A based on allometric scaling, and it was expected to achieve similar $C_{min,ss}$ for younger children as the 150mg dose did for patients >12 years old. PK data was collected from 9 patients aged 6 to 11 with at least one copy of the G551D mutation in CFTR who received a single dose of 100mg VX-770. Computer modeling simulations were performed using the population mean estimates of PK parameters from population analysis of PK data from Part A and from additional bioavailability data from healthy volunteers from earlier clinical pharmacology trials. The Applicant chose allometric estimates of clearances and volumes to use in the model, and the final dose selected for Study 103 Part B was 150mg every 12 hours.

Reviewer's Comment:
The exponents of allometric scaling chosen for use in the modeling to determine a dose for the 6-11 year-old population was higher than that selected for the 12 and older population from Study 102; please refer to the Clinical Pharmacology Review by Dr. Lokesh Jain for more details.

Overall, the dose-finding studies in patients with CF with at least one G551D allele in combination with PK modeling were adequate to determine that a dose of 25mg every 12 hours of VX-770 was not sufficient to provide any clinically-meaningful benefit, and that doses over 150mg did not provide any additional benefit to patients.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

For studies 102 and 103 Part B, the primary efficacy time point was measured at week 24. The Applicant named the first 24 week block of double-blind, placebo-controlled treatment as the "Treatment Period," and the second 24-week block (to week 48) as the "Treatment Extension Period." Since both time periods are placebo-controlled and double-blinded, this review describes the entire 48 week period as the Treatment period. There was consistent efficacy demonstrated throughout this 48-week period, with primary and supportive efficacy endpoints providing both clinically and statistically meaningful outcomes.

Uncontrolled Extensions: Study 105 Data

Study 105 is the ongoing open-label extension for patients from Studies 102 and 103B. An additional 12 weeks of open-label data suggest that efficacy as determined by FEV1 persists at least through 60 weeks of treatment. [Source: Module 2.7.3, Summary of Clinical Efficacy, Section 5.2, and Module 5.3.5.2, VX08-770-105 Study Synopsis-interim report]

6.1.10 Additional Efficacy Analyses and Issues

Patients who are homozygous for the ΔF508 mutation in the CFTR gene

Study 104 was performed in patients with cystic fibrosis who are homozygous for the ΔF508- CFTR allele, as described previously in this review. Study 104 Part A was a 16-week, 4:1 randomized, double-blind, placebo-controlled, parallel-group study in 140 patients with CF age 12 years and older who were homozygous for the ΔF508 mutation in the CFTR gene and who had FEV1 (b) (4) predicted (see 5.3 Discussion of Individual Studies/Clinical Trials for full details of the study design). 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 103, patients who had *Burkholderia cenocepacia*, *dolosa*, or *Mycobacterium abcessus* at screening isolated from sputum, and those with abnormal liver function defined as liver function tests ≥ 3 times the upper limit of normal, were excluded. Use of inhaled hypertonic saline was not permitted.

The primary endpoint was the same as that for studies 102 and 103; 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 CF patients homozygous for the ΔF508 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-770and placebo-treated groups, respectively (p = 0.15). See Table 16: Study 104 Primary and Secondary Efficacy Endpoints, FAS, below. There were no meaningful differences between patients treated with VX-770 compared to placebo for secondary endpoints including change in CFQ-R respiratory domain score, change in weight, or risk of pulmonary exacerbations.

Table 16: Study 104 Primary and Secondary Efficacy Endpoints, FAS

Endpoint Through 16 Weeks	Absolute Change from Baseline		Treatment Effect (VX-770 minus Placebo)	
	Placebo N=28	VX-770 N=112	Difference (95% CI)	p-Value
Change from Baseline in Percent Predicted FEV1	(b) (4)			
Change from Baseline in Sweat Chloride				
Change from Baseline in CFQ-R Respiratory Domain Score (pooled)				
Change from Baseline in Weight (kg)				

[Source: Modified from Dr. Hoberman's Biostatistical Review, Section 3.1.2, page 30]

The lack of efficacy in ΔF508-homozygous patients is consistent with expectations based on VX-770's mechanism of action. VX-770 allows the CFTR chloride channel to remain open longer, but patients homozygous for the ΔF508-allele are lacking sufficient amounts of CFTR protein at the cell surface that could be "potentiated" by VX-770.

Uncontrolled Extension Data: Study 104 Part B

Part B was the open-label extension of Study 104A, for patients who were ΔF508-homozygous. Thirty-eight patients continued to at least 40 weeks' treatment with VX-770 if they met previously defined "responder" criteria. Since there was no overall treatment effect in this group, Part B was terminated for futility at week 40.

Reviewer's Comments:

Lack of efficacy in this ΔF508/ ΔF508 CF population is important to note, because VX-770 represents the first entity that appears to treat one underlying defect of CFTR function that causes disease. It is therefore important to state that VX-770 demonstrated no clinical benefit in patients homozygous for the ΔF508-CFTR mutation, because this is the most common genetic allele combination in the US, accounting for approximately 70% of children and adults with CF. If not clearly stated in labeling, this

reviewer could imagine a large proportion of ΔF508/ ΔF508 patients, providers, and families willing to use VX-770 in an off-label usage for individual patients to see if any perceived benefit could be achieved. Strong evidence from the double-blind, placebo-controlled trial should be able to prevent much off-label usage, which would not presumably provide benefit, but could lead to financial burden to these patients and families.

Potential Flaws in Conduct or Analysis

Overall, the conduct of this clinical program was very good, with no significant flaws or problems with conduct. The clinical site inspections found no irregularities in data reporting, and studies were conducted in accordance with the current ICH-GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki. FDA Biostatisticians found no faults in the analysis of data for efficacy in the VX-770 NDA package.

Strengths of Data

It is important to note that the FEV1 improvement measured in these clinical trials was noted in addition to standard of care therapies and respiratory treatments currently recommended for patients with cystic fibrosis, with the exception of use of hypertonic saline. The improvement in patient weight was demonstrated in addition to standard of care for pancreatic enzyme therapy, vitamin and mineral supplements, GI medications, and additional dietary management including increased caloric intake and additional supplementation with fat/ carbohydrates/ proteins. Therefore, the demonstration of clinically-meaningful improvements in both lung function and weight is robust evidence of efficacy in this subpopulation of patients with CF with at least one copy of the G551D-mutation in CFTR.

7 Review of Safety

Safety Summary

The safety information for VX-770 is derived primarily from studies 102, 103, and 104. As the studies were of almost identical design and were conducted in patients with CF with similar demographics, the data from these studies were pooled in order to assess the safety of VX-770. In addition, since studies 102 and 103 were in the specific indicated population of patients with CF, (those with the G551D mutation) data from these studies were also analyzed separately. Safety assessments were adequate and included adverse events, physical examinations, vital signs, ECGs, and clinical laboratory testing. There were a total of 221 patients treated with VX-770 150 mg every 12 hours, and 132 patients treated with placebo. The mean treatment duration was

similar between the treatment groups with mean 218 days for the VX-770 group and 265 days for those who received placebo.

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.

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. There were a few SAEs reported in the VX-770-treated group not reported in the placebo group, and these are discussed individually. 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 studies.

Dropout and discontinuation data provided numbers overall, and in each subset, that were small, and do not suggest any specific safety issue or signal. The overall incidence of drug interruption was similar between treatment groups, with 8% of the placebo patients and 7% of the VX-770 patients interrupting study drug for a variety of events.

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). These were AEs of interest in the Applicant's clinical program.

The Applicant provided adequate monitoring of liver function, and appropriately altered clinical monitoring based on an early identification of increased liver function parameters in blinded safety review. There was one SAE of hepatic enzyme increased in a placebo patient, and two in patients treated with VX-770. When considering liver-related adverse events leading to study discontinuation, there were 2 placebo-treated and one VX-770-treated patients, respectively. Interruption of study drug for elevated transaminases was also similar between treatment groups. While there were a greater number of interruptions for "hepatic enzymes increased" in the VX-770-treated patients, these AEs were balanced by AEs of "AST, ALT, and transaminases increased" by patients in the placebo group. Of the common liver-related adverse events in the G551D safety set, the numbers suggest a small increase in overall transaminase adverse events for the VX-770-treated group. Finally, when all transaminase events were evaluated by prior history of elevated transaminases, the data was similar as well. Therefore, the data with regard to liver safety is reassuring, and does not represent a significant safety concern for the use of VX-770 in the indicated patient population. Given the small increase in liver adverse events in the VX-770 group, 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 labeled accordingly.

The second safety concern identified early in the VX-770 program on the basis of non-clinical findings was that of cardiac effects. Subjects were appropriately monitored throughout the clinical program. The 24-hour ECG data from the pooled safety set showed similar findings to the 12-lead ECGs, with clinically-significant events being similar in both groups, but occurring at slightly decreased rates in the VX-770-treated groups at baseline and throughout the treatment periods, to the last scheduled visit. The Thorough QT study demonstrated no significant QTc prolongation effect of VX-770 at therapeutic or supra-therapeutic doses. So there is no apparent cardiac safety signal for VX-770.

VX-770 is both an inhibitor and inducer of CYP3A, so there are a number of drug-drug interactions possible with VX-770 that will require drug adjustment, or even discontinuation. This is important to note, because a number of the drugs potentially affected are commonly prescribed in patients with cystic fibrosis, either to treat CF or the infections to which subjects are predisposed. These interactions have been evaluated by clinical pharmacology, and will be addressed appropriately in the labeling for VX-770.

The overall common adverse event profile identifies headache, rash, dizziness, and upper respiratory tract infections at increased rates over placebo, none of which pose a serious safety risk.

Overall, the safety risks of VX-770 are relatively small, as identified in the safety database. The full discussion of safety, below, will describe this in more detail. The safety data provided in this NDA is adequate for determination of safety of VX-770 in the indicated population, and no additional clinical trials data is needed. However, due to potential P-gp interactions of VX-770, the clinical pharmacology group has determined that one additional post-marketing requirement study will be needed, to assess this additional safety parameter. No REMS is required for VX-770, as all safety information can be appropriately addressed in the labeling.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical development program for VX-770 consists of 23 studies; please refer to Table 2: Late-Phase Studies Relevant to Clinical Regulatory Decision-Making, and Table 3: Additional Studies in the VX-770 Clinical Development Program. A total of 700 persons received at least one dose of study drug of any dose and any duration. Of that

number, 376 were healthy volunteers or subjects with hepatic impairment, and 324 were patients with cystic fibrosis.

Of the total 23 studies reported by the Applicant, one was a single-patient IND not controlled by the Sponsor, five were the late-phase studies relevant to this regulatory decision-making (the evaluable studies to be described in more detail), and three studies were ongoing at the time of NDA submission (so did not contribute to the safety numbers). The remaining 14 completed studies involved healthy volunteers or subjects with hepatic impairment; eleven evaluated specific PK or food effect parameters, including 6 drug-drug interaction (DDI) studies. Many of these involved cross-over design. The three remaining studies included the QTc study (described in detail in 7.4.4 Electrocardiograms (ECGs)), the study in non-CF subjects with hepatic impairment, and an open-label palatability of formulation study in 4 healthy volunteers. Healthy volunteers in 6 of the completed 14 studies received only a single dose of VX-770. Given the different objectives and short-term exposure to VX-770 in the majority of these healthy subject studies, the data from non-CF patients will be considered supportive, and discussed only where pertinent in the broader view of safety of VX-770.

The 5 later-phase studies in patients with cystic fibrosis are described in Table 2: Late-Phase Studies Relevant to Clinical Regulatory Decision-Making. Study 101 was the proof-of-concept trial in CF patients with the G551D mutation, which also contributed to the dose-ranging safety. Part A of study 103 provided dose-finding in 6 to 11 year olds. Part B of Study 104, and Study 105, are both open-label long-term safety studies, which will be discussed briefly throughout the safety evaluation as uncontrolled safety data. This leaves the evaluable Studies 102, 103 Part B, and 104 Part A to provide the basis for the determination of safety in the CF population.

For the purposes of this review, the pooled safety set includes a total of 353 patients with CF (G551D- or ΔF508- CFTR-mutation) who received either placebo or VX-770 in one of those 3 clinical trials, because a larger number of patients would facilitate the detection of less common adverse reactions. Of that total pooled safety set, 221 patients with CF received VX-770 at a dose of 150mg every 12 hours during double-blind, placebo-controlled clinical trials (Studies 102, 103 Part B, and 104 Part A), with study periods ranging from 16 through 48 weeks, and 132 patients received placebo treatment. 213 patients carried at least one G551D mutation in the CFTR gene (Studies 102 and 103), of which 109 received VX-770 and 104 received placebo treatment; these patients comprise the G551D safety set. The other 112 CF patients that support the safety database were enrolled in Study 104, and were homozygous for the ΔF508-CFTR allele. The initial focus of this safety discussion will be on analysis of the pooled data from these 3 double-blind, placebo-controlled trials, hereafter referred to as the safety set, for the evaluation of deaths and major safety events. The discussion of supportive safety (common adverse events) will be based upon the data collected in the proposed patient population who carry at least one G551D mutation in the CFTR gene (Studies 102 and 103B), as will be described in the product labeling.

The Applicant also includes safety data from uncontrolled open-label extension studies (with a cut-off date of July 01, 2011), which includes additional data collected on 182 patients who participated in the VX-770 in the double-blinded studies and continued on VX-770 in open-label extension and were rolled over to receive open-label VX-770 in the extension studies. Due to design differences, data from the open-label extension studies are not pooled, but listed separately as pertinent.

7.1.2 Categorization of Adverse Events

For the purposes of this development program, the Applicant defined adverse event (AE) as any untoward medical occurrence in a patient during the study, which does not require a causal relationship with study drug, and whether or not it is considered to be study drug-related. It includes any newly occurring event, or previously-existing condition that has increased in severity. Any abnormal laboratory assessment, ECG, vital sign or physical exam finding that was judged by the investigator as clinically meaningful were to be reported as adverse events.

Adverse events were classified using MedDRA Version 12.0 for all studies.

The Applicant also created special search categories for rash, abdominal pain, upper respiratory tract infection, and elevated transaminases, and grouped these terms, even if actual line item listing was from a different System Organ Class (SOC), if the medical concept was similar. Discussion of these special search analyses are briefly discussed under section 7.4.1 Common Adverse Events of this review.

This reviewer examined the individual narratives for serious adverse events (SAEs) and discontinuations for treatment, and verbatim terms from narratives agreed with the Applicant's coding as preferred terms. There was no evidence of splitting or lumping in the individual coding noted, and it was appropriate. In general, SAEs and discontinuations appeared within the scope of what might be expected for patients with cystic fibrosis, and were not significantly different across studies, as age and level of lung disease would predict. Because this database is small, it is difficult to identify the appropriate weight to ascribe to events that occurred only in the VX-770-treated group; a single event might represent coincidence, or might be a suggestion of a potential safety signal. Since there is no way to determine at this time, brief synopses of single events that fall outside the expected norm for patients with cystic fibrosis are included where appropriate.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse event data was examined as pooled Phase 3 data in the G551D population, versus total safety set data, versus individual study data from each of Studies 102, 103B, and 104A. In general, AE data was fairly similar, with adverse events that are typically found in older patients and adults noted more often in Study 102, and more complex disease complications noted in Study 102 as well. While Study 103 did have a few AE which occurred with a higher incidence than in Study 102, the small overall number of patients limits further comparison.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Adequacy of Overall Clinical Experience

The Applicant's safety submission provides information from double-blinded study periods of 48 weeks, which is a reasonable length of time for a drug planned to be used chronically, as outlined in Guidance ICH E1A. While this Guidance is not directly applicable because those numbers it specifies are designed for more common conditions, and CF is an orphan population, the Applicant has collected data in 109 patients with a G551D mutation treated with VX-770 150mg every 12 hours for 48+ weeks, which is close to the recommended 100+ patients for one year. In addition, Study 104 adds safety data from another 112 patients homozygous for the ΔF508 mutation for an additional 16 weeks. When the duration of treatment includes those patients from Studies 102 and 104 who continued onto open-label extension studies (Studies 104B and 105) through the safety cutoff date of July 01, 2011, there have been 63 patients who have received greater than 60 weeks' exposure to VX-770, which equals 74 person-years of drug exposure overall. This is not out of the range expected for drugs developed for small orphan programs, and is reasonable. It is notable that there is data available for patients with the G551D-mutation treated with VX-770 for over a year. Given that these patients will likely remain on the drug throughout their lifetime, except when requiring antibiotic or other drug treatment that is contraindicated due to the drug-drug interaction profile, information regarding safety and durability of treatment of at least one year is reassuring from a clinical safety perspective.

The studies in this clinical program were well-designed to assess safety of VX-770 in a general population of CF patients, which covers a reasonable spectrum of disease. The program was also designed to evaluate potential concerns identified in the non-

clinical program (such as ECG changes including atrioventricular block and supraventricular premature contractions in dogs, and dose-related liver findings in rat/mouse), which were specifically assessed with clinical testing to monitor for such issues. In addition, when a potential concern for elevations in liver transaminases arose from blinded data, the Applicant made appropriate changes to better be able to fully assess for any increased liver toxicity signal. This safety population excluded CF patients with severe or end-stage lung disease, but the Applicant's rationale that changes in this group might be difficult to measure, given the severity and irreversibility of their disease processes, is reasonable.

Extent of Exposure

The extent of overall exposure to VX-770 is listed below, in Table 17: VX-770 Exposure, Pooled Safety Set. While numbers in this clinical program are relatively small, excellent patient retention with few dropouts bolstered the safety set data.

Table 17: VX-770 Exposure, Pooled Safety Set

		Placebo-Controlled Studies (102, 103B, 104A)[a]			Overall (102, 103B, 104A, 104B, 105)[b]
Duration of Exposure	**Statistic**	**Placebo N= 132**	**VX-770 N=221**		**All VX-770 exposure N=293**
Exposed	N Mean (days) SD Median (max/min)	132 265 110.9 335 (7, 385)	221 218 114.5 364 (5, 364)		293 233 146.3 126 (5, 457)
≥1 day	N	132	221		293
≥8 Weeks	N	125	218		290
≥16 Weeks[c]	N	118	188		201
≥24 Weeks	N	94	106		142
≥40 Weeks	N	91	105		133
≥48 Weeks	N	60	74		101

a= Studies 102 and 103B were double-blind, placebo-controlled for 48 weeks; Study 104A was for 16 weeks
b= Overall includes the placebo-controlled study periods as well as Uncontrolled data from Studies 104B and 105 to cutoff date of July 01, 2011
c= Study 104A ran for 16 weeks, so drop in patient years after this point is expected

Source: Modified from the Sponsor's, Module 2.7.4, Summary of Clinical Safety, Section 2.2.2, Table 8

Demographics of the Safety Set

Overall, 92% of patients in the safety set completed the double-blind, placebo-controlled treatment period, with 94% of those receiving VX-770, and 88% of those receiving placebo completing. The most common reason for discontinuation was for adverse events, which occurred in 1.8% of the VX-770 group, and 5.3% of the placebo group. Overall, there were 30 patients who discontinued treatment (20 have been previously described as the FAS in the efficacy section of this review, in 6.1.3 Patient Disposition); the additional 10 patients from Study 104 include five patients who discontinued for an adverse event (2 placebo and 3 VX-770), and the remaining 5 were VX-770-treated patients: 2 who discontinued for non-compliance, and one each for requiring a prohibited medication, loss to follow-up, and other reason (the patient wished to become pregnant, and therefore no longer met eligibility criteria).

In total, 76% of patients were from North America, 16% from the European Union, and 8% from Australia. The proportion of males to females was similar, with 51% of patients being female. Roughly 60% of patients in both VX-770 and placebo groups were age 18 or older, with a median age of 21 for the pooled safety set.

Table 18: Demographics, Pooled Safety Set

	Placebo-Controlled Studies (102, 103B, 104A)	
Variable	**Placebo N=132**	**VX-770 N=221**
Sex, n (%)		
Male	70 (53)	106 (48)
Female	62 (47)	115 (52)
Race, n (%)		
White	128 (97)	214 (97)
Other[a]	4 (3)	7 (3)
Ethnicity		
Hispanic	1 (1)	3 (2)
other[b]	131 (99)	218 (98)
Region		
N. America	93 (71)	174 (79)
European	24 (18)	29 (13)
Australia	15 (11)	18 (8)
Age (yrs)		
Mean (SD)	21.7 (10.26)	22.4 (10.80)
Median	21	20
Min, max	6, 53	6, 53
Age Group		
6 to <12	25 (19)	23 (10)
≥12 and <18	24 (18)	66 (30)
≥ 18	83 (63)	132 (60)
Weight (kg)		
Mean (SD)	55.5 (4.0)	56.4 (3.6)
Median	56.75	55.2
Min, max	17.8, 109.9	18.8, 107.2

a= other combines Black/AA, other race, or cannot ask by local regulation
b= non-Hispanic or Latino, or cannot ask by local regulation
Source: Modified from Sponsor's Module 2.7.4, Summary of Clinical Safety, Section3.1.1, Table 11

7.2.2 Explorations for Dose Response

The Sponsor identified 150mg every 12 hours as the dose to be explored early on in the clinical program, so there is little clinical experience with doses at levels higher or lower than 150mg.

The Thorough QT study (Study 008) exposed healthy volunteers to VX-770 dose of 450mg every 12 hours for 9 doses (4.5 days). The safety data from this study demonstrated no deaths and no SAEs, with no significant cardiac changes as a result of high-dose VX-770. There were three adverse events reported which occurred at a higher frequency in VX-770-treated groups over placebo, and included contact dermatitis, dizziness, and diarrhea. Rates for each are as follows:

- Contact dermatitis: 7.5% placebo, 4.3% VX-770 150mg, 14.7% VX-770 450mg

- Dizziness: 1.5% placebo, 7.1% VX-770 150mg, 2.9% VX-770 450mg
- Diarrhea: 1.5% placebo, 7.1% VX-770 150mg, 5.9% VX-770 450mg

The Applicant determined that the contact dermatitis was a result of the ECG lead application.

Study 101 Part 2 assessed doses of 150mg or 250mg every 12 hours for 28 days in patients with cystic fibrosis and at least one copy of the G551D mutation, aged >18years. Four patients received placebo, 8 received 150mg, and 7 received 250mg twice daily for the 28-day period. There were no deaths, no SAEs, and no AEs leading to discontinuation or drug interruption in this study. The adverse event profile was similar between the groups, and did not appear dose-related. There were no clinically-significant elevations from baseline in laboratory results (including AST, ALT, glucose, or Total bilirubin) or ECG findings at any time point at the 250mg dose group.

Overall, there is a small amount of data that examines doses greater than the proposed 150mg every 12 hours, but what data is there does not appear to demonstrate any significant safety concerns above the overall risk-benefit profile of VX-770.

Reviewer's Comment:
This is somewhat reassuring, given that the risk of off-label use in children less than 6 years of age may occur when the 150mg dose becomes commercially available. Noting no severe or significant adverse events in those that received higher than proposed dosing is helpful to delineate that the therapeutic window for VX-770 is not narrow.

7.2.4 Routine Clinical Testing

Routine clinical testing for this safety program included evaluations of hematology, serum chemistries including liver transaminases, coagulation studies, and urinalyses. Testing was adequate and appropriate. No important parameters were left out of evaluations.

7.2.5 Metabolic, Clearance, and Interaction Workup

General information regarding the metabolism and clearance of VX-770 is found in section 4.4 Clinical Pharmacology, of this review. Specific safety consequences of drug-drug interactions are located in section 7.5.5 Drug-Drug Interactions.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

This section is not applicable, as there are no other drugs with the same mechanism of action as VX-770 with which to compare.

7.3 Major Safety Results

Major safety results for the VX-770 program are described in detail in the sections below. Table 19: Overview of Safety gives a high-level overview of each of the major categories to be discussed further in this section.

Table 19: Overview of Safety, Pooled Safety Set

	Placebo-Controlled Studies (102, 103B, 104A)[a]	
Patient group	**Placebo N= 132 N (%)**	**VX-770 N= 221 N (%)**
Deaths	0	0
Patients with at least one SAE	46 (35)	39 (18)
Patients who Discontinued from Study for Any Reason	16 (12)	14 (6)
Patients with any AE Leading to Study Drug Discontinuation	7 (5)	4 (2)
Patients with any AE leading to Study Drug Interruption	10 (8)	16 (7)
Patients with at least one Adverse Event Reported	128 (97)	204 (92)

a= Studies 102 and 103B were double-blind, placebo-controlled for 48 weeks; Study 104A was for 16 weeks
[Source: Module 5.3.5.3.28, ISS Tables 2.1.1.2, 2.1.3.1, 2.1.3.9, 2.2.3.3]

7.3.1 Deaths

No deaths occurred during the conduct of any of the 23 studies in this clinical program for VX-770.

7.3.2 Nonfatal Serious Adverse Events

The Applicant utilized the appropriate definition of Serious Adverse Event throughout their development program, as defined in 21CFR. Data was evaluated from the Applicant's Integrated Summary of Safety, as well as the full narrative reports for any patient with a SAE from each of the 3 placebo-controlled studies which form the pooled safety set. Table 20: SAEs Which Occurred in More Than One Patient, Pooled Safety

Set, below, lists the total number of SAEs and the number of patients who experienced them. All events, regardless of causality, were evaluated.

Table 20: SAEs Which Occurred in More Than One Patient, Pooled Safety Set

	Placebo-Controlled Studies (102, 103B, 104A)[a]			
	Placebo N= 132		VX-770 N= 221	
System Organ Class Preferred Term	**Total event count**	**# Patients (%)**	**Total event count**	**# Patients (%)**
Any SAE[b]	75	46 (35)	69	39 (18)
Congenital, Familial, and Genetic Disorders	**47**	**35 (27)**	**36**	**23 (10)**
Cystic fibrosis lung	47	35 (27)	36	23 (10)
Respiratory, Thoracic and Mediastinal Disorders	**9**	**7 (5)**	**7**	**7 (3)**
Hemoptysis	4	4 (3)	2	2 (1)
Productive Cough	1	1 (1)	1	1 (0.5)
Gastrointestinal Disorders	**3**	**3 (2)**	**5**	**4 (2)**
Abdominal Pain	0	0	3	2 (1)
Investigations	**1**	**1 (1)**	**3**	**3 (2)**
Hepatic Enzyme Increased	0	0	2	2 (1)
Metabolism and Nutrition Disorders	**0**	**0**	**2**	**2 (1)**
Hypoglycemia	0	0	2	2 (1)

a= Studies 102 and 103B were double-blind, placebo-controlled for 48 weeks; Study 104A was for 16 weeks
b= All SAE other than those listed occurred as one event in only one patient (by PT)
[Source: Module 5.3.5.3.28, ISS Table 2.2.3.3]

In general, the 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.

There were a few notable reports of events which occurred in the VX-770-treated group only, and include cervical adenocarcinoma, IgA nephropathy, spontaneous abortion, depression/suicidal ideation, myopathy, and anaphylactic shock, each described briefly below.

- *Pregnancy/ Spontaneous Abortion:* A 32 year-old woman in Study 102 was noted on Day 151 of VX-770 to have a positive pregnancy test (approximately 2 weeks' conception at that time). Study drug was discontinued that day. On Study Day 188, 38 days after VX-770 discontinuation, the woman was noted to have spontaneously aborted.

- *Anaphylactic Shock:* A 12 year-old young man 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.
- *IgA Nephropathy:* A 20 year-old woman in Study 102, with a past medical history including episodes of hematuria and rhabdomyolysis, presented to an Emergency Department on Day 72 of VX-770 treatment for an episode of hematuria. She was admitted to the hospital for IV rehydration and treatment; study drug continued. She presented with another SAE of hematuria on Day 100, and was again admitted to the hospital. She was seen by a nephrologist, who gave a presumptive diagnosis of IgA nephropathy based on history, physical, and laboratory findings (no renal biopsy was obtained). Patient continued in the study, and completed VX-770 treatment.
- *Cervical Carcinoma:* A 25 year-old woman enrolled in Study 102 was noted to have an abnormal Pap smear on Day 71 of study treatment with VX-770. She had a history of abnormal Pap smear 3 months prior to enrollment in Study 102, which was followed by her medical team. On Day 204 of study treatment, she underwent surgical procedure for the treatment of cervical cancer; the surgeon felt the carcinoma was secondary to Human Papilloma Virus. The patient remained on VX-770 treatment throughout this time, and completed study treatment.
- *Depression/ Suicidal Ideation:* An 18 year-old man enrolled in Study 104 with prior history of depression experienced on Day 43 of VX-770 treatment a SAE noted as "fatigue." The patient was driving at 4am, and reportedly fell asleep while driving, which led to a single-vehicle car accident. The patient was transported to the 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. He continued treatment with VX-770 throughout the entire treatment period of the study, even when hospitalized.
- *Myopathy:* A 15 year-old male patient enrolled in Study 104 was noted to complain of myopathy beginning on Day 2 of study treatment with VX-770. He was hospitalized on Day 5 with severely abnormal laboratory values, and treatment with VX-770 was discontinued on Day 5. The patient continued to have intermittent episodes of elevated enzymes and myopathy throughout the follow-up period, and subsequent genetic testing demonstrated homozygous mutations of the AMPD1 gene, resulting in a diagnosis of myoadenylate deaminase deficiency.

Of these cases described above, most had symptoms, lab findings, or histories noted before enrollment in these studies that were supportive of an underlying disease process (myopathy, IgA nephropathy, cervical carcinoma, depression/suicidal ideation). Anaphylaxis due to VX-770 would be unusual to be caused at Day 44 of drug, and with the study drug dose held, exceedingly rare. A much more likely mechanism is that the reaction was caused by the temporally-related infusion of levofloxacin.

It is difficult to ascribe relatedness of VX-770 to the occurrence of spontaneous abortion; pregnancy and wish to become pregnant were exclusion factors for these trials, so the number of female patients who might have become pregnant during the conduct of the study is small. The non-clinical reproductive data demonstrated no teratogenicity, and no effects on peri- and post-natal development. Please also refer to section 7.6.2 of this review, to discuss all pregnancy data.

SAEs in the Uncontrolled Safety Data

The interim 60-week data from 72 patients enrolled in open-label extensions (either Study 104 Part B or Study 105) were evaluated for serious adverse events. Specifically, the group of patients who received placebo in their earlier study, and converted to VX-770 treatment, was examined.

For the 5 patients treated with placebo in Study 104 Part A, who transitioned to VX-770 for Part B, 2 SAEs were reported, both of CF lung (CF exacerbation). Of the 67 patients who received placebo in Study 102 and transitioned to VX-770 in Study 105, there were a total of 3 SAEs, including one report of hemoptysis, one of distal intestinal obstruction syndrome (DIOS), and one report of acute suicidal depression; this case will be noted in section 7.3.3 for discontinuations, below. Overall, there were no new safety signals identified from patients enrolled in the open-label extension studies.

7.3.3 Dropouts and/or Discontinuations

The Applicant's rules for discontinuation are discussed under each individual protocol in section 5.3 of this document, and were the similar for the 3 placebo-controlled studies from which the safety population is made.

Overall Profile of Discontinuations, Pooled Safety Set

Of the total 353 patients in the safety set, 92% completed the treatment period (to week 48 for Studies 102 and 103, and to week 16 for Study 104). Thirty patients discontinued for any reason, the most common of which are for 11 patients discontinuing due to Adverse Event, 5 for requiring a prohibited study medication, and 4 for non-compliance with study requirements. These numbers overall, and in each subset, are small, and do not suggest any specific safety issue or signal, nor do they have significant impact upon

the determination of efficacy. Of note, no discontinuations were categorized as lack of efficacy, although one patient was discontinued due to physician decision. All patients who discontinued are listed below in Table 21: Discontinuations from Study, Pooled Safety Set. Only one patient was classified as lost to follow-up; this patient enrolled in Study 104 had experienced 2 hospitalizations (SAEs) for abdominal pain within the first few weeks of study participation, and never returned for the Week 8 visit. The study site attempted to contact the patient multiple times by phone and registered letter, but the patient did not respond, and therefore met the definition of a loss to follow-up as defined in the protocol.

Table 21: Discontinuations from Study, Pooled Safety Set

	Placebo-Controlled Studies (102, 103B, 104A)[a]		
Pooled Safety Set	**Placebo N (%)**	**VX-770 N (%)**	**Total N (%)**
Safety Set	**132**	**221**	**353**
Completed Treatment	**116 (88)**	**207 (94)**	**323 (92)**
Reason for Discontinuation	**16 (12)**	**14 (6)**	**30 (8)**
Adverse Event	7 (5)	4 (2)	11
Lost to Follow-up	0	1 (0.5)	1
Noncompliance with Study Requirements	0	4 (2)	4
Physician Decision	1 (1)	0	1
Pregnancy	0	1 (0.5)	1
Requires Prohibited Medication	3 (2)	2 (1)	5
Withdrawal of Consent	2 (1.5)	1 (0.5)	3
Lack of Efficacy	0	0	0
Death	0	0	0
Early Termination by Sponsor's Request[b]	0	1 (0.5)	1
Incorrect Genotype[c]	2 (1.5)	0	2
Discomfort with Phlebotomy	1 (1)	0	1

a= Studies 102 and 103B were double-blind, placebo-controlled for 48 weeks; Study 104A was for 16 weeks
b= Patient was hospitalized for CF Lung x 5 days and forgot to continue study drug, re-started drug at hospital discharge despite instruction to d/c by study site; Sponsor requested Early Termination
c= One patient each in Study 102 and 103 enrolled based on chart history of genotype; later found not to meet inclusion criterion of at least one G551D allele
[Source: Module 5.3.5.3.28 ISS Table 2.1.1.2; Module 5.3.5.1.16 Listing 16.2.1.1 from Reports for Studies 102, 103, and 104]

Discontinuation due to Adverse Events, Safety Set

As noted in the table above, eleven patients discontinued due to an adverse event in the placebo-controlled studies. These eleven patients experienced a total of 18 adverse events out of the total 353 patients in the safety set. Events are described below, by System Organ Class (SOC) and Preferred Term (PT) for each treatment group, in Table 22: Discontinuations Due to Adverse Events, Pooled Safety Set.

Table 22: Discontinuations Due to Adverse Events, Pooled Safety Set

	Placebo-Controlled Studies (102, 103B, 104A)[a]			
	Placebo N= 132		VX-770 N= 221	
System Organ Class Preferred Term	**Total Event Count**	**# Patients[b] (%)**	**Total Event Count**	**# Patients[b] (%)**
Patients with Any AE Leading to Study Drug Discontinuation	12	7 (5)	6	4 (2)
Musculoskeletal and Connective Tissue Disorders	**0**	**0**	**2**	**2 (1)**
Arthritis	0	0	1	1 (0.5)
Myopathy	0	0	1	1 (0.5)
Respiratory, Thoracic and Mediastinal Disorders	**1**	**1 (1)**	**0**	**0**
Respiratory Failure	1	1 (1)	0	0
General Disorders and Administration Site Cond.	**1**	**1 (1)**	**2**	**1 (0.5)**
Asthenia	0	0	1	1 (0.5)
Fatigue	0	0	1	1 (0.5)
Feeling Abnormal	1	1 (1)	0	0
Investigations	**4**	**2 (1.5)**	**1**	**1 (0.5)**
Hepatic Enzyme Increased	0	0	1	1 (0.5)
ALT Increased	2	2 (1.5)	0	0
AST Increased	1	1 (1)	0	0
Blood LDH Increased	1	1 (1)	0	0
Nervous System Disorder	**1**	**1 (1)**	**1**	**1 (0.5)**
Headache	0	0	1	1 (0.5)
Cognitive Disorder	1	1 (1)	0	0
Cardiac Disorders	**1**	**1 (1)**	**0**	**0**
AV Block Complete	1	1 (1)	0	0
Psychiatric Disorders[c]	**4**	**2 (1.5)**	**0**	**0**

a= Studies 102 and 103B were double-blind, placebo-controlled for 48 weeks; Study 104A was for 16 weeks
b= Patient columns do not tally, since individual Patients had AE in more than one SOC group

c= Two placebo Patients experienced psychiatric AEs that led to discontinuation; Study 102 patient 02-605-01 discontinued on Day 6 due to panic attacks, and Study 103 patient 03-203-02 discontinued on Day 169 due to violent outbursts classified as adjustment disorder, affective disorder, and anxiety
[Source: Module 5.3.5.3.28, ISS Table 2.1.3.9]

Since there are so few events in the VX-770-treated group, meaningful analyses of time to dropout cannot be made; the few discontinuations are scattered throughout the 48-week treatment period. The individual events that occurred in the VX-770-treated patients include arthritis, myopathy, asthenia, fatigue, headache, and hepatic enzymes increased. There were two patients in the placebo group who discontinued for increased hepatic enzymes which were specifically coded as AST and ALT increased, so the incidence of discontinuation for elevated transaminases was actually higher in the placebo group.

Overall Discontinuations in the Uncontrolled Safety Data

There were few discontinuations in the uncontrolled open-label extension studies. Looking specifically at those patients who initially received placebo treatment, then transitioned to VX-770 treatment, there was only one report of adverse event leading to discontinuation. This was a 24 year-old woman who did not have a formal history of psychiatric issues, but who had been referred for counseling in the past, as documented in her medical records. On Day 85 of treatment with VX-770, the patient had suicidal ideation, and was admitted for psychiatric treatment. Study drug was discontinued at that time.

The only other discontinuation for any reason in the uncontrolled extension studies by a patient (initially receiving placebo in the double-blind portion of the study who then transitioned to VX-770) is for a 36 year-old woman enrolled in Study 105 who had a positive pregnancy test on Day 52 of VX-770. Please refer to section 7.6.2 of this review for more details.

No Patients from Study 104B who received placebo in Part A discontinued early; however, Study 104B in its entirety was discontinued for futility in June of 2011. (Study 104 enrolled CF patients homozygous for the ΔF508- CFTR mutation, in which VX-770 was shown to be ineffective. Please refer to section 6.1.10 Additional Efficacy Analyses and Issues, for more details.)

7.3.4 Significant Adverse Events

Drug Interruptions Due to Adverse Events, Safety Set

Twenty-six of the total 353 patients in the pooled safety set had an interruption in study drug dosing due to an adverse event; overall incidence in treatment groups was similar,

with 8% of the placebo patients and 7% of the VX-770 patients interrupting study drug for a variety of events, described below in Table 23: Drug Interruptions Due to Adverse Events, Pooled Safety Set. Overall, there was no difference in the types of adverse events which led to drug interruption between the VX-770- and placebo-treated groups. While there were a greater number of interruptions for “hepatic enzymes increased” in the VX-770-treated patients, these AE were balanced by AE of “AST, ALT, and transaminases increased” by patients in the placebo group. Patients either went on to restart study drug, or were discontinued from the studies, as described in section 7.3.3 Dropouts and/or Discontinuations, above.

Table 23: Drug Interruptions Due to Adverse Events, Pooled Safety Set

	Placebo-Controlled Studies (102, 103B, 104A)[a]			
	Placebo N= 132		VX-770 N= 221	
System Organ Class Preferred Term	**Total Event Count**	**# Patients[b] (%)**	**Total Event Count**	**# Patients[b] (%)**
Patients with Any AE Leading to Study Drug Interruption	17	10 (8)	23	16 (7)
Congenital, Familial, and Genetic Disorders	**1**	**1 (1)**	**6**	**6 (3)**
Cystic Fibrosis Lung	1	1 (1)	6	6 (3)
Investigations	**5**	**3 (2)**	**5**	**5 (2)**
Hepatic Enzyme Increased	0	0	4	4 (2)
Weight Decreased	0	0	1	1 (0.5)
ALT Increased	2	2 (1.5)	0	0
AST Increased	1	1 (1)	0	0
Blood LDH Increased	1	1 (1)	0	0
Transaminases Increased	1	1 (1)	0	0
Gastrointestinal Disorders	**3**	**2 (1.5)**	**2**	**2 (1)**
Abdominal Pain	0	0	1	1 (0.5)
Diarrhea	0	0	1	1 (0.5)
Nausea	1	1 (1)	0	0
Vomiting	2	2 (1.5)	0	0
Infections and Infestations	**1**	**1 (1)**	**3**	**2 (1)**
Vulvovaginal Mycotic Infxn.	0	0	1	1 (0.5)
Oral Candidiasis	0	0	1	1 (0.5)
Upper Respiratory Tract Infxn.	0	0	1	1 (0.5)
Bronchopulm. Aspergillosis	1	1 (1)	0	0
Nervous System Disorder	**1**	**1 (1)**	**1**	**1 (0.5)**
Migraine	1	1 (1)	1	1 (0.5)
Respiratory, Thoracic, and Mediastinal Disorders	**1**	**1 (1)**	**1**	**1 (0.5)**
Hemoptysis	0	0	1	1 (0.5)
Respiratory Distress	1	1 (1)	0	0
Musculoskeletal and Connective Tissue Disorders	**0**	**0**	**2**	**2 (1)**
Joint Swelling	0	0	1	1 (0.5)
Myalgia	0	0	1	1 (0.5)
Other- Single Events Reported in VX-770 Group[c]	**0**	**0**	**3**	**3 (1.5)**
Other- Single Events Reported in Placebo Group[d]	**5**	**4 (4)**	**0**	**0**

a= Studies 102 and 103B were double-blind, placebo-controlled for 48 weeks; Study 104A was 16 weeks
b= Patient columns do not tally, since individual Patients had AE in more than one SOC group
c= Events include one each of gynecomastia, lymph node pain, and anaphylaxis

d= Events include one each of feeling abnormal, procedure pain, nephrolithiasis/renal colic, and rash
[Source: Module 5.3.5.3.28, ISS Table 2.1.3.10]

7.3.5 Submission Specific Primary Safety Concerns

Two potential safety signals identified in the nonclinical development included ECG changes including atrioventricular block and supraventricular premature contractions in dogs, and dose-related liver findings in both rodent species (rat and mouse). The safety information for ECG data will be described under 7.4.4 Electrocardiograms (ECGs), later in this review. The liver safety is examined in more detail, below.

Liver Safety

In the placebo-controlled safety and efficacy studies of VX-770, abnormal liver function was an exclusion criterion at screening, defined as ≥3 x upper limit of normal (ULN) of 3 or more of the following values: AST, ALT, GGT, alkaline phosphatase, and total bilirubin.

During the conduct of these studies, 3 patients were identified as having marked elevations in transaminases levels, with AST and/or ALT levels > 8 x ULN. As a result, the Applicant adjusted the frequency of monitoring liver parameters to every 2 weeks for all study participants, in order to more closely monitor for potential liver toxicities. During a pre-planned interim review of Studies 102 and 104 Part A, there were no imbalances in severity or frequency of elevated transaminases. Subsequently, monitoring of transaminases was amended to every 4 weeks. When later unblinded, one patient with highly elevated transaminases was identified as receiving VX-770, and the other 2 as receiving placebo treatment. In addition, a blinded review of data from all 3 studies did not note any concerning imbalances f data with regard to frequency or severity of liver function abnormalities between the two treatment groups, so transaminases monitoring was adjusted to every 12 weeks thereafter.

The actual number of patients reporting adverse events of hepatic enzymes, AST, or ALT increased, are described in the table below for the G551D safety set. The numbers suggest a small increase in overall transaminase adverse events for the VX-770-treated group.

Table 24: Adverse Events of Transaminase Elevations, G551D Safety Set

	Phase 3 Safety Data, Adverse Events (Studies 102, 103 Part B)		
Preferred Term	**Placebo N=104 n (%)**	**VX-770 N=109 n (%)**	**Difference %**
AST Increased	4 (3.8)	8 (7.3)	+ 3.5
Hepatic Enzyme Increased	3 (2.9)	5 (4.6)	+1.7
ALT Increased	8 (7.7)	7 (6.4)	-1.3
[Source: Module 5.3.5.3.28, ISS, Table 2.3.3.3]			

Because the adverse event data relied upon investigator's assignation of an elevated laboratory value to be reported, some values might not have been captured. So data was also evaluated based on the actual laboratory values reported. Delineated below, Table 25: Cumulative Incidence of Maximum On-Treatment Transaminase Values, Safety Set, describes the percent of patients who had elevations in their transaminase levels by subgroup throughout the entire safety set. 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. Of those with elevations, there are no significant differences between treatment groups at any of the different levels of the shift-table. No patients in the VX-770-treated group concomitantly demonstrated a bilirubin $\geq$1.5 x ULN with AST +/- ALT $\geq$3 x ULN, which would meet the criteria for Hy's Law, and signal a significant liver toxicity. One patient receiving VX-770 was noted to have transient total bilirubin $\geq$1.5 to <2 x ULN at a time different than when the same patient's ALT was increased at $\geq$ 3 to <5 x ULN. Another VX-770-treated patient was noted to have elevation in ALT $\geq$8 x ULN and a total bilirubin of >1 to $\leq$ 1.5 x ULN concurrently; total bilirubin levels decreased as transaminases improved.

Table 25: Cumulative Incidence of Maximum On-Treatment Transaminase Values, Safety Set

Cumulative Incidence[a] in Safety Set (Studies 102, 103B, 104A)										
	<2 x ULN n (%)		≥2 to <3 x ULN n (%)		≥3 to <5 x ULN n (%)		≥5 to <8 x ULN n (%)		≥8 x ULN n (%)	
Parameter	Plcbo N=131	VX-770 N=221	Plcbo N=131	VX-770 N=221	Plcbo N=131	VX-770 N=221	Plcbo N=131	VX-770 N=221	Plcbo N=131	VX-770 N=221
ALT	115 (88)	191 (86)	16 (12)	30 (14)	8 (6)	12 (5)	3 (2)	4 (2)	2 (2)	2 (1)
AST	119 (91)	203 (92)	12 (9)	18 (8)	5 (4)	7 (3)	2 (2)	5 (2)	1 (1)	4 (2)
ALT or AST[b]	109 (83)	185 (84)	22 (17)	36 (16)	11 (8)	14 (6)	3 (2)	6 (3)	2 (2)	4 (2)

a= Cumulative Incidence descr bes each patient tabulated for every category, such that a patient with AST >8x ULN is calculated in each of the categories, from ≥2 to <3 x ULN through the last ≥8 x ULN
b= each patient tabulated only once according to level of maximum on-treatment transaminase, except for the <2 ULN column, which included patient for whom both maximum AST and ALT were <2 x ULN

[Source: Module 5.3.5.3.28, ISS, Table 2.2.4.8, and Module 2.7.4, Summary of Clinical Safety, Table 25]

Numbers of patients with prior medical history of liver involvement was similar between the two treatment groups, which helps to support the notion that baseline liver function was similar between the VX-770- and placebo-treated groups. In the pooled safety set (Studies 102, 103B, and 104A), incidences between placebo and VX-770-treated patients of elevated transaminases (15.2 vs. 14.9%), non-cirrhotic liver disease (9.8 vs. 9.0%), and cirrhosis with portal hypertension (1.5 vs. 0.9%), were similar. When patients were categorized by prior history of liver disease or elevated transaminases and compared to on-treatment maximum transaminases levels, there were no significant differences for risk of increased transaminases between treatment groups. Table 26: Incidence of Elevated AST by Prior History of Elevated LFTs, Safety Set below, compares patients with prior medical history of elevated AST to those with no prior history, to maximum on-treatment value for AST during the total treatment period. The data comparing ALT values and by history of liver disease are similar, showing no clinically-meaningful differences between the placebo and VX-770 treated groups. Neither was any difference apparent when the Applicant utilized exploratory analyses to evaluate exposure of VX-770 or its major metabolites (M1 and M6) over time. [Source: Module 5.3.3.5, Report G198, Table 38].

The potential risk of elevations in liver transaminases in a population with an underlying risk of such will be addressed in the labeling for VX-770; the Applicant proposes monitoring LFTs periodically, or if symptoms of liver dysfunction become apparent while taking VX-770, which is appropriate.

Table 26: Incidence of Elevated AST by Prior History of Elevated LFTs, Safety Set

	Prior History of Elevated LFTs		No Prior History of Elevated LFTs	
Safety Set[a]	**Placebo Total N=131**	**VX-770 Total N=221**	**Placebo Total N=131**	**VX-770 Total N=221**
Maximum On-treatment level				
N	**22**	**34**	**109**	**187**
No elevation	6 (27)	8 (24)	57 (52)	119 (64)
>1 x ULN	16 (73)	26 (76)	52 (48)	68 (36)
≥2 x ULN	3 (14)	10 (29)	9 (8)	8 (4)
≥3 x ULN	1 (5)	3 (9)	4 (4)	4 (2)
≥5 x ULN	1 (5)	3 (9)	1 (1)	2 (1)
≥8 x ULN	1 (5)	3 (9)	0	1 (0.5)

a= Studies 102, 103b, and 104A, for the double-blinded, placebo-controlled study periods
[Source: Module 5.3.5.3.28, ISS, Tables 2.2.4.13 and 2.2.4.14, and Module 2.7.4, Summary of Clinical Safety, Table 28]

7.4 Supportive Safety Results

Common adverse events described below are for the G551D safety set, from the two clinical safety and efficacy studies in patients with at least one copy of the G551D mutation in the CFTR gene, which will be the indicated population for VX-770, and be included in the AE table in the label. Common AE data from patients with CF who are homozygous for the ΔF508 mutation who were evaluated in Study 104 is similar; overall common adverse event safety data for the entire pooled safety CF population notes the most common adverse events, listed below.

7.4.1 Common Adverse Events

Applicant's Approach to Eliciting AE in the Development Program

Adverse events were evaluated at every clinic visit, at least every 4 weeks throughout the 48-week double-blinded, placebo-controlled study period. All Patients were queried, using non-leading questions, about the occurrence of adverse events at each visit. All spontaneously reported adverse events were also collected. Adverse events were recorded as indicated by the protocols, and described by duration, severity, seriousness, investigator's opinion of relatedness to study drug, action taken toward study drug, outcome, and concomitant therapy use.

Incidence of Common AEs

Almost every patient enrolled in the clinical trials reported at least one adverse event, which is not unexpected with an underlying disease process such as cystic fibrosis. Table 27: Common Adverse Events by System Organ Class, listed below, demonstrates the number of patients that reported any adverse event. The highest rates of incidence occur in those SOCs which would be expected to have events for this patient population, and include respiratory, infectious, GI, laboratory investigations, and congenital disorders.

Table 27: Common Adverse Events by System Organ Class, G551D Safety Set

	Placebo-Controlled Studies in CF Patients With the G551D-CFTR Mutation (102, 103B)		
System Organ Class	**Placebo N=104**	**VX-770 N=109**	**Total N=213**
Patients with Any AE	103 (99)	107 (98)	210 (99)
Respiratory, Thoracic & Mediastinal Disorder	75 (72)	76 (70)	151 (71)
Infections and Infestations	61 (59)	67 (62)	128 (60)
Gastrointestinal Disorders	52 (50)	52 (48)	104 (49)
Investigations	48 (46)	50 (46)	98 (46)
Congenital, Familial & Genetic Disorders	57 (55)	40 (37)	97 (46)
Nervous System Disorders	28 (27)	40 (37)	68 (32)
Musculoskeletal and Connective Tissue Dis.	25 (24)	33 (30)	58 (27)
Skin and Subcutaneous Tissue Disorders	28 (27)	30 (28)	58 (27)
General Disorder & Admin. Site Condition	29 (28)	28 (26)	57 (27)
Injury, Poisoning & Procedural Complications	19 (18)	21 (19)	40 (19)
Ear and Labyrinth Disorders	5 (5)	10 (9)	15 (7)
Metabolism and Nutrition Disorders	12 (12)	10 (9)	22 (10)
Psychiatric Disorders	9 (9)	10 (9)	19 (9)
Blood and Lymphatic System Disorders	7 (7)	5 (5)	12 (6)
Immune System Disorders	4 (4)	5 (5)	9 (4)
Cardiac Disorders	2 (2)	4 (4)	6 (3)
Renal and Urinary Disorders	5 (5)	4 (4)	9 (4)
Reproductive System and Breast Disorders	5 (5)	4 (4)	9 (4)
Vascular Disorders	2 (2)	4 (4)	6 (3)
Eye Disorders	2 (2)	3 (3)	5 (2)
Neoplasms benign, malignant & unspecified	1 (1)	2 (2)	3 (1)
Hepatobiliary disorders	0	1 (1)	1 (0.5)

[Source: Module 5.3.5.3.28, ISS Table 2.3.3.1]

Listings of adverse events by preferred term are noted in the table below. These adverse events occurred in greater than or equal to 5% of VX-770-treated patients with at least one copy of the G551D-allele in CFTR and with an incidence greater than

placebo in two clinical trials; events are listed in declining order of frequency in the VX-770 group. The column to the right demonstrates the difference in incidence between the VX-770-treated and placebo-treated patients. Overall, individual event numbers are small, as are differences between the groups.

Table 28: Adverse Events Occurring in >5% of VX-770 Patients and Greater Than Placebo, G551D Safety Set

	Placebo-Controlled Studies in CF Patients With the G551D-CFTR Mutation (102, 103B)		
Event by Preferred Term	**VX-770 N=109**	**Placebo N= 104**	**Difference in Incidence Over Placebo, (%)**
Headache	26 (24)	17 (16)	7.6
Oropharyngeal Pain	24 (22)	19 (18)	3.7
Upper Respiratory Tract Infection	24 (22)	14 (14)	8.5
Nasal Congestion	22 (20)	16 (15)	4.8
Abdominal Pain	17 (16)	13 (13)	3.1
Nasopharyngitis	16 (15)	12 (12)	3.2
Diarrhea	14 (13)	10 (10)	3.2
Rash	14 (13)	7 (7)	6.1
Nausea	13 (12)	11 (11)	1.3
Dizziness	10 (9)	1 (1)	8.2
Arthralgia	8 (7)	6 (6)	1.5
AST Increased	8 (7)	4 (4)	3.5
Bacteria Sputum Identified	8 (7)	4 (4)	3.5
Rhinitis	8 (7)	4 (4)	3.5
Sinus Congestion	8 (7)	4 (4)	3.5
Wheezing	8 (7)	7 (7)	0.6
Acne	6 (6)	3 (3)	2.6
Myalgia	6 (6)	3 (3)	2.6
Sinus Headache	6 (6)	4 (4)	1.7

[Source: Module 5.3.5.3.28, ISS, Table 2.3.3.3]

Common Adverse Events, Polled Safety Set

Safety data from Study 104, which included a ΔF508-homozygous population of patients with CF, but not the indicated G551D-population, showed similar findings. Overall, the most common adverse reactions in the entire pooled safety set (353 patients with CF) were very similar to those of the G551D safety set: 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%).

Common and Drug-related AE

Rash

Rash was a finding identified early in Phase 1/2 portions of the VX-770 clinical development program as being potentially-related to drug. As a result, the Applicant designed the large clinical study protocols to have a specific guidance and recommendation plan for the identification and management of rash during the later clinical trials.

Overall in the pooled safety set, there were no SAEs of rash, and no drug discontinuations or interruptions due to an adverse event of rash. In the G551D safety data, rash was a common AE noted to have a higher incidence in the VX-770-treated population than in the placebo group, at a rate of 13% in the VX-770-treated group, vs. 7% of the placebo group.

Looking at individual study incidences, rash was reported as an adverse event in 3 (4%) of placebo- and 8 (10%) of VX-770-treated patients in Study 102, in 3 (12%) of placebo and 2 (8%) of VX-770-treated patients in Study 103B, and in 0 of placebo and 9 (8%) of patients in Study 104.

In the Pooled Phase 1 safety data from this program, rash occurred in less than 3% of patients in any treatment group, and in the uncontrolled data from the open-label extension studies (104 Part B and 105) there were 3 patients who reported rash as an adverse event, all of whom had received VX-770 in the double-blinded, placebo-controlled trials. So while associated with an increased incidence with use of VX-770, rash has not been demonstrated to be at a severity which would lead to drug discontinuation, interruption, or reporting of severe or serious adverse events. The risk of rash while taking VX-770 will be incorporated into the labeling.

Dizziness

Dizziness was reported as an adverse event in 9% of VX-770-treated patients, versus in 1% of placebo-treated patients, in the G551D safety set. Dizziness was also reported in the pooled Phase 1 findings of healthy volunteers, with 0 placebo-treated patients reporting dizziness, versus 4% of those receiving only VX-770, and 5% of those who received VX-770 alone or in combination with another drug. Dizziness will be included in the labeling for VX-770.

Headache

Headache was reported in 24% of those treated with VX-770, versus 16% of those treated with placebo, in the G551D safety set. Headache was also reported in the pooled Phase 1 studies of healthy volunteers, reported with an incidence of 9% in placebo-treated, versus 12% in VX-770-treated individuals. Headache will be included in the labeling for VX-770.

Upper Respiratory Tract Infection

Upper respiratory tract infection (URTI) was reported in the G551D safety set with an incidence of 22% in the VX-770-treated group, versus 14% in the placebo-treated group. The mechanism of action by which VX-770 would cause increased URTIs is not clear, and since the incidence of URTIs is relatively high in humans in general, it is difficult to ascertain whether or not this represents a real treatment effect. The Applicant evaluated this by combining 6 adverse event terms (oropharyngeal pain, nasal congestion, nasopharyngitis, rhinitis, sinus congestion, and pharyngeal edema, and upper respiratory tract infection) in *post hoc* analysis, to further quantitate the extent of such events which might be captured under different preferred terms and system organ class categories. However, this analysis does not seem to take into consideration a number of equally-URI-related AE that were not incorporated into this analysis, including "upper respiratory tract congestion," "respiratory tract infection," "respiratory tract congestion," and an additional thirty other terms arguably also related, including 11 that occurred more frequently in the placebo group than in the VX-770-treated patients. For example, "rhinitis" was chosen to pool under the URTI special search, but "rhinorrhea," which occurred more frequently in the placebo group, was not.

The Phase 1 data does not commonly report URTI; the complaint of nasopharyngitis was noted to occur in 0 of the placebo-treated healthy volunteers, 0 of the VX-770-alone treated volunteers, but 6% of those treated with VX-770 and a co-administered drug, with an overall incidence of 3% in any VX-770-treated volunteers. Upper respiratory Tract Infection will be included in the labeling for VX-770.

Subpopulations

The data was examined for any differences in potential safety signal with regard to sex, gender, and age. Overall, there were no sub-populations with greater risk than the overall risk profile of the entire pooled safety set.

Safety Data in Healthy Volunteers

The safety data collected in healthy volunteers and non-CF subjects with hepatic impairment is very similar to the overall safety data from the VX-770 clinical program for patients with cystic fibrosis, with similar percentages of subjects who discontinued due to adverse events, and similar type of overall adverse events, including rash, headache, dizziness, and nausea and vomiting. Two caveats to this statement are that CF-related adverse events were not noted in healthy volunteers (as would be expected), and that a large proportion of healthy volunteers described a bad taste for the early formulation of VX-770 (b) (4) the formulation was changed before proceeding into later-phase studies.

7.4.2 Laboratory Findings

Routine clinical testing for this safety program included evaluations of hematology, serum chemistries including liver transaminases (discussed above), coagulation studies, and urinalyses. Overall, there were no significant differences in either median or mean values for those receiving VX-770 versus placebo-treatment, throughout the treatment periods.

Glucose Values

Study 101 had noted a total of 6 SAEs, 5 of which were observed in a known diabetic patient, who had 5 reports of abnormal blood and urine glucose levels.

During the conduct of the Phase 2B/3 Studies, the informed consent document was modified at the recommendation of the Data Monitoring Committee, to note a report of SAE of hypoglycemia in a patient with CF-related diabetes. A 20-year-old woman enrolled in Study 102 with history of CF-related diabetes was noted to have a blood glucose measurement of 25mg/dL, and accompanying symptoms of confusion, feeling hot, perspiration, weakness, and inability to feed herself. The patient was given oral carbohydrates, and subsequently improved.

Because of the above events, the Applicant performed additional analyses regarding glucose levels, including summary statistics and shift tables for the pooled safety set. Overall, there were no significant differences in median, mean, maximum or minimum glucose values for those receiving VX-770 versus placebo-treatment, throughout the double-blinded treatment periods.

7.4.3 Vital Signs

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, as noted in the Safety set data. Changes in body weight were assessed as measures of efficacy; see Section 6.1.5 Change in Weight, of this review for more details.

7.4.4 Electrocardiograms (ECGs)

Standard 12-lead ECG data for the pooled safety set noted that greater than 60% of both treatment groups had abnormal but not clinically significant findings and 2% had potentially-clinically significant findings at baseline. These incidences were similar for both groups at the treatment visits where ECG was performed. Summary statistics of heart rate, PR interval, RR interval, QT, QTcB, QTcF, QRS Axis, and QRS duration were similar between treatment groups.

24-hour ECG monitoring was performed throughout the Phase 2/3 development program, since the 12-month chronic toxicity in dogs demonstrated supraventricular premature complex runs in 3 of 40 dogs at the higher dose levels, which resolved after the one-month recovery period (suggesting it was treatment-related). The 24-hour ECG data from the pooled safety set showed similar findings to the 12-lead ECGs, with clinically-significant events being similar in both groups, but occurring at slightly decreased rates in the VX-770-treated groups at baseline and throughout the treatment periods, to the last scheduled visit. At the last scheduled visit, potentially –clinically significant events were noted in 7.2% of placebo, versus 4.7% of VX-770-treated patients. Study 008, the thorough QT study performed in healthy volunteers, did not demonstrate any clinically-significant treatment effects; see section 7.4.5, below.

7.4.5 Special Safety Studies/Clinical Trials

A number of drug-drug interaction safety studies were conducted in the VX-770 program, including those for the use of VX-770 with ketoconazole, rifampin, midazolam, rosiglitasone, fluconazole, desipramine, and oral contraceptives. These studies are evaluated in detail in Dr. Lokesh Jain's Clinical Pharmacology Review.

Study 008, the Thorough QTc study, has been discussed briefly with regard to the safety profile of the 450mg-dose, in section 7.2.2 Explorations for Dose Response. Below is a description of the QT safety results.

A thorough QT study was conducted for this program and reviewed by the FDA's 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 supra-therapeutic 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 supra-therapeutic 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 ΔΔQTcF for the active comparator moxifloxacin was greater than 5 ms (see table below).

Table 29: Thorough QTc Study Results

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)**	**ΔΔQTcF (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.

7.4.6 Immunogenicity

VX-770 is a small molecule, and as such, immunogenicity would not be expected. There was one report of anaphylaxis in the clinical safety program that bears note. The patient presented with a serious adverse event of hospitalization for CF exacerbation, and study drug was held due to need for treatment with a restricted medication. After infusion with antibiotic, the patient developed anaphylaxis, as described in section 7.3.2 Nonfatal Serious Adverse Events, of this review. It is unlikely that this episode of anaphylaxis was caused by VX-770, and a much more likely etiology of antibiotic reaction can explain this event.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There were no adverse events noted at higher incidences in patients who received higher doses of VX-770 than the to-be-marketed dosage of 150mg every 12 hours. There were no adverse events that occurred at a significantly higher rate in Study 103B than in other studies, which might have suggested an increased exposure leading to increased events.

7.5.2 Time Dependency for Adverse Events

No significant patterns or trends are apparent when evaluating either time-to-onset, or duration of adverse event of patients who received VX-770 versus placebo study treatment.

7.5.3 Drug-Demographic Interactions

Based on sub-group analysis of adverse events by sex, race, and age, no meaningful differences were detected between patients in VX-770 and placebo groups. Analyses of adverse events by geographic region were also similar.

7.5.4 Drug-Disease Interactions

Recommendations will be made in labeling for VX-770 to be administered with caution or with dose adjustments in special populations; brief descriptions of such are listed below. Please refer to full evaluations presented in detail in Dr. Lokesh Jain's Clinical Pharmacology Review for more information. Each of these will be addressed in the labeling for VX-770.

Patients with Hepatic Impairment

Patients with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had a similar VX-770 C_{max}, but an approximately two-fold increase in VX-770 $AUC_{0-\infty}$ compared with healthy subjects matched for demographics. Therefore, a reduced VX-770 dose of 150 mg once daily is recommended for patients with moderate hepatic impairment. The impact of mild hepatic impairment (Child-Pugh Class A) on pharmacokinetics of VX-770 has not been studied, but the increase in VX-770 AUC0-∞ is expected to be less than two-fold. Therefore, no dose adjustment is necessary for patients with mild hepatic impairment. The impact of severe hepatic impairment (Child-Pugh Class C) on pharmacokinetics of VX-770 has not been studied. VX-770 is not recommended in these patients, as exposure is expected to be substantially higher and the magnitude of increase is unknown.

Patients with Renal Impairment

VX-770 has not been studied in patients with mild, moderate or severe renal impairment (creatinine clearance less than or equal to 60 mL/min) or in patients with end stage renal disease. No dose adjustments are recommended for mild and moderate renal impairment patients, because of negligible elimination of VX-770 and its metabolites in urine (only 6.6% of total radioactivity was recovered in the urine in a human PK study); however, caution is recommended when administering VX-770 to patients with severe renal impairment or end stage renal disease.

7.5.5 Drug-Drug Interactions

VX-770 has the potential to interact with several classes of drugs commonly used to treat patients with CF. As a result, drug interaction studies were performed with VX-770 and other drugs likely to be co-administered, or those used as probes for pharmacokinetic interaction studies. Significant drug-drug interactions were identified with CYP3A inducers, CYP3A inhibitors, and CYP3A substrates.

Inhibitors of CYP3A
VX-770 is a sensitive CYP3A substrate. Co-administration 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 (separated by at least 3 days) is recommended for co-administration with strong CYP3A inhibitors, such as ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin.

Co-administration with fluconazole, a moderate inhibitor of CYP3A, increased VX-770 exposure by 3-fold. Therefore, a reduction of the VX-770 dose to 150 mg once daily is recommended for patients taking concomitant moderated CYP3A inhibitors, such as fluconazole and erythromycin.

Co-administration of VX-770 with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of VX-770. Therefore, food containing grapefruit or Seville oranges should be avoided during treatment with VX-770.

Inducers of CYP3A
Co-administration with rifampin, a strong CYP3A inducer, significantly decreased VX-770 exposure (AUC), by approximately 9-fold. Therefore, co-administration with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazeipne, phenytoin, and St. John's Wort is not recommended.

Potential for VX-770 to affect other drugs

CYP3A and/or P-gp Substrates
VX-770 and its M1 metabolite have the potential to inhibit CYP3A and P-gp. Administration of VX-770 may increase systemic exposure of drugs which are substrates of CYP3A and /or P-gp, which may increase or prolong their therapeutic effect and adverse events. Therefore, caution is recommended when co-administering VX-770 with CYP3A and/or P-gp substrates, such as digoxin, cyclosporine and tacrolimus.

These studies are evaluated in detail in Dr. Lokesh Jain's Clinical Pharmacology Review; please refer there for further information. Each of these will be addressed in the labeling for VX-770.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies have been performed for VX-770. Two-year mouse and 2-year rat carcinogenicity studies demonstrated that there were no test article-related tumor findings in either study. The clinical program for VX-770 noted one case of cervical carcinoma in a 20-year old woman with history of abnormal Pap smear prior

to enrolling in the clinical trials. Please refer to section 7.3.2 Nonfatal Serious Adverse Events, for more information.

7.6.2 Human Reproduction and Pregnancy Data

The use of VX-770 in pregnant or lactating women has not been studied in adequate and well-controlled trials, so the effects of VX-770 on conception, pregnancy, and lactation in humans are not known. Animal data demonstrated that VX-770 at 200 mg/kg/day decreased fertility indices in male and female rats, but that the drug was non-teratogenic in rats and rabbits. VX-770 had no effects on peri- and post-natal development in rats. VX-770 was noted to be excreted into the milk of lactating rats.

All the clinical studies with VX-770 have noted pregnancy and lactation, as well as the inability to comply with appropriate contraception practices, as exclusion criteria. Nevertheless, there were three cases of pregnancy by patient or partner reported for this development program. The first case was described in section 7.3.2 of this review, under Serious Adverse Events leading to discontinuation, which describes a 32 year-old woman treated with VX-770 noted to have a positive pregnancy test on screening. Study drug was discontinued at that time, but subsequently, she had a spontaneous abortion.

An additional case is noted of a 36 year-old woman who received placebo treatment in Study 102, and rolled over to treatment with VX-770 in Study 105, who had a positive pregnancy test on Day 52 of drug. She discontinued from the open-label extension the same day. The Safety Update for this NDA submission notes that the patient delivered a female infant on (b) (6), and that mother and baby were well.

A healthy (non-CF) male patient in Study 009 was discontinued initially after reporting his wife's pregnancy during the study period, but further follow-up disclosed that the study patient "was not involved in his partner's becoming pregnant."

7.6.3 Pediatrics and Assessment of Effects on Growth

Cystic Fibrosis is an orphan disease, and, as such, is not directly subject to pediatric study requirements as defined under the Pediatric Research Equity Act (PREA). However, CF is a disease usually diagnosed early in life, and often identified on prenatal testing or newborn screening, and the disease has a significant impact on its pediatric population, given the morbidity, mortality, and shortened life expectancy for children born with this disease. Therefore, the Applicant chose to evaluate patients with CF who were 12 years of age and greater for Studies 102 and 104 (incorporating adolescent patients), and children aged 6 to 11 years in Study 103, in the course of their development program. The efficacy data noted in Section 6 of this review discusses the 12.5% improvement in percent predicted FEV1 at week 24 for Study 103, and section

6.1.7 Subpopulations discusses Dr. Hoberman's statistical analysis to look at efficacy in the under 18 years pediatric group versus their adult counterparts in Study 102, noting no differences in overall efficacy between groups.

Overall safety in the pediatric population is demonstrated with the results from Study 103, showing no new or increased rates of AE, SAE, or discontinuations due to AE when compared to the entire CF patient population studied. FDA is already in discussion with the Applicant in regard to their development program for studying VX-770 in a younger pediatric population, as well.

Effect on pediatric growth is evaluated in an NDA review, since some drugs might have a negative impact on children's growth. For this program, the opposite was demonstrated. Study 103 in children with CF aged 6 to 11 years, and Study 102 in patients 12 years and older, noted significant efficacy data of increased weight, and BMI-for-age-z-scores were significantly greater at weeks 24 and 48 for the VX-770-treated patients than those treated with placebo. The BMI data supports that linear growth increased for patients treated with VX-770, as well as weight. Therefore there is no negative effect on growth or safety for children as young as 6 years of age treated with VX-770.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No examination of abuse potential for VX-770 was performed during the non-clinical and clinical phases of this development program. The clinical program does not demonstrated adverse events that would be suggestive of mood alteration.

There have been no reports of overdose in the clinical program. Single doses as high as 800mg in healthy volunteers, and repeat doses of 450mg x 9 doses and 250mg twice daily for 28 days in CF patients, were well-tolerated; see Section 7.2.2 Explorations for Dose Response for further information.

The potential for VX-770 to cause withdrawal and rebound were not formally studied in this development program. However, there were no apparent changes in the safety or tolerability profiles of VX-770 for Patients evaluated in the double-blind, placebo-controlled studies with regard to drug interruption, discontinuation, or treatment completion, which suggests that the potential for such is unlikely.

7.7 Additional Submissions / Safety Issues

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a Safety Update including data from clinical studies, animal studies, and other sources is required for a NDA submission. The Applicant submitted their safety update for VX-770 on January 6, 2012, covering the reporting period of July 2, 2011, through November 1, 2011.

This safety information provided covers the Applicant's 4 ongoing studies, including the open-label safety extensions 104B and 105, and studies 106 and 107 (exploratory biomarker studies). It also includes study VX11-770-901, which is the Applicant's Expanded Access Program for patients who have at least one copy of G551D-allele in CFTR and who have severe lung impairment (FEV1< 40% predicted), which began enrolling subjects in the summer of 2011.

Deaths

There was one death reported for a patient enrolled in the Expanded Access Program (Study 901). The patient was a 29-year-old man with end-stage CF lung disease, and a history of rapid decline in lung function in the previous 3 years. At the time of screening, his FEV1 was 38% predicted, he required chronic supplemental oxygen at 2-3L/min at night, and had past medical history complicated by frequent CF exacerbations, chronic respiratory insufficiency and hypoxia, pulmonary hypertension, and history of pulmonary embolism, chronically treated with Coumadin. He began treatment with VX-770 on July 23, 2011. On (b) (6), he began evaluation for lung transplantation. His condition continued to deteriorate, and drug was held on September 19th, to allow for treatment with voriconazole for a presumed *Aspergillus* infection. His condition continued to deteriorate, and the patient and family made the decision to begin palliative and comfort care only; he died on (b) (6)

SAEs

The SAEs reported in the Safety Update are similar to those reported in the NDA submission, and are consistent with the safety profile of VX-770 already described in this review. There were no events that would suggest a new safety signal.

8 Postmarket Experience

No post-marketing data is available for VX-770 since it is not approved in any country at this time.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Labeling discussions are ongoing with the Applicant and will not be complete by the time this review is finalized. High level labeling issues from a clinical standpoint include:

- Indication: The proposed mutation-specific indication is appropriate. A "Limitation of Use" statement will be added to note that VX-770 is not efficacious in CF patients with the most common CF mutation (F508del).
- Warnings and Precautions: There are two precautions included in the labeling. The first is with regard to monitoring of liver transaminases and drug interruption for AST or ALT greater than 5 times the upper limit of normal, and the second is that co-administration with CYP3A inducers is not recommended. Both of these warnings are reasonable, given the safety findings delineated in this review, as well as that of the Clinical Pharmacology team.
- Drug-Drug interactions: The drug-drug interaction profile for VX-770 is significant with regard to CYP3A inhibitors, and will require a reduction in dosage with concomitant use of drugs in this group. A number of drugs in this group are prescribed for patients with cystic fibrosis (ie, to treat infections), so appropriate labeling that identifies these drugs, and alternate dose recommendations, is important with regard to safety.
- Special Populations: There will be a dose adjustment in pts with moderate hepatic impairment, and a recommendation for careful monitoring of patients with severe renal impairment.
- Clinical Studies: These sections of the label have been modified to clearly differentiate the indicated G551D-allele CF patient population from those with the most common CF mutation (ΔF508-allele), since Study 104 provides evidence that VX-770 is not efficacious in that more common patient population. The labeling now divides clinical information into mutation-specific sections, and fully describes the results of Study 104.
- Patient Counseling Information: This section needs to be updated to reflect the changes to the prescribing information, especially regarding DDI.

9.3 Advisory Committee Meeting

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

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/s/

KIMBERLY A WITZMANN
01/17/2012

ANTHONY G DURMOWICZ
01/17/2012