

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203188Orig1s000

OTHER REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: January 9, 2012

TO: Miranda Raggio, Regulatory Project Manager
Kimberly Witzmann, M.D., Medical Officer
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FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations (*formerly* Division of Scientific Investigations)

SUBJECT: Evaluation of Clinical Inspections

NDA: 203188

APPLICANT: Vertex Pharmaceuticals Incorporated

DRUG: ivacaftor
NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Fast-track (6-month clock) Review
INDICATION: Treatment of cystic fibrosis patients > 6 yrs of age with a G551D mutation in the CFTR gene

CONSULTATION REQUEST DATE: November 22, 2011 (signed)
DIVISION ACTION GOAL DATE: April 18, 2012 (original) January 27, 2012 (revised)
PDUFA DATE: April 18, 2012 (original)

I. BACKGROUND:

This NDA submission from Vertex Pharmaceuticals is for VX-770 (ivacaftor), for the proposed indication, “treatment of cystic fibrosis (CF) in patients 6 years and older who have a G551D mutation in the CFTR gene.” Patients with the G551D mutation are the targeted population because VX-770 is a potentiator of the gating effect of the cystic fibrosis transmembrane conductance regulator. The most prevalent mutation with a gating defect in CF is the G551D mutation.

The product is supplied as a 150mg tablet and the proposed dose is 150mg every 12 hours. The drug is an NME and designated as an orphan drug.

Two adequate and well-controlled studies were submitted in support of this NDA submission. For each study protocol, data from each clinical site were sparse, and two of high enrollment centers were subject of a clinical audit.

Protocol VX-08-770-102 entitled “A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-770 in Subjects with Cystic Fibrosis and the G551D Mutation” was a Phase III randomized, double-blind, placebo-controlled, parallel-group multicenter study of orally administered VX-770 in cystic fibrosis patients, 12 years and older, who had the G551D-cystic fibrosis transmembrane conductance regulator (CFTR) mutation on at least 1 allele. The primary study efficacy endpoint was the primary absolute change from baseline in percent predicted forced expiratory volume in 1 second (% predicted FEV₁) through Week 24.

Protocol VX08-770-103 (Part B) entitled “A Phase 3, 2-Part, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Pharmacokinetics, Efficacy and Safety of VX-770 in Subjects Aged 6 to 11 Years with Cystic Fibrosis and the G551D Mutation” was a Phase III, randomized, double-blind, placebo-controlled, parallel-group multicenter study of orally administered VX-770 in cystic fibrosis patients, 6 to 11 years of age, who had the G551D-cystic fibrosis transmembrane conductance regulator mutation on at least 1 allele. The primary study efficacy endpoint was the absolute change from baseline in percent predicted forced expiratory volume in 1 second (% predicted FEV₁) through Week 24.

II. RESULTS (by protocol/site):

Name of CI	City, State	Protocol/Study Site#/# of subjects	Insp. Date	Final Classification
Joanne Billings, M.D.	Minneapolis, MN	Protocol VX08-770-102 Site #011/ Subjects: 5	12/12-12/16, 2011	Pending (Preliminary: NAI)

Ahmet Uluer, D.O.	Boston, MA	Protocol VX08-770-102 Site #045/ Subjects: 5 Protocol VX08-770-103B Site #045/ Subjects: 2	12/12-12/14, 2011	Pending (Preliminary: NAI)
Vertex Pharmaceuticals Incorporated	Cambridge, MA	Sponsor	12/18/-12/20, 2011	Pending (Preliminary: NAI)

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable/Critical findings may affect data integrity.

Preliminary= The Establishment Inspection Report (EIR) has not been received and findings are based on preliminary communication with the field.

CLINICAL STUDY SITE INVESTIGATOR

1. Joanne Billings, M.D. /Study Protocol 102/Site #011

University of Minnesota
410 Delaware St. SE, MMC276
Minneapolis, MN 55455

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from December 12-16, 2011.

For Study Protocol 102, a total of 5 subjects were screened, 5 were randomized and 2 completed the study. There was no under-reporting of serious adverse events. An audit of 5 randomized subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for randomized subjects whose records were audited, were verified against the case report forms and NDA subject line listings.

No discrepancies were noted. In general, this clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection.

d. Data acceptability/reliability for consideration in the NDA review decision.

Data submitted by this clinical site appear acceptable for this specific indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

2. Ahmet Uluer, M.D./Study Protocol 102 and 103 (Part B)/Site #45

Children's Hospital Boston
300 Longwell Ave, Hunnewell 2
Boston, MA 02115

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from December 12-14, 2011.

For Study 102, a total of 5 subjects were screened, randomized, and who completed the study. There was no under-reporting of serious adverse events noted. An audit of 5 randomized subjects' records was conducted.

For Study 103 (Part B), a total of 2 subjects were screened, randomized and who completed the study.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and NDA subject line listings.

This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

d. Data acceptability/reliability for consideration in the NDA review decision.

The data, in support of clinical efficacy and safety from this clinical site, appear acceptable for this specific indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

SPONSOR INSPECTION

3. Vertex Pharmaceuticals Incorporated

130 Waverly Street
Cambridge, MA 02139-4242

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.810, from December 18-20, 2011.

The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed FDA forms 1572, monitoring reports, communication with the Sponsor and drug accountability, staff training and site monitors.

b. Limitations of inspection

None.

c. General observations/commentary

Sponsor maintained adequate oversight of the clinical trial. There were no noncompliant sites, and monitoring of the investigator sites was considered adequate. No salient issues were identified. There was no evidence of under-reporting of adverse events. No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued at the end of the Sponsor inspection.

d. Data acceptability/reliability for consideration in the NDA review decision.

Data submitted by this Sponsor site appear acceptable for this specific indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigator sites and Sponsor (Vertex Pharmaceuticals, Inc) were inspected in support of this application for Protocols VX-08-770-102 and VX-08-770-103 (Part B),

respectively. No regulatory violations were noted. Based on review of inspectional findings for these clinical investigators, the study data collected appear generally reliable in support of the requested indication.

Note: Observations noted above are based on the preliminary communications from the field investigator; an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

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

/s/

ANTHONY J ORENCIA
01/09/2012

SUSAN LEIBENHAUT
01/09/2012

TEJASHRI S PUROHIT-SHETH
01/09/2012

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	203188
Brand Name	Ivacaftor
Generic Name	VX-770
Sponsor	Vertex Pharmaceuticals, Inc
Indication	Cystic Fibrosis
Dosage Form	Film Coated Tablets
Drug Class	CFTR potentiator
Therapeutic Dosing Regimen	150 mg b.i.d
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not established
Submission Number and Date	27 October 2011
Review Division	DPARP

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of VX-770 (150 mg b.i.d and 450 mg b.i.d) was detected in this TQT study from Part B on Day 5. 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 as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 5, indicating that assay sensitivity was established.

Part B was a double-blind, randomized, placebo- and active-controlled, single center, 4-period crossover study design, 72 subjects received VX-770 150 mg b.i.d, VX-770 450 mg b.i.d, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

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

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

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

The supratherapeutic dose (450 mg b.i.d) produces mean $C_{\max}$ values of 3.9-fold higher than the mean $C_{\max}$ for the therapeutic dose (150 mg b.i.d). At these concentrations, there are no detectable prolongations of the QT-interval. It is expected from drug interaction studies that co-administration of VX-770 with ketoconazole can elevate VX-770's steady state $C_{\max}$ higher than observed with 450 mg b.i.d. However, dosing interval in patients taking ketoconazole will be increased to match exposures achieved with the therapeutic dose. VX-770 is not recommended in patients with severe hepatic impairment.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL

The sponsor proposed the following language in the package insert:

(b) (4)

2.2 QT-IRT RECOMMENDED LABEL

QT-IRT recommends the following label language. Our recommendations are suggestions only. We defer final decisions regarding labeling to the review division.

The effect of multiple doses of ivacaftor 150 mg and 450 mg twice daily on QTc interval was evaluated in a randomized, placebo- and active- controlled (moxifloxacin 400 mg) four-period crossover thorough QT study in 72 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on Fridericia's correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The dose of 450 mg twice daily ivacaftor is adequate to represent the high exposure clinical scenario.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Cystic fibrosis (CF), affecting approximately 30,000 in the United States, is a recessive genetic disease caused by a defect in the CFTR gene. VX-770, a compound being developed for the treatment of CF, has been shown to have CFTR potentiator properties.

3.2 MARKET APPROVAL STATUS

VX-770 is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From eCTD 2.6.2

“Ivacaftor was screened against 11 non-voltage and voltage-gated ion channels in assays conducted using a human embryonic kidney cell line (HEK293) stably transfected with human ion channels and evaluated by electrical field stimulation, coupled to voltage-

sensitive fluorescent dyes, to monitor membrane potential (Table 2.6.3.1, Report B227). In this model system, DMSO solutions of a (b) (4) ivacaftor inhibited only CaV1.2 ($IC_{50} = 1.3 \mu M$) and KV1.5 ($IC_{50} = 3.4 \mu M$) with moderate potency and had little or no measurable activity (b) (4) on the other sodium, calcium, and potassium channels tested. The significance of these results in terms of human safety is unclear, since ivacaftor did not bind any of the 4 calcium channel targets or any of the 5 potassium channel targets in the receptor binding panel at (b) (4) potency.

“Ivacaftor was also tested in a GLP study to assess potential inhibition of the hERG channel, which is a standard system used evaluate the potential risk of drug-induced QT prolongation (Table 2.6.3.4, Report VRT-813077-TX-012). HEK 293 cells stably transfected with the hERG channel were evaluated in a whole-cell, patch-clamp system for effects on tail current amplitudes in the presence of ivacaftor, measured as a percentage of pretreatment control (% of control). Functionality of the test system was verified by application of 100 nM E-4031 (reference substance), a potent inhibitor of hERG channel activity. (b) (4) ivacaftor was used in this study and DMSO stock solutions were prepared to achieve final target bath solution concentrations of 0.8, 2.5, and 8 μM with 0.3% DMSO. Exposure of cells to 8 μM ivacaftor for approximately 15 minutes reduced hERG tail current to $65.4 \pm 4.4\%$ ($n = 4$) of pretreatment control value, a total inhibition of 34.6% (22.1% vs. DMSO vehicle alone), and this effect was significantly different from that of the vehicle group. It was not possible to determine the IC_{50} for ivacaftor in this system due to limited solubility at concentrations above 8 μM in the bath solution. By contrast, exposure of cells to 100 nM concentrations of the potent hERG inhibitor E-4031 for approximately 10 minutes reduced tail current to $9.7\% \pm 5.1\%$ ($n = 2$) of pretreatment control, which equates to an inhibition of 90.3% and is consistent with its known pharmacological action. Although ivacaftor had a concentration-dependent inhibitory effect on hERG tail currents, when compared to results obtained for the positive control (E-4031), it was concluded that ivacaftor is not a potent hERG inhibitor.

“The effects of oral gavage administration of ivacaftor on arterial blood pressure (ABP), heart rate (HR), and lead II electrocardiogram (ECG) parameters were also evaluated in a GLP study in conscious, treatment-naïve, telemeterized dogs (Table 2.6.3.4, Report VRT-813077- TX-011). Male beagles ($N=4$), surgically implanted with telemetry probes, were dosed orally with ivacaftor at 0 (vehicle control), 15, 30, or 60 mg/kg single doses, using a 4×4 Latin Square paradigm (all dogs receiving all dose levels) with a minimum washout period of three days between each dose. (b) (4)

“Hemodynamic effects attributed to oral administration of ivacaftor included a dose-related, but transient increase in the ABP parameters (SBP, DBP, and MAP) at 60 minutes postdose, relative to the time-matched vehicle control. The blood pressure effect was not considered adverse due to the small magnitude and brief nature of the response. Oral administration of ivacaftor did not affect mean HR, lead II ECG variables (PR interval, QRS duration, RR interval, or QT interval), or HR-adjusted QTcF and QTcQ intervals at any dose level and there were no abnormalities in ECG waveform

morphology or rhythm observed. The NOAEL for cardiovascular effects (including QT interval assessment) after oral administration of ivacaftor to dogs was the high dose of 60 mg/kg. Thus, ivacaftor demonstrated little to no potential for adverse effects on the cardiovascular system”.

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4

“Table 2 provides the incidence of subjects with abnormal findings from standard 12-lead ECG monitoring at baseline and/or at the last scheduled visit in the Phase 2b/3 placebo-controlled studies. The majority (>60%) of subjects in both treatment groups had abnormal, non-clinically significant findings and approximately 2% of subjects had potentially clinically significant abnormalities on 12-lead ECG at baseline. The incidence of potentially clinically abnormal findings was similar in the ivacaftor treatment group compared to the placebo treatment group at the majority of study visits (including the last scheduled visit) where 12-lead ECGs were performed.

Table 2: Incidence of Subjects With Abnormal Findings From Standard Digital ECG Monitoring by Treatment Group and Visit: Pooled Placebo-Controlled Phase 2b/3 Studies, Safety Set

Visit	Category	Placebo-Controlled Studies (102, 103 Part B, 104 Part A)	
		Placebo (N = 132) n (%)	Ivacaftor (N = 221) n (%)
Baseline	N	131	221
	Normal	46 (35.1)	82 (37.1)
	Abnormal (NCS)	82 (62.6)	135 (61.1)
	Abnormal (PCS)	3 (2.3)	4 (1.8)
Last Scheduled Visit	N	132	221
	Normal	48 (36.4)	77 (34.8)
	Abnormal (NCS)	84 (63.6)	141 (63.8)
	Abnormal (PCS)	0	3 (1.4)

Source: [Module 5.3.5.3/VX-770 ISS/Table 2.2.6.5](#)

ECG: electrocardiogram; NCS: not clinically significant; PCS: potentially clinically significant.

Notes: Baseline is defined as the most recent measurement prior to intake of the first dose of study drug. Percentage is based on the number of subjects with data at the time point. Subjects in Study 102 and Study 103 Part B received 48 weeks of treatment, and subjects in Study 104 Part A received 16 weeks of treatment.

Source: eCTD 2.7.4, Table 35

“There were 3 (1.4%) subjects in the ivacaftor treatment group and 0 subjects in the placebo treatment group with potentially clinically significant abnormalities on 12-lead ECG at the last scheduled visit. All 3 of these subjects had non-clinically significant or potentially clinically significant abnormalities on 12-lead ECG at baseline as well as at other times during the treatment period. Overall, no clinically meaningful trends were identified.

“Subjects with any history of prolonged QTcF (>450 msec) were excluded from the studies as a precaution since the Thorough QT study (Study 008) was conducted in parallel with the Phase 2b/3 studies. Table 3 provides the maximum on-treatment values and increases from baseline in QTcF intervals through the dosing period. There were no subjects with an on-treatment QTcF prolongation of >60 msec. The proportion of

subjects with maximum on-treatment QTcF increases from baseline of >30 to ≤60 msec was similar between the ivacaftor treatment group (13.6% [30 subjects]) and the placebo treatment group (13.6% [18 subjects]) (Module 5.3.5.3/VX-770 ISS/Table 2.2.6.3). There were no subjects with maximum QTcF intervals >480 msec. Four (1.8%) subjects in the ivacaftor treatment group and 2 (1.5%) subjects in the placebo treatment group had maximum on-treatment QTcF intervals of >450 to ≤480 msec during the dosing period

Table 3: Incidence of Subjects With Maximum On-Treatment Value in QT/QTc Intervals: Pooled Placebo-Controlled Phase 2b/3 Studies, Safety Set

Maximum On-Treatment Value	QT Interval Type	Placebo-Controlled Studies (102, 103 Part B, 104 Part A)	
		Placebo (N = 132) n (%)	Ivacaftor (N = 221) n (%)
≤450 msec	QTcF	130 (98.5)	217 (98.2)
	QTcB	108 (81.8)	178 (80.5)
	QT	130 (98.5)	217 (98.2)
>450 to ≤480 msec	QTcF	2 (1.5)	4 (1.8)
	QTcB	23 (17.4)	39 (17.6)
	QT	2 (1.5)	3 (1.4)
>480 to ≤500 msec	QTcF	0	0
	QTcB	1 (0.8)	3 (1.4)
	QT	0	0
>500 msec	QTcF	0	0
	QTcB	0	1 (0.5)
	QT	0	1 (0.5)

Source: [Module 5.3.5.3/VX-770 ISS/Table 2.2.6.4](#)

QTcB: QT interval with Bazett's correction; QTcF: QT interval with Fridericia's correction.

Note: Subjects in Study 102 and Study 103 Part B received 48 weeks of treatment, and subjects in Study 104 Part A received 16 weeks of treatment.

Source: *eCTD 2.7.4, Table 36*

“In all Phase 2b/3 studies the number and percentage of subjects with abnormal 24-hour ambulatory ECG findings at all applicable study visits were low and balanced between the 2 treatment groups.”

“Table 38 provides the incidence of adverse events that may be associated with ECG abnormalities in the pooled placebo-controlled Phase 2b/3 studies. Overall, 7 (2.4%) subjects reported adverse events in the SOC of cardiac disorders; the incidence of adverse events that may be associated with ECG abnormalities in the ivacaftor treatment groups (5 [2.3%] subjects) was similar to the placebo treatment groups (2 [1.5%] subjects).

**Table 4: Incidence of Adverse Events of Related to ECGs by Preferred Term:
Pooled Placebo-Controlled Phase 2b/3 Studies, Safety Set**

Preferred Term	Placebo-Controlled Studies (102, 103 Part B, 104 Part A)	
	Placebo N = 132 n (%)	Ivacaftor N = 221 n (%)
Number of subjects with any ECG associated adverse events	2 (1.5)	5 (2.3)
Palpitations	0	3 (1.4)
Tachycardia	0	1 (0.5)
Extrasystoles	0	1 (0.5)
Supraventricular extrasystoles	0	1 (0.5)
Atrioventricular block complete	1 (0.8)	0
Left ventricular dysfunction	1 (0.8)	0

Source : [Module 5.3.5.3/VX-770 ISS/Table 2.1.3.2](#)

ECG: electrocardiogram

Note: A subject with multiple events within a PT is counted only once in the PT. Percentages are based on the number of subjects in the Safety Set. Subjects in Study 102 and Study 103 Part B received 48 weeks of treatment, and subjects in Study 104 Part A received 16 weeks of treatment.

Source: eCTD 2.7.4, Table 38

Reviewer's comments: No seizures, sudden cardiac death or ventricular arrhythmias were reported in these trials. No clinically relevant ECG changes were reported. No subject in the studies had a QTcF >480 ms.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of VX-770's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 74633. The sponsor submitted the study report VX09-770-008 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Randomized, Placebo- and Active-Controlled, Double-Blind, 4-way Crossover Design, Thorough ECG Study of VX-770 in Healthy Adult Subjects

4.2.2 Protocol Number

VX09-770-008

4.2.3 Study Dates

11 May 2010 - 07 November 2010

4.2.4 Objectives

Part A:

To evaluate the safety and tolerability of increasing doses of VX-770 up to 450 mg every 12 hours (b.i.d) in healthy male subjects

Part B:

To determine if therapeutic or supratherapeutic systemic exposure to multiple doses of VX-770 prolongs the mean Fridericia-corrected QT (QTcF) interval by more than 5 ms (based on an upper limit of 1-sided 95% confidence interval [CI] of 10 ms) in healthy male and female subjects, as compared with placebo dosing and baseline.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, 4 way crossover design. Each dosing occasion will be followed by a 7-day washout period.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The study used over-encapsulated VX-770 treatment groups, moxifloxacin 400 mg tablets and matching placebo capsules.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

The four dose groups from Part B are the following:

- Therapeutic Dose: 150 mg of VX-770 (1 × 150-mg tablet of VX-770 and 2 × VX-770-matching placebo tablets) b.i.d on Days 1 to 4, and 1 morning dose on Day 5.
- Supratherapeutic Dose: 450 mg of VX-770 (3 × 150-mg tablets of VX-770) q12h on Days 1 to 4, and 1 morning dose on Day 5.
- Placebo Control: (3 × VX-770-matching placebo tablets) b.i.d on Days 1 to 4, and 1 morning dose on Day 5.
- Positive Control: Placebo (3 × VX-770-matching placebo tablets) b.i.d on Days 1 to 4, and a single 400-mg dose of moxifloxacin (1 × 400-mg tablet of moxifloxacin and 2 × VX-770-matching placebo tablets) on the morning of Day 5.

4.2.6.2 Sponsor's Justification for Doses

The VX-770 doses selected for Part B were 150 mg and 450 mg b.i.d. The 150-mg dose of VX-770 was considered as the therapeutic dose of VX-770 because it has shown favorable clinical benefits in the proof-of-concept study (Study 101) and is being tested in current VX-770 studies. The proposed supratherapeutic dose of VX-770 450 mg b.i.d was expected to provide a VX-770 maximum observed concentration (C_{max}) approximately 3-fold greater than that from the therapeutic dose, assuming that the exposure would increase proportionally with dose. Furthermore, the metabolites M1 and

M6 were also expected to achieve approximately exposure 3-fold that following the 150-mg dose assuming that the exposure would increase proportionally with dose.

Several considerations were weighed in the selection of the proposed supratherapeutic dose. VX-770 is metabolized mainly via the cytochrome P450 3A4 (CYP3A4) pathway. In Study 006, the coadministration of ketoconazole 400 mg q.d. increased the VX-770 $C_{\max}$ and area under the concentration versus time curve (AUC) to approximately 2.7-fold and 8.5-fold, respectively, of that when 150 mg VX-770 was administered alone. With maximum inhibition of CYP3A4 pathway, the $C_{\max}$ of VX-770, the most relevant parameter for QTc considerations, was roughly 3-fold of that at the therapeutic dose of 150 mg.

Reviewer's Comments: The doses selected for the study are acceptable. Based on the data from registration trials, sponsor is seeking approval of 150 mg b.i.d dose. The selection of 450 mg b.i.d, as supratherapeutic dose, is acceptable based on the observed changes in pharmacokinetics of VX-770 upon administration with 400 mg ketoconazole. It is expected from drug interaction studies that co-administration of VX-770 with ketoconazole can elevate VX-770's steady state $C_{\max}$ higher than observed with 450 mg b.i.d. However, dosing interval in these patients will be increased to match exposures achieved with the therapeutic dose.

4.2.6.3 Instructions with Regard to Meals

Study drug was to be dosed approximately 30 minutes after the start of a meal or snack. The meal was to be completed before the time of study drug administration. Study drug was to be administered with 240 mL of water.

Reviewer's Comments: Administration of VX-770 under fed conditions is acceptable. The proposed label states that the drug should be taken under fed conditions (fat-containing food).

4.2.6.4 ECG and PK Assessments

Pharmacokinetics

Part A:

Blood samples were to be collected for assessment of plasma concentrations of VX-770 and metabolites (M1 and M6) at the following time points:

- Day 1: 0.75 h before the morning dose and 0.5, 1, 2, 3, 4, 6, 9, and 12 h after the morning dose
- Days 2 to 8: 0.75 h before the morning dose and 3, 6, 9, and 12 h after the morning dose
- Day 9: 0.75 hour before the morning dose and 0.5, 1, 2, 3, 4, 6, 9, 12, 16, 24 (Day 10), 36 (Day 10), 48 (Day 11), and 72 (Day 12) h after the morning dose on Day 9

Part B:

Blood PK samples were to be collected for assessment of plasma concentrations of VX-770 and metabolites (M1 and M6) at the following time points:

- Day 1: 0.75 h before the morning dose and 0.5, 1, 2, 3, 4, 6, 9, and 12 h after the morning dose
- Days 2 to 4: 0.75 h before the morning dose
- Day 5: 0.75 h before the morning dose and 0.5, 1, 2, 3, 4, 6, 9, 12, 16, and 24 (Day 6) h after the morning dose

Continuous Electrocardiogram

Part B:

On Day 1 of each period, continuous 12-lead ECG recorder was to be applied to subjects 1.5 hours before the morning dose and recording was to continue until the evening dose was administered on Day 1 (approximately 13.5 h from the initiation of the recorder). Triplicate ECG tracings, separated by approximately 2 min, were to be extracted from Day 1 (of each period) at 1.25, 1, and 0.75 h before the morning dose and 6 and 9 h after the morning dose.

On Day 5 of each period, continuous 12-lead ECG recorder was to be applied to subjects 1 h before the morning dose and recording was to continue until Day 6 (approximately 24 hours after the morning dose on Day 5). Triplicate ECG tracings, separated by approximately 2 minutes, were to be extracted from Day 5 (of each period) at 0.75 h before the morning dose and 0.5, 1, 2, 3, 4, 6, 9, 12, 16, and 24 (Day 6) h after the morning dose.

Reviewer's Comments: The timing of ECGs and PK samples is acceptable. The T_{max} of VX-770 and its metabolites is in the range of 4-6 h.

4.2.6.5 Baseline

The sponsor used QTc values collected on Day -1 as baseline values.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs.

Standard 12-Lead ECGs were obtained while subjects are recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Seventy-two subjects were planned and 72 subjects were enrolled in Part B of the study; 70 subjects received at least 1 dose of VX-770. Sixty-three subjects completed dosing and all 72 subjects completed safety follow-up. All 72 subjects were included in the safety analyses.

In Part A, the mean (SD) age of subjects was 24.0 (5.10) years. All subjects were male 8 (100%), White 8 (100%) by race, and not Hispanic or Latino 8 (100%) by ethnicity. In Part B, the mean (SD) age of subjects was 26.6 (7.01) years. The majority of the subjects in Part B were male 40 (55.6%), White 63 (87.5%) by race, and not Hispanic or Latino 69 (95.8%) by ethnicity.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

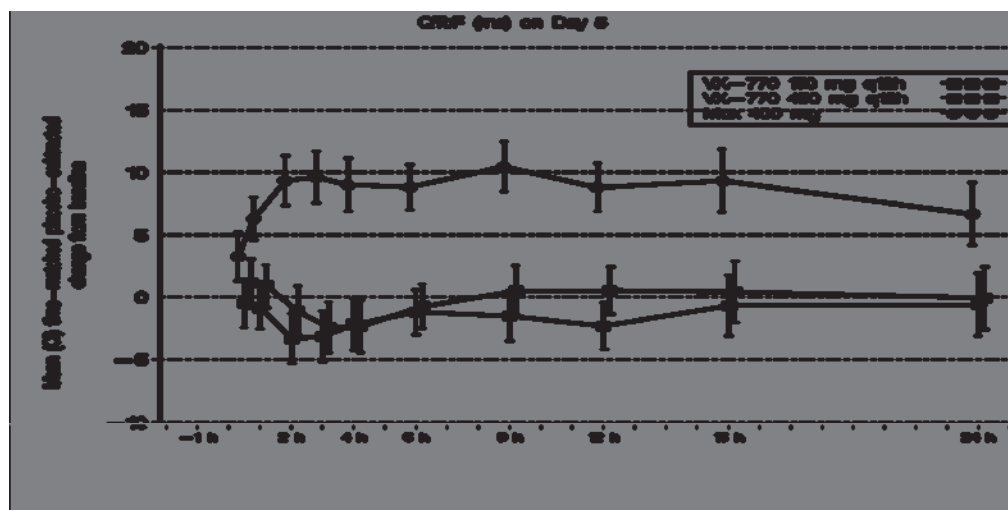
The primary endpoint was the time-matched baseline-adjusted mean differences between VX-770 (150 mg and 450 mg) and placebo in QTcF from Part B on Day 5. The sponsor used an analysis of variance (ANOVA) including period and doses as fixed effects and subjects as a random effect. The results are presented in Table 5 and Figure 1. The upper limits of the 2-sided 90% CI for the mean differences between VX-770 150 mg and placebo, and VX-770 450 mg and placebo were below 10 ms.

Table 5: Sponsor's results $\Delta\Delta$ QTcF for VX-770 150 mg, VX-770 450 mg and Moxifloxacin 400 mg, Part b on Day 5

	VX-770 150 mg q12h N=63		VX-770 450 mg q12h N=63		Moxifloxacin N=63	
Time point	Mean	(90% CI)	Mean	(90% CI)	Mean	(90% CI)
Baseline	-1.1		-1.3		-0.8	
Day 5, 0.5 h post-dose	1.1	(-0.8; 3.1)	-0.5	(-2.4; 1.4)	3.3	(1.3; 5.2)
Day 5, 1 h post-dose	0.9	(-0.8; 2.6)	-0.8	(-2.6; 0.9)	6.3	(4.6; 8.0)
Day 5, 2 h post-dose	-1.1	(-3.1; 0.9)	-3.3	(-5.3; -1.3)	9.3	(7.3; 11.3)
Day 5, 3 h post-dose	-2.4	(-4.5; -0.4)	-3.2	(-5.2; -1.1)	9.6	(7.5; 11.7)
Day 5, 4 h post-dose	-2.3	(-4.4; -0.3)	-2.2	(-4.3; -0.1)	9.0	(6.9; 11.1)
Day 5, 6 h post-dose	-0.7	(-2.5; 1.0)	-1.2	(-3.0; 0.6)	8.8	(7.0; 10.6)
Day 5, 9 h post-dose	0.5	(-1.5; 2.5)	-1.5	(-3.5; 0.5)	10.5	(8.5; 12.5)
Day 5, 12 h post-dose	0.5	(-1.4; 2.4)	-2.3	(-4.2; -0.4)	8.8	(6.9; 10.7)
Day 5, 16 h post-dose	0.4	(-2.0; 2.9)	-0.7	(-3.1; 1.8)	9.3	(6.8; 11.8)
Day 6, 24 h post-dose	-0.1	(-2.6; 2.4)	-0.6	(-3.1; 1.9)	6.7	(4.2; 9.2)

Source: Sponsor's CSR Table 11-6 on page 99/1968

Figure 1: Sponsor's Mean and 90% CI $\Delta\Delta$ QTcF Time Course for VX-770 150 mg, VX-770 450 mg and Moxifloxacin 400 mg



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Source: Sponsor's CSR Figure 11-7 on page 98/1968

4.2.8.2.2 Assay Sensitivity

The sponsor used the same model to analyze Δ QTcF effect for moxifloxacin. The results are presented in Table 5. The lower limit of the 2-sided 90% CI for the mean difference was above 5 ms threshold, which demonstrate assay sensitivity.

Reviewer's Comments: We will provide our independent analysis result in Section 5.2.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc > 450 ms, > 480 ms, and > 500 ms, and changes from baseline QTc > 30 ms and > 60 ms. No subject's absolute QTc > 480 ms and Δ QTc > 60 ms.

4.2.8.3 Safety Analysis

In Part A, a total of 6 (75%) subjects had at least 1 adverse event each. There were no adverse events reported that led to withdrawal of subjects from the study.

In Part B, a total of 67 (93.1%) subjects had at least 1 adverse event each. Five (6.9%) subjects were withdrawn from the study drug treatment due to 1 adverse event each.

- Subject 02043 (Treatment Sequence ABCD) was withdrawn from the study drug treatment due to moderate constipation after completion of dosing on Day 5 in the VX-770 450 mg q12h Treatment Period.
- Subject 02045 (Treatment Sequence BCAD) was withdrawn from the study drug treatment due to mild supraventricular extrasystoles during Moxifloxacin Treatment Period, prior to moxifloxacin dosing.

- Subject 02053 (Treatment Sequence CDBA) was withdrawn from the study drug treatment due to moderate influenza-like illness during VX-770 150 mg q12h Treatment Period.
- Subject 02060 (Treatment Sequence BDAC) was withdrawn from the study drug treatment due to mild hematoma after completion of dosing on Day 5 in the VX-770 150 mg q12h Treatment Period.
- Subject 02066 (Treatment Sequence BDAC) was withdrawn from the study drug treatment due to moderate vomiting during Placebo Treatment Period.

In Part B, at least 1 possibly related adverse event was reported by 5 (7.1%) subjects in VX-770 150 mg q12h treatment, 5 (7.4%) subjects in VX-770 450 mg q12h treatment, 5 (7.5%) subjects in placebo treatment, and 9 (12.9%) subjects in moxifloxacin treatment.

Most frequent possibly related adverse events (reported by more than 1 subject) were as follows: headache was reported by 2 (2.9%) subjects in VX-770 150 mg q12h treatment and by 3 (4.4%) subjects in VX-770 450 mg q12h treatment; nausea was reported by 2 (3.0%) subjects in placebo treatment and by 2 (2.9%) subjects in the moxifloxacin treatment; dizziness was reported by 3 (4.3%) subjects, abdominal pain was reported by 2 (2.9%) subjects, and diarrhea was reported by 2 (2.9%) subjects in moxifloxacin treatment. In Part B, headache was considered by the investigator to be possibly related to the study drug in 7(9.7%) of subjects in all treatments.

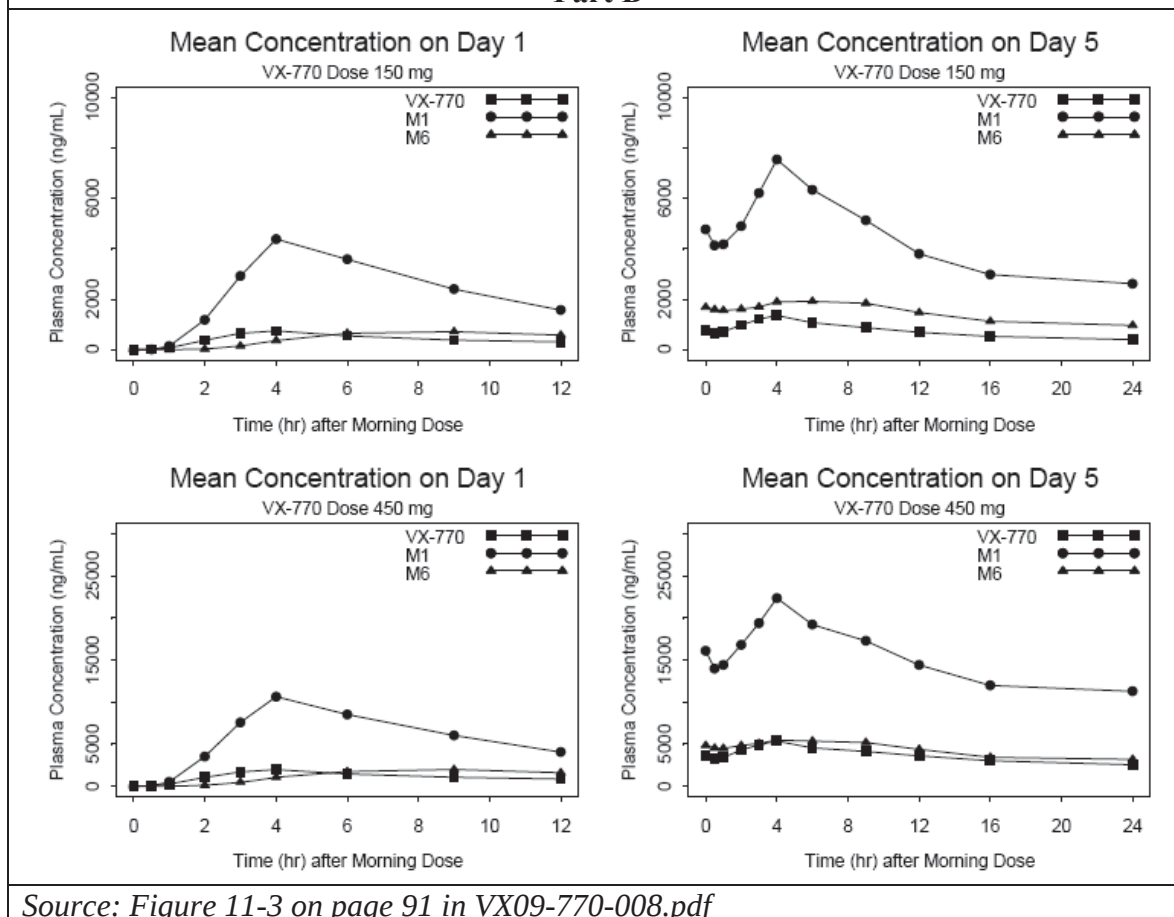
There were no SAEs reported throughout the study. There were no deaths during the study.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Figure 2 shows the mean plasma concentrations of VX-770 and its metabolites (M1, M6) on days 1 and 5 after administration of 150 mg b.i.d and 450 mg b.i.d.

Figure 2. Arithmetic Mean Plasma Concentration Profiles of VX-770, M1, and M6 on Days 1 and 5 after Administration of VX-770 at 150 mg b.i.d and 450 mg b.i.d in Part B



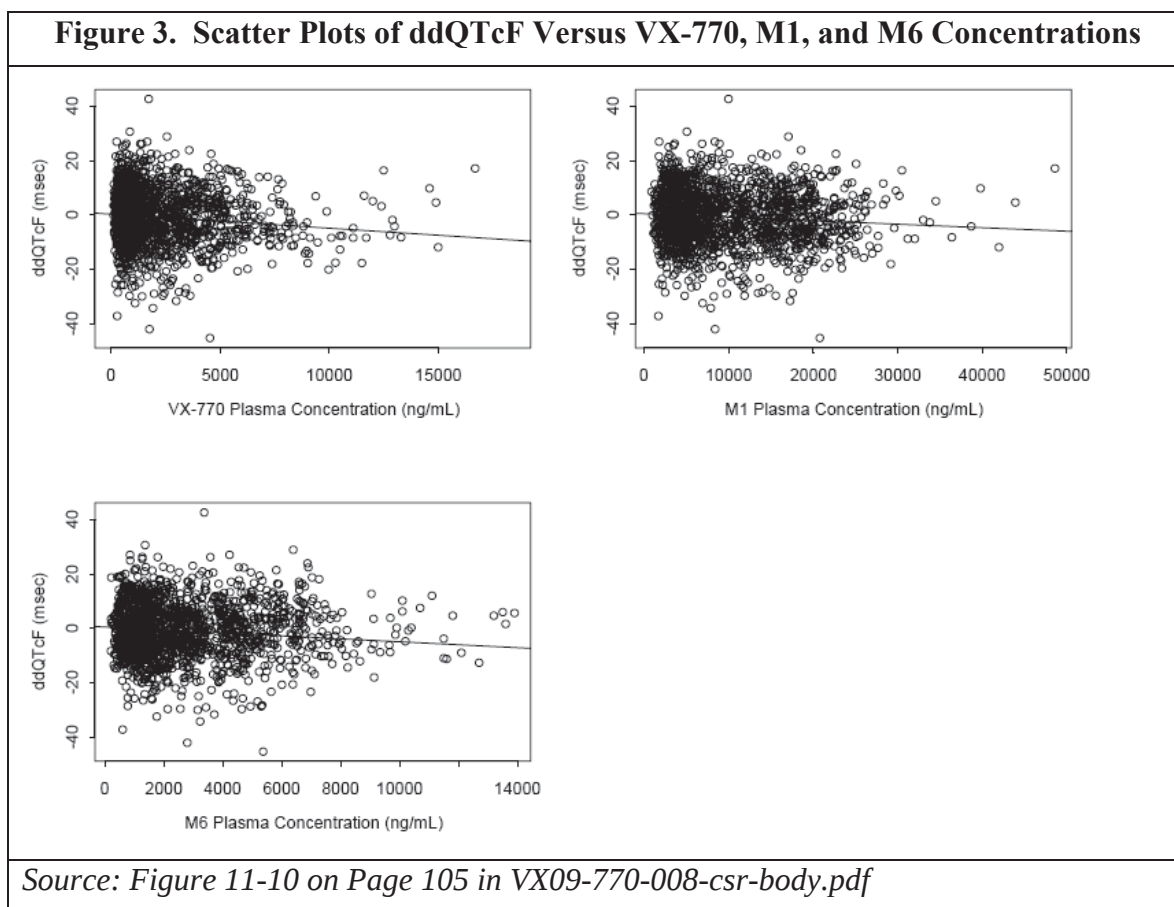
Source: Figure 11-3 on page 91 in VX09-770-008.pdf

The PK results are presented in Table 6. C_{max} and AUC values in the thorough QT study were 3.9-fold, on Day 5, those following administration of 450 mg supratherapeutic drug compared with 150 mg therapeutic drug, the intended clinical dose.

Table 6. Summary of PK Parameters of VX-770, M1, and M6 in Part B						
Analyte	Day	Dose (mg)	N	t_{max} (hr) Median (Min; Max)	C_{max} (ng/mL) Mean (SD)	AUC_{tau} (ng*hr/mL) Mean (SD)
VX-770	1	150	70	4.00 (2.00; 9.00)	820 (272)	5190 (1580)
		450	68	4.00(2.00; 9.00)	2090 (625)	13900 (4340)
	5	150	69	4.00 (2.00; 6.00)	1390 (522)	11600 (4700)
		450	68	4.00 (2.00; 6.00)	5450 (2560)	51600 (28000)
M1	1	150	70	4.00 (3.00; 9.02)	4630 (1400)	29000 (7260)
		450	68	4.00 (3.00; 9.00)	11300 (2820)	72100 (17300)
	5	150	69	4.00 (3.00; 9.05)	7640 (1960)	65500 (18000)
		450	68	4.00 (3.00; 6.02)	22500 (5450)	213000 (58900)
M6	1	150	70	9.00 (4.00; 12.0)	773 (323)	5380 (2330)
		450	68	9.00 (4.00; 12.0)	2060 (841)	14800 (6070)
	5	150	69	6.00 (0.00; 9.02)	2020 (983)	21100 (10500)
		450	68	4.00 (0.00; 12.0)	5680 (2420)	60500 (26800)
C_{max} = maximum observed drug concentration; t_{max} = time to reach C_{max} after dosing; AUC_{tau} = area under the concentration - time curve during the dosing interval.						
Source: Table 2-2 on Page 10 in VX09-770-008-csr-body.pdf						

4.2.8.4.2 Exposure-Response Analysis

Figure 3 shows the scatter plot of VX-770, M1 and M6 plasma concentrations versus $\Delta\Delta QTcF$.



The estimates of slope and intercept, based on linear mixed effects analysis, are shown in Table 7.

Table 7. Parameter Estimates of the Linear Mixed-Effect Model of $\Delta\Delta$QTcF Versus VX770, M1, and M6 Plasma Concentrations				
Dependent Variable	Model Parameter	Mean Estimates	95% CI (Model derived)	95% CI (Bootstrap)
VX-770	Intercept (msec)	0.332	-1.39; 2.06	-1.33; 1.99
	Slope (msec/ μ g/mL)	-0.519	-1.09; 0.0553	-1.10; 0.0582
M1	Intercept (msec)	0.504	-1.32; 2.33	-1.31; 2.32
	Slope (msec/ μ g/mL)	-0.130	-0.264; 0.00406	-0.265; 0.00504
M6	Intercept (msec)	0.512	-1.31; 2.33	-1.28; 2.30
	Slope (msec/ μ g/mL)	-0.546	-1.10; 0.0126	-1.11; 0.0197
Source: Table 14.2.4.1 , Table 14.2.4.2 , Table 14.2.4.3 , Table 14.2.5.1 , Table 14.2.5.2 , and Table 14.2.5.3				
Source: Table 11-7 on Page 105 in VX09-770-008-csr-body.pdf				

The estimated changes in $\Delta\Delta$ QTcF at $C_{\max}$ of VX-770 after 150 and 450 mg q12h are shown in Table 8.

Table 8. Expected QTcF Change at Mean $C_{\max}$				
Dose Regimen	Analyte	Mean $C_{\max}$ (ng/mL) on Day 5	Expected ddQTcF (msec) at Mean $C_{\max}$	90% CI of ddQTcF (msec)
VX-770 150 mg q12h	VX-770	1390	-0.722	-1.39; -0.0482
	M1	7640	-0.970	-1.86; -0.128
	M6	2020	-1.07	-2.06; -0.144
VX-770 450 mg q12h	VX-770	5450	-2.83	-5.45; -0.189
	M1	22500	-2.86	-5.48; -0.377
	M6	5680	-2.99	-5.80; -0.405
Source: Table 14.2.2.3 , Table 14.2.2.5 , Table 14.2.2.7 , Table 14.2.2.9 , Table 14.2.5.1 , Table 14.2.5.2 , and Table 14.2.5.3				
ddQTcF = placebo-subtracted differences of QTcF; $C_{\max}$ = maximum observed drug concentration				
Source: Table 11-8 on Page 106 in VX09-770-008-csr-body.pdf				

The results show that VX-770 and its metabolites do not prolong the QTcF interval at therapeutic and supratherapeutic doses.

Reviewer's Analysis: A plot of $\Delta\Delta$ QTcF vs. drug concentrations is presented in Figure 6.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based

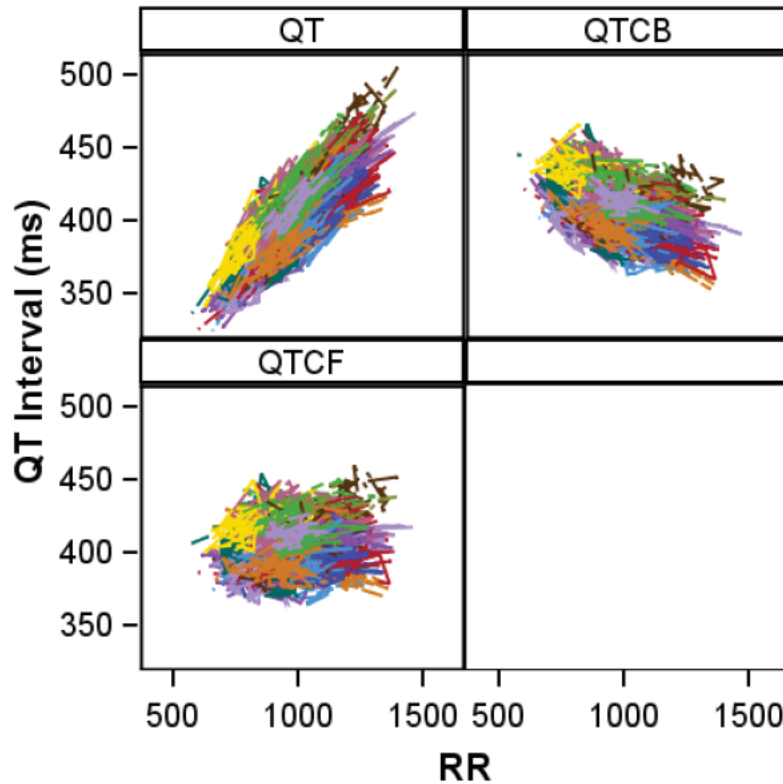
on the results listed in Table 9, it appears that QTcF is better than QTcB. This FDA reviewer used QTcF as the primary statistical analysis.

Table 9: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method			
	QTcB		QTcF	
	N	MSSS	N	MSSS
Moxifloxacin	70	0.0035	70	0.0019
Placebo	67	0.0048	67	0.0018
VX-770 150 mg	69	0.0048	69	0.0012
VX-770 450 mg	68	0.0049	68	0.0017
All	72	0.0038	72	0.0011

The QT-RR interval relationship is presented Figure 4 together with the Bazett's (QTcB) and Fridericia (QTcF).

Figure 4: QT, QTcB and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes treatment as fixed effects and baseline values as covariate. The analysis results are presented in Table 10. 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 are 3.1 ms and 1.8 ms, respectively.

Table 10: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for VX-770 150 mg b.i.d, VX-770 450 mg b.i.d and Moxifloxacin 400 mg, Part B on Day 5

	Placebo	Moxifloxacin						VX-770 150 mg				VX-770 450 mg			
	Δ QTcF	Δ QTcF		$\Delta\Delta$ QTcF				Δ QTcF		$\Delta\Delta$ QTcF		Δ QTcF		$\Delta\Delta$ QTcF	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	Adj. 90% CI	N	LS Mean	LS Mean	90% CI		N	LS Mean	LS Mean	90% CI
0.5	-11.4	70	-8.7	2.7	(0.4, 5.0)	(-0.5, 5.9)	68	-10.6	0.8	(-1.5, 3.1)		66	-11.9	-0.5	(-2.9, 1.8)
1	-12.5	70	-6.8	5.7	(3.4, 8.0)	(2.6, 8.8)	69	-12.6	-0.1	(-2.4, 2.2)		67	-13.4	-0.9	(-3.2, 1.4)
2	-13.0	70	-4.3	8.7	(6.4, 11.0)	(5.6, 11.8)	69	-14.2	-1.1	(-3.4, 1.2)		68	-15.4	-2.4	(-4.7, -0.1)
3	-11.5	68	-1.8	9.7	(7.4, 12.1)	(6.5, 12.9)	69	-13.8	-2.3	(-4.7, -0.0)		68	-14.1	-2.6	(-4.9, -0.2)
4	-6.8	68	2.0	8.8	(6.5, 11.1)	(5.6, 12.0)	69	-9.6	-2.8	(-5.1, -0.5)		68	-8.9	-2.1	(-4.4, 0.3)
6	-13.3	67	-5.2	8.1	(5.8, 10.4)	(5.0, 11.2)	69	-14.1	-0.8	(-3.0, 1.5)		68	-14.6	-1.3	(-3.6, 1.0)
9	-12.3	69	-2.5	9.8	(7.6, 12.0)	(6.8, 12.8)	69	-12.6	-0.3	(-2.5, 1.9)		68	-14.0	-1.7	(-3.9, 0.5)
12	-11.9	69	-3.4	8.5	(6.3, 10.7)	(5.5, 11.5)	69	-12.2	-0.3	(-2.5, 1.9)		68	-14.0	-2.1	(-4.3, 0.1)
16	-3.7	68	5.1	8.9	(6.0, 11.7)	(5.0, 12.8)	68	-4.7	-0.9	(-3.8, 1.9)		68	-4.7	-1.0	(-3.8, 1.8)
24	-10.7	68	-5.1	5.6	(3.0, 8.2)	(2.0, 9.1)	67	-11.6	-0.9	(-3.6, 1.7)		67	-11.6	-1.0	(-3.6, 1.6)

* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

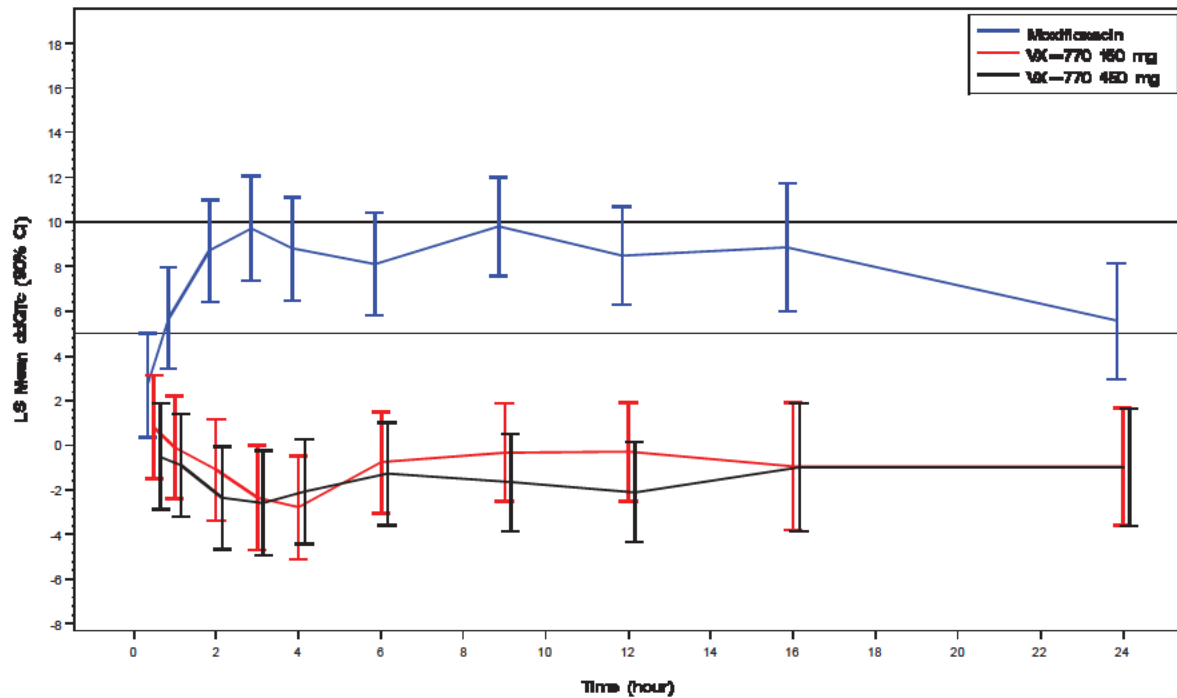
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 10. The largest unadjusted 90% lower confidence interval is 7.6 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 6.8 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

Figure 5 displays the time profile of $\Delta\Delta$ QTcF for different treatment groups.

Figure 5: Mean and 90% CI $\Delta\Delta$ QTcF Time Course for VX-770 150 mg b.i.d, VX-770 450 mg b.i.d and Moxifloxacin 400 mg



5.2.1.4 Categorical Analysis

Table 11 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, and between 450 ms and 480 ms. No subject's QTcF is above 480 ms.

Table 11: Categorical Analysis for QTcF

Treatment Group	Total N	Value ≤ 450 ms	450 ms < Value ≤ 480 ms
Moxifloxacin	70	66 (94.3%)	4 (5.7%)
Placebo	67	65 (97.0%)	2 (3.0%)
VX-770 150 mg	69	69 (100%)	0 (0.0%)
VX-770 450 mg	68	67 (98.5%)	1 (1.5%)

Table 12 lists the categorical analysis results for ΔQTcF . No subject's change from baseline is above 60 ms.

Table 12: Categorical Analysis for ΔQTcF

Treatment Group	Total N	Value ≤ 30 ms	30 ms < Value ≤ 60 ms
Moxifloxacin	70	68 (97.1%)	2 (2.9%)
Placebo	67	67 (100%)	0 (0.0%)
VX-770 150 mg	69	69 (100%)	0 (0.0%)
VX-770 450 mg	68	68 (100%)	0 (0.0%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR interval. The point estimates and the 90% CI are presented in Table 13. 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 are 2.9 bpm and 4.5 bpm, respectively. Table 14 presents the categorical analysis of HR. Two subjects who experienced HR interval greater than 100 bpm were in VX-770 450-mg group.

Table 13: Analysis Results of Δ HR and $\Delta\Delta$ HR for VX-770 150 mg b.i.d., VX-770 450 mg b.i.d. and Moxifloxacin 400 mg, Part B on Day 5

	Placebo	Moxifloxacin				VX-770 150 mg				VX-770 450 mg			
	Δ HR	Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	9.3	70	8.3	-1.0	(-2.8, 0.8)	68	9.4	0.2	(-1.7, 2.0)	66	9.5	0.3	(-1.6, 2.1)
1	8.0	70	6.8	-1.2	(-3.1, 0.8)	69	7.4	-0.5	(-2.4, 1.4)	67	7.9	-0.0	(-2.0, 1.9)
2	5.7	70	5.9	0.2	(-1.7, 2.2)	69	5.6	-0.1	(-2.1, 1.9)	68	6.6	0.9	(-1.0, 2.9)
3	2.1	68	2.7	0.6	(-1.2, 2.4)	69	3.0	0.9	(-0.9, 2.7)	68	3.3	1.2	(-0.6, 3.0)
4	1.8	68	1.9	0.0	(-1.8, 1.9)	69	1.7	-0.1	(-2.0, 1.7)	68	2.2	0.4	(-1.5, 2.2)
6	8.5	67	8.8	0.3	(-1.7, 2.3)	69	8.6	0.1	(-1.9, 2.0)	68	9.9	1.3	(-0.7, 3.3)
9	1.6	69	2.3	0.7	(-1.2, 2.6)	69	2.6	0.9	(-1.0, 2.8)	68	2.8	1.2	(-0.7, 3.1)
12	5.1	69	5.3	0.2	(-1.8, 2.2)	69	5.7	0.6	(-1.4, 2.6)	68	7.6	2.5	(0.4, 4.5)
16	-1.0	68	-1.1	-0.1	(-2.1, 1.9)	68	-1.0	0.0	(-1.9, 2.0)	68	0.5	1.5	(-0.5, 3.5)
24	5.6	68	5.2	-0.4	(-2.7, 1.9)	67	6.2	0.6	(-1.7, 2.9)	67	6.9	1.4	(-0.9, 3.7)

Table 14: Categorical Analysis of HR

Treatment Group	Total N	HR < 100 bpm	HR $\geq$ 100 bpm
Moxifloxacin	70	70 (100%)	0 (0.0%)
Placebo	67	67 (100%)	0 (0.0%)
VX-770 150 mg	69	69 (100%)	0 (0.0%)
VX-770 450 mg	68	66 (97.1%)	2 (2.9%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 15. 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 are 3.8 ms and 4.9 ms, respectively. Table 16 presents the categorical analysis of PR. Six subjects who experienced PR interval greater than 200 ms were in VX-770 150-mg and 450-mg groups.

Table 15: Analysis Results of Δ PR and $\Delta\Delta$ PR for for VX-770 150 mg b.i.d., VX-770 450 mg b.i.d. and Moxifloxacin 400 mg, Part B on Day 5

	Placebo	Moxifloxacin				VX-770 150 mg				VX-770 450 mg			
	Δ PR	Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	-0.3	70	-0.7	-0.4	(-2.8, 2.0)	68	-0.1	0.2	(-2.2, 2.6)	66	1.1	1.4	(-1.0, 3.8)
1	-2.8	70	-2.2	0.6	(-1.8, 3.0)	69	-2.7	0.1	(-2.3, 2.4)	67	-0.9	1.9	(-0.5, 4.3)
2	-4.7	70	-4.8	-0.2	(-2.4, 2.1)	69	-4.2	0.5	(-1.7, 2.8)	68	-4.6	0.1	(-2.2, 2.3)
3	-3.4	68	-6.0	-2.5	(-4.8, -0.2)	69	-4.4	-0.9	(-3.2, 1.4)	68	-3.4	0.0	(-2.3, 2.3)
4	-4.9	68	-5.5	-0.7	(-2.9, 1.6)	69	-3.3	1.6	(-0.7, 3.8)	68	-3.2	1.7	(-0.6, 3.9)
6	-4.8	67	-6.1	-1.3	(-3.6, 0.9)	69	-3.5	1.3	(-1.0, 3.5)	68	-3.2	1.6	(-0.6, 3.9)
9	-3.8	69	-4.4	-0.5	(-2.5, 1.5)	69	-4.1	-0.3	(-2.3, 1.7)	68	-3.4	0.5	(-1.6, 2.5)
12	-5.7	69	-4.4	1.3	(-1.0, 3.7)	69	-3.5	2.3	(-0.1, 4.6)	68	-3.2	2.6	(0.2, 4.9)
16	-0.3	68	-0.2	0.1	(-2.4, 2.5)	68	-0.3	-0.0	(-2.5, 2.4)	68	0.2	0.5	(-2.0, 2.9)
24	-2.7	68	-2.9	-0.2	(-2.6, 2.2)	67	-3.6	-0.9	(-3.3, 1.5)	67	-3.5	-0.7	(-3.1, 1.7)

Table 16: Categorical Analysis of PR

Treatment Group	T	PR < 200 ms	PR $\geq$ 200 ms
Moxifloxacin	70	66 (94.3%)	4 (5.7%)
Placebo	67	65 (97.0%)	2 (3.0%)
VX-770 150 mg	69	67 (97.1%)	2 (2.9%)
VX-770 450 mg	68	64 (94.1%)	4 (5.9%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 17. 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 are 1.4 ms and 0.6 ms, respectively. Table 18 presents the categorical analysis of QRS. Nine subjects who experienced QRS interval greater than 200 ms were in VX-770 150-mg and 450-mg groups.

Table 17: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for VX-770 150 mg b.i.d., VX-770 450 mg b.i.d. and Moxifloxacin 400 mg, Part B on Day 5

	Placebo	Moxifloxacin				VX-770 150 mg				VX-770 450 mg			
	Δ QRS	Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	1.1	70	0.8	-0.3	(-1.3, 0.7)	68	1.2	0.1	(-0.9, 1.1)	66	0.7	-0.4	(-1.4, 0.6)
1	0.3	70	0.2	-0.1	(-1.1, 0.9)	69	0.7	0.4	(-0.5, 1.4)	67	-0.2	-0.5	(-1.5, 0.5)
2	-0.6	70	-0.8	-0.2	(-1.1, 0.7)	69	-1.0	-0.4	(-1.3, 0.5)	68	-1.8	-1.2	(-2.2, -0.3)
3	-1.1	68	-0.7	0.4	(-0.6, 1.3)	69	-1.4	-0.3	(-1.3, 0.6)	68	-1.9	-0.8	(-1.8, 0.1)
4	-0.8	68	-1.0	-0.2	(-1.2, 0.8)	69	-1.1	-0.2	(-1.2, 0.7)	68	-1.7	-0.9	(-1.9, 0.1)
6	-0.2	67	-1.1	-0.8	(-2.0, 0.3)	69	-0.5	-0.3	(-1.4, 0.8)	68	-1.4	-1.1	(-2.2, -0.0)
9	-0.8	69	-1.2	-0.5	(-1.4, 0.4)	69	-1.4	-0.7	(-1.6, 0.3)	68	-1.9	-1.1	(-2.1, -0.2)
12	-1.1	69	-1.1	0.1	(-0.9, 1.0)	69	-1.5	-0.4	(-1.4, 0.5)	68	-2.5	-1.3	(-2.3, -0.4)
16	0.8	68	0.3	-0.5	(-1.5, 0.4)	68	0.6	-0.2	(-1.2, 0.7)	68	-1.0	-1.8	(-2.8, -0.9)
24	-0.8	68	-0.9	-0.1	(-1.1, 0.8)	67	-1.2	-0.4	(-1.3, 0.6)	67	-1.8	-1.1	(-2.0, -0.1)

Table 18: Categorical Analysis of QRS

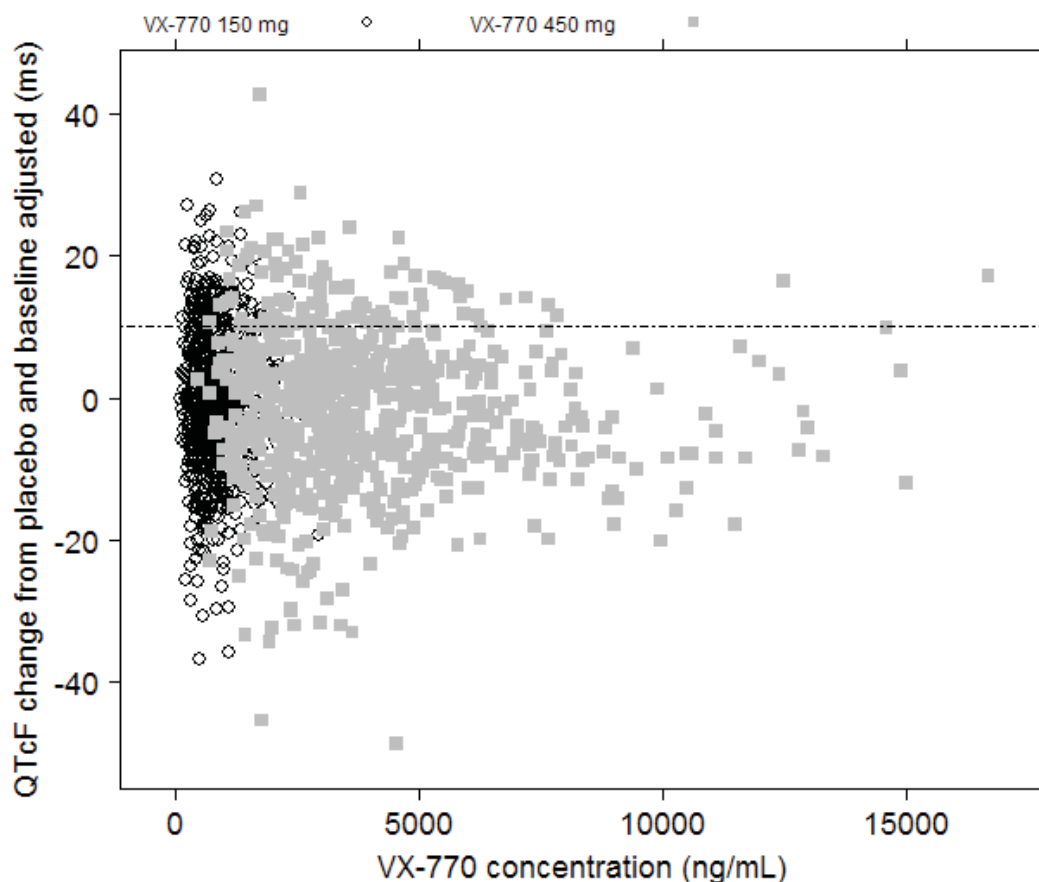
Treatment Group	Total N	QRS < 110 ms	QRS $\geq$ 110 ms
Moxifloxacin	70	66 (94.3%)	4 (5.7%)
Placebo	67	63 (94.0%)	4 (6.0%)
VX-770 150 mg	69	63 (91.3%)	6 (8.7%)
VX-770 450 mg	68	65 (95.6%)	3 (4.4%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated in Figure 2.

The relationship between $\Delta\Delta$ QTcF and VX-770 concentrations is visualized in Figure 6 with no evident exposure-response relationship.

Figure 6: $\Delta\Delta$ QTcF vs. VX-770 Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. Measurements were performed on the 'global' presentation of superimposed representative (median) PQRST complexes from all leads. According to ECG warehouse statistics less than 0.3% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Four subjects had a PR>200 ms and post-baseline increases did not exceed 15% of baseline values. Seven subjects had QRS >110 ms at baseline, and no further increases in QRS duration were observed.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology of Ivacaftor (VX-770)

Therapeutic dose	150 mg q12h for subjects $\geq$ 6 years old	
Maximum tolerated dose	Maximum tolerated dose has not been established in humans. In the chronic toxicity studies, ivacaftor exposures at the no observed adverse effect level (NOAEL) in rats (50 mg/kg/day) and dogs (60 mg/kg/day), were at least 9- to 21-fold times the expected, steady-state AUC ₀₋₂₄ at the human therapeutic dosage (150 mg q12h), derived from population-PK model estimates of AUC ₀₋₂₄ in patients with CF (ages 6 years to adult) in the Phase 3 studies (Module 2.4/Section 4.2).	
Principal adverse events	In both pooled placebo-controlled Phase 2b/3 and Phase 3 studies, the incidence of upper respiratory tract infection, dizziness, and rash was higher (at least a 3% difference) in the ivacaftor group than the placebo group (Module 2.7.4/Section 8.2). Based on the difference in incidence observed in both the pooled placebo-controlled Phase 2b/3 and Phase 3 studies, these events are likely to represent adverse drug reactions (ADRs) for ivacaftor. In addition, the incidence of the following adverse events was higher (at least 3%) in the ivacaftor group than the placebo group in the pooled placebo-controlled Phase 3 studies: headache, bacteria in sputum, diarrhea, and abdominal pain. These adverse events are likely to represent ADRs for ivacaftor.	
Maximum dose tested	Single Dose	Ivacaftor 800 mg of a PEG solution formulation in healthy subjects (Study 001)
	Multiple Dose	Ivacaftor 450 mg q12h of the commercial tablet formulation for 5 days (9 doses) in healthy subjects (Study 008)
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (SD) of ivacaftor C _{max} and AUC from Study 001 : C _{max} : 2335 (473) ng/mL

		AUC _{0-∞} : 43496 (9473) ng·hr/mL
	Multiple Dose	Mean (SD) of ivacaftor steady-state C _{max} and AUC from Study 008 Part B : C _{max} : 5450 (2560) ng/mL AUC ₀₋₁₂ : 51600 (28000) ng·hr/mL
Range of linear PK	Following single-dose (25- to 800-mg) administrations of an ivacaftor PEG solution formulation, the AUC _{0-∞} of ivacaftor increased proportionally with dose, and C _{max} increased less than proportionally at doses greater than 375 mg (Study 001).	
Accumulation at steady state	Ivacaftor 125 mg q12h to 450 mg q12h reached steady-state within 3 to 7 days. The median accumulation ratio was approximately 2.2 to 2.7 up to 150 mg q12h (Study 001 ; Study 005 ; Study 809-005 ; Study 008), 2.9 at 250 mg q12h (Study 001), and 3.7 at 450 mg q12h (Study 008).	
Metabolites	Metabolite profiling in urine and feces indicated extensive metabolism of ivacaftor in humans following oral dose administration (Study 003). M1 (hydroxymethyl-ivacaftor, also known as VRT-837018) and M6 (ivacaftor carboxylate, also known as VRT-842917) are the two major metabolites in humans and accounted for approximately 65% of dose excreted following a single dose of 133 mg ¹⁴C-ivacaftor in healthy male subjects (Study 003). At 150 mg q12h in the fed state, the mean steady-state exposure (AUC₀₋₁₂ metabolite/AUC₀₋₁₂ ivacaftor) ratio was approximately 6 for M1 and 2 for M6 (Study 008). In potentiating CFTR-mediated chloride transport in <i>G551D/F508del</i>-HBE (Module 2.7.2/Section 1.1.1): M1: 1/6th potency of ivacaftor M6: <1/50th potency of ivacaftor	
Absorption	Absolute Bioavailability	The absolute bioavailability of ivacaftor in humans has not been determined because ivacaftor has very low solubility (<0.001 mg/mL in water) and no intravenous formulation was available. Ivacaftor is orally bioavailable (Module 2.7.2/Section 3.1).
	t _{max}	In Study 008 Part B , on Day 5 of ivacaftor 150 mg q12h, the median (range) of t _{max} for ivacaftor and its M1 and M6 metabolites are:

		• Ivacaftor: 4 (2, 6) hours • M1: 4 (3, 9) hours • M6: 6 (0, 9) hours Similar $t_{\max}$ was observed in other studies (Study 005; Study 809-005).
Distribution	Vd/F	For ivacaftor as a tablet formulation for an 18-year-old, 70-kg male subject with CF, the population mean estimate (95% CI) was 186 (170, 200) L for V_c/F (V_d/F of the central compartment), and 118 (77.2, 187) L for V_p/F (V_d/F of the peripheral compartment) (Module 2.7.2/Section 3.2).
	% bound	Ivacaftor, M1, and M6 were highly bound to proteins in human plasma at all concentrations tested in vitro (>98% over a concentration range of 0.1 to 10 or 20 μM ; Module 2.6.4/Section 4.2).
Elimination	Route	Study 003 (a single oral dose of 133 mg ^{14}C-ivacaftor solution): • 88% of total radioactivity was excreted in feces (mainly as metabolites with 2.5% as unchanged ivacaftor). • 6.6% of total radioactivity was excreted in urine (mainly as metabolites with negligible amount as unchanged ivacaftor).
	Terminal $t_{1/2}$	Following a single oral dose in the fed state, the mean apparent terminal half-life of ivacaftor was approximately 12 hours across studies (Module 2.7.2/Section 3.5.1). In Study 007, the mean (SD) of apparent terminal half-life for ivacaftor and its M1 and M6 metabolites are: • Ivacaftor: 10.8 (1.1) hours • M1: 15.7 (1.5) hours • M6: 16.9 (1.9) hours

	CL/F	The population mean estimate (95% CI) was 19.0 (17.5, 20.5) L/h for CL/F (Module 2.7.2/Section 3.5.4).
Intrinsic Factors	Age	The population PK dataset included subjects age 6 through 53 years. Compared to adult subjects, at 150 mg q12h, subjects age 6 to 11 years had approximately 52% and 8% higher mean and median C_{min} of ivacaftor, and approximately 2-fold higher mean and median AUC of ivacaftor (Module 2.7.2/Section 3.5.7).
	Sex	In healthy subjects, mean exposures of ivacaftor and M1 were similar in male and female subjects, and mean exposures of M6 were higher in female subjects. Population PK analyses of pooled data from healthy and CF subjects found no effect of gender on CL/F for ivacaftor, M1, or M6 (Module 2.7.2/Section 3.5.6).
	Race	CF is most prevalent in Caucasians. Because the majority of subjects in the population PK dataset were White (“self-identified”) with little representation in other racial categories, race was not considered as a descriptor in the covariate model in population PK analysis (Module 2.7.2/Section 3.10.1).
	Hepatic & Renal Impairment	Subjects with moderate hepatic impairment (Child-Pugh Class B, clinical score 7 to 9 points) had similar ivacaftor C_{max} but an approximately 2-fold increase in ivacaftor $AUC_{0-\infty}$ compared to healthy subjects (Study 013). A dose of 150 mg once daily is recommended for patients with CF who have moderate hepatic impairment. No dose adjustment is necessary for subjects with CF who have mild hepatic impairment (Child-Pugh Class A). Studies have not been conducted in subjects with severe hepatic impairment (Child-Pugh Class C) and ivacaftor is not

		recommended for use in this population (Module 2.7.2/Section 3.10.2). Ivacaftor has not been studied in patients with renal impairment and is not recommended in patients with severe renal impairment or end-stage renal disease. No dose adjustment is necessary for patients with mild to moderate renal impairment as the majority (88%) of ivacaftor is excreted from body via feces after metabolic conversion while only 6.6% is excreted via urine as metabolites (Module 2.7.2/Section 3.10.3).
Extrinsic Factors	Drug interactions	See attached Table 1 and Table 2.
	Food Effects	Administration with food (high-fat breakfast) increases the bioavailability of ivacaftor approximately 2- to 4-fold (Study 002, Study 007, Study 012). See attached Table 3.
Expected High Clinical Exposure Scenario	Ivacaftor is extensively metabolized with CYP3A being the major metabolic pathway. It is expected that the inhibitory effect of a strong CYP3A inhibitor at maximum dose (e.g., ketoconazole at 400 mg qd) would represent the worst case scenario. In Study 006, ivacaftor $AUC_{0-\infty}$ increased almost 8.5-fold and C_{max} increased approximately 2.7-fold when a single dose (150 mg) of ivacaftor was coadministered on Day 4 of multiple dose (400 mg qd for 10 days) administration of ketoconazole in healthy adult male subjects. The M1 AUC_{0-last} was increased 1.69-fold and C_{max} decreased by 77%, and the M6 AUC_{0-last} and C_{max} decreased by 70% and 94% respectively. Moderate hepatic impairment is unlikely to be additive to the increases in C_{max} due to strong CYP3A inhibition. When ivacaftor was administered at 450 mg q12h to healthy adult male and female subjects, ivacaftor steady-state C_{max} increased 3.8-fold and AUC_{0-12} increased 4.3-fold compared to ivacaftor 150 mg q12h. The steady-state C_{max} and AUC_{0-12} of its M1 and M6 metabolites increased about 3- fold compared to ivacaftor 150 mg q12h (Study 008). Therefore, the increase in C_{max} of ivacaftor (the most relevant parameter for QTc considerations) by a strong CYP3A inhibitor such	

	as ketoconazole is expected to be within the range of exposures of the suprathapeutic dose of 450 mg q12h.
--	--

Note: data sources given in [blue text](#); the following attached Tables are referred to in above text.

Table 1 Summary of PK Parameters for Ivacaftor in the Presence of Coadministered Drugs

Drug	Dose and Schedule		N	Effect on Ivacaftor PK ^a	GLS Mean Ratio (90% CI) of Ivacaftor PK With/Without Coadministered Drug		
	Drug	Ivacaftor			C _{max}	AUC	C _{min}
Fluconazole	400 mg on Day 1 and subsequently 200 mg qd for 8 days	Ivacaftor, 150 mg q12h for 8 days	18	↑	2.47 (1.93, 3.17)	2.95 ^d (2.27, 3.82)	3.42 (2.61, 4.48)
Ketoconazole	Ketoconazole 400 mg qd 10 days	Ivacaftor, 150-mg single dose on Day 4 of ketoconazole dosing	24 ^b	↑	2.65 (2.21, 3.18)	8.45 ^c (7.14, 10.01)	NA
Oral Contraceptive	Norethindrone/ethinyl estradiol 0.5 mg/0.035 mg qd for 21 days	Ivacaftor, 150 mg q12h for 28 days	22	↔	0.98 (0.90; 1.06)	0.99 ^d (0.92; 1.06)	1.00 (0.92; 1.07)
Rifampin	600 mg qd for 10 days	Ivacaftor, 150-mg single dose on Day 6 of rifampin dosing	20 ^e	↓	0.20 (0.17; 0.24)	0.11 ^c (0.10; 0.14)	NA

Source: [Module 2.7.2/Table 26](#)

Abbreviations: NA, not applicable

^a ↔: drug has no effect on ivacaftor exposure (AUC GLS Mean Ratio and 90% CI fall within 0.80 – 1.25);

↑: drug increases ivacaftor exposure (AUC); ↓: drug decreases ivacaftor exposure (AUC)

^b N = 23 for AUC_{0-∞}

^c AUC_{0-∞}

^d AUC₀₋₁₂

^e N = 15 for AUC_{0-∞}

Table 2 Summary of PK Parameters for Coadministered Drugs in the Presence of Ivacaftor

Drug	Dose and Schedule		N	Effect on Drug PK ^a	GLS Mean Ratio (90% CI) of Drug PK With/Without Ivacaftor		
	Drug	Ivacaftor			C _{max}	AUC	C _{min}
Desipramine	50-mg, single dose, on Day 5 of ivacaftor dosing	Ivacaftor, 150 mg q12h for 9 days	24 ^d	↔	1.00 (0.94; 1.07)	1.04 ^b (0.99; 1.10)	NA
Ethinyl estradiol	EE 0.035 mg + 0.5 mg NE, qd for 21 days	Ivacaftor, 150 mg q12h for 28 days	22	↔	1.22 (1.10; 1.36)	1.07 ^c (1.00; 1.14)	1.04 (0.90; 1.22)
Midazolam	2-mg, single dose, on Day 6 of ivacaftor dosing	Ivacaftor, 150 mg q12h for 6 days	24	↑	1.38 (1.26, 1.52)	1.54 ^b (1.39, 1.69)	NA
Norethindrone	EE 0.035 mg + 0.5 mg NE, qd for 21 days	Ivacaftor, 150 mg q12h for 28 days	22	↔	1.09 (1.01; 1.19)	1.05 ^c (0.99; 1.12)	1.16 (0.98; 1.38)
Rosiglitazone	4-mg, single dose, on Day 7 of ivacaftor dosing	Ivacaftor, 150 mg q12h for 7 days	20	↔	0.93 (0.86, 1.00)	0.98 ^b (0.90, 1.06)	NA

Source: [Module 2.7.2/Table 27](#)

Abbreviations: EE, ethinyl estradiol; NA, not applicable; NE, norethindrone

^a ↔: Ivacaftor has no effect on substrate exposure (AUC GLS Mean Ratio and 90% CI fall within 0.80 – 1.25); ↑: drug increases substrate exposure (AUC); ↓: drug decreases substrate exposure (AUC)

^b AUC_{0-∞}

^c AUC₀₋₂₄

^d N = 23 for AUC

Table 3 Food Effect on PK Parameters After Administration of Ivacaftor 150-mg Tablets

Ivacaftor Dose; Formulation	Fasted/ Fed	Number of Subjects With PK Data (M/F)	Median t _{max} (min, max) (h)	Arithmetic Mean (SD)			GLS Mean Ratio ^a (90% CI)	
				C _{max} (ng/mL)	t _{1/2} (h)	AUC _{0-∞} (ng h/mL)	C _{max}	AUC _{0-∞}
Study 007								
150 mg; T1 tablet	Fasted	17M Healthy	3.0 (2.0, 4.0)	218 (147)	18.83 (10.09)	2864 (1410)		
150 mg; T1 tablet	Fed	16M Healthy	6.0 (3.0, 6.1)	506 (111)	10.81 (1.06)	6649 (1853)	2.83 (2.14, 3.76)	2.55 (2.26, 2.87)
Study 012								
150 mg; waxed, film-coated tablet	Fasted	18M Healthy	4.0 (3.0; 12.0)	218 (110)	16.71 (4.92)	3620 (1840)		
150 mg; waxed, film-coated tablet	Fed	18M Healthy	4.0 (3.0; 6.0)	768 (233)	11.87 (2.70)	10600 (5260)	3.89 (3.12, 4.86)	2.98 (2.56, 3.48)

Source: [Module 2.7.1/Table 8](#)

^a GLS Mean Ratio with 90% CI, value for ivacaftor fed/value for ivacaftor fasted

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

/s/

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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: January 6, 2012

To: Miranda Raggio, Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Matt Falter, Regulatory Review Officer
Division of Direct-to-Consumer Promotion (DDTCP)
Office of Prescription Drug Promotion (OPDP)

Roberta Szydlo, Regulatory Review Officer
Division of Professional Promotion (DPP), OPDP

CC: Lisa Hubbard, Group Leader, DPP
Robyn Tyler, Group Leader, DDTCP
Olga Salis, Project Manager, OPDP

Subject: NDA 203188
OPDP labeling comments for KALYDECO™ (ivacaftor) Film-Coated Tablets

OPDP has reviewed the proposed Package Insert (PI), proposed Patient Package Insert (PPI), and Carton and Container Labeling for KALYDECO™ (ivacaftor) Film-Coated Tablets submitted for consult on October 21, 2011, and offers the following comments.

OPDP's comments on the PI are based on the proposed draft marked-up labeling titled "12-15-11 SC Vertex label-dparp.doc" that was sent via e-mail from DPARP to OPDP on December 15, 2011.

OPDP's comments on the PPI are based on the proposed draft labeling titled "Kalydeco clean PPI DMPP 12 28 11.doc" that was sent via e-mail from DMPP to DPARP and OPDP on December 28, 2011.

OPDP's comments on the PI and PPI are provided directly in the marked-up document attached (see below).

OPDP has reviewed the proposed carton and container labeling submitted by the sponsor on December 27, 2011, and located in the EDR at:

- <\\cdsesub1\EVSPROD\NDA203188\0002\m1\us\blister-backing.pdf>
- <\\cdsesub1\EVSPROD\NDA203188\0002\m1\us\blister-carton.pdf>
- <\\cdsesub1\EVSPROD\NDA203188\0002\m1\us\bottle-label.pdf>
- <\\cdsesub1\EVSPROD\NDA203188\0002\m1\us\bottle-carton.pdf>

OPDP has no comments at this time on the proposed Carton and Container labeling.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions regarding the PI or the Carton and Container Labeling, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

If you have any questions regarding the PPI, please contact Matt Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

16 Pages of Draft Labeling
have been Withheld in Full
as b4 (CCI/TS)
immediately following this
page

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

/s/

ROBERTA T SZYDLO
01/06/2012

MATTHEW J FALTER
01/06/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: January 3, 2012

Reviewer(s): Reasol S. Agustin, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Carlos Mena-Grillasca, RPh
Division of Medication Error Prevention and Analysis

Drug Name(s): Kalydeco (Ivacaftor) Tablets, 150 mg

Application Type/Number: NDA 203188

Applicant: Vertex Pharmaceuticals, Inc

OSE RCM #: 2011-4078

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed container labels, carton and insert labeling for Kalydeco (Ivacaftor) Tablets, 150 mg, for areas of vulnerability that can lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant submitted a New Drug Application for Kalydeco, dated October 18, 2011. The Application received a Priority Review due to orphan drug designation.

1.2 PRODUCT INFORMATION

The following product information is provided in the October 18, 2011 submission.

- Established Name: Ivacaftor
- Indication of Use: Treatment of Cystic Fibrosis in patients 6 years of age and older who have a G551D mutation in the CFTR gene.
- Route of administration: Oral
- Dosage form: Tablets
- Strength: 150 mg
- Dose: One tablet every 12 hours with food
- How Supplied: 56-count carton containing 4 weekly blister cards of 14 tablets each
60-count bottles
- Storage: Store between 15°C to 30°C
- Container and Closure systems:
14-count blister card - (b) (4) blister film with heat seal foil lidding
60-count bottles – 75cc HDPE bottle/33 mm induction sealed (b) (4) closure

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted October 18, 2011 (Appendix A)
- Carton Labeling submitted December 27, 2011 and December 29, 2011 (Appendix B)
- Insert Labeling submitted October 18, 2011

3 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling introduce vulnerability that can lead to medication errors. We recommend the following be implemented prior to approval of this NDA.

A. GENERAL COMMENTS (ALL CONTAINER LABELS AND CARTON LABELING)

1. Ensure the presentation of the established name is at least ½ the size of the proprietary name and has a prominence commensurate with the proprietary name, taking into account all

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

pertinent factors, including typography, layout, contrast and other printing features as stated in 21 CFR 201.10 (g)(2).

2. Increase the prominence and relocate the strength statement to immediately follow the proprietary and established names. For example:

Kalydeco
(Ivacaftor) Tablets
150 mg

B. CONTAINER LABEL (60-COUNT BOTTLE)

1. Decrease the prominence and relocate the net quantity statement (i.e. '60 tablets') so that it appears away from the product strength.
2. Remove the phrase (b) (4) to reduce clutter and improve readability of other important information on the label.

3. Revise the statement (b) (4) to read "Usual Dosage: See Prescribing Information."

C. BLISTER CARD LABEL

1. Increase the size and prominence of the strength statement '150 mg'.

D. CARTON LABELING (60-COUNT BOTTLE AND BLISTER CARDS)

1. Relocate the net quantity statement '60 tablets' and '56 tablets' so that it appears on the principal display panel but away from the product strength.
2. Revise the statement (b) (4) to read "Usual Dosage: See Prescribing Information."
3. Remove or reduce the prominence of the graphic located on the lower portion of the carton labeling as it distracts from the most important information such as the proprietary name, established name, and strength statements.

E. CARTON LABELING FOR BLISTER CARD ONLY

1. Revise the statement (b) (4) to read "Carton contains 4 individual blister cards of 14 tablets per card."
2. Revise the strength statement to read "150 mg per tablet". For example:

Kalydeco
(Ivacaftor) Tablets
150 mg per tablet

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

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/s/

REASOL AGUSTIN

01/03/2012

CARLOS M MENA-GRILLASCA

01/03/2012

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 203188

Name of Drug: Ivacaftor (VX-770)

Applicant: Vertex Pharmaceuticals, Inc.

Labeling Reviewed

Submission Date: 10-18-11

Receipt Date: 10-18-11

Background and Summary Description

Ivacaftor is an NME for the treatment of cystic fibrosis in patients > 6 years of age with a G115D mutation in the CFTR gene. Due to the orphan designation of this product, this NDA has been given a priority review status.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

Conclusions/Recommendations

No deficiencies were identified in the review of this labeling.

Miranda Raggio	11-10-11
Regulatory Project Manager	Date
Sandy Barnes	12-28-11
Chief, Project Management Staff	Date

APPEARS THIS
WAY ON
ORIGINAL

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/s/

MIRANDA B RAGGIO
12/30/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: December 28, 2011

To: Badrul Chowdhury, MD, Director
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

From: Robin Duer, MBA, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs

Subject: DMPP Review of Patient Labeling (Patient Package Insert)

Drug Name (established name): KALYDECO (ivacaftor)

Dosage Form and Route: Film-Coated Tablets

Application Type/Number: NDA 203-188

Applicant: Vertex Pharmaceuticals Inc.

1 INTRODUCTION

This review is written in response to a request by the Division of Pulmonary, Allergy, and Rheumatology (DPARP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) for KALYDECO (ivacaftor) Film-Coated Tablets.

The purpose of the Applicant's October 18, 2011 new drug application (NDA) is to propose a new molecular entity (NME) in the form of a selective potentiator of the CFTR protein for the treatment of cystic fibrosis in patients age six years and older who have a G551D mutation in the CFTR gene. The Applicant requested and was granted a priority review for this orphan drug product.

2 MATERIAL REVIEWED

- Draft KALYDECO (ivacaftor) Film-Coated Tablets Patient Package Insert (PPI) received on October 18, 2011, revised by the Review Division throughout the current review cycle and received by DMPP on December 15, 2011
- Draft KALYDECO (ivacaftor) Film-Coated Tablets Prescribing Information (PI) received October 18, 2011, revised by the Review Division throughout the current review cycle and received by DMPP on December 15, 2011

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

ROBIN E DUER

12/28/2011

This version should be OK.

LASHAWN M GRIFFITHS

12/28/2011

DSI CONSULT: Request for Clinical Inspections

Date: 11-22-2011

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Anthony Orendia, Primary Reviewer
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Kimberly Witzmann, M.D., Clinical Reviewer
Tony Durmowicz, M.D., Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Miranda Raggio, Senior Regulatory Project Manager, DPARP

Subject: Request for Clinical Site Inspections

I. General Information

Application#: NDA-203188

Applicant/ Applicant contact information (to include phone/email):

Mark A. De Rosch, PhD
Senior Director, Regulatory Affairs
Vertex Pharmaceuticals Incorporated
130 Waverly Street
Cambridge, MA 02139-4242
Phone: 617-444-6765
Fax: 617-444-6803
Email: Mark_DeRosch@vrtx.com

Drug Proprietary Name: Kalydeco™ (request for Proprietary Name submitted 10-18-11 but not yet approved) Product is ivacaftor or VX-770

NME or Original BLA (Yes/No): Yes

Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): Yes

Is this for Pediatric Exclusivity (Yes/No): Not requested

Proposed New Indication(s): Cystic Fibrosis in patients > 6 yrs of age with a G551D mutation in the CFTR gene

PDUFA: April 18, 2012

Action Goal Date: April 18, 2012

DSI Consult

version: 5/08/2008

Inspection Summary Goal Date: March 31, 2012

II. Protocol/Site Identification

This NDA submission from Vertex Pharmaceuticals is for VX-770 (ivacaftor), for the proposed indication, “treatment of cystic fibrosis (CF) in patients 6 years and older who have a G551D mutation in the CFTR gene.” VX-770 received Orphan Drug designation in December 2006. Two pivotal studies were completed in subjects with CF and at least one copy of the G551D allele, and all were conducted under an open IND. Study 102 studied subjects ≥ 12 years of age, and Study 103 Part B evaluated children 6 through 11 years of age. Due to the rarity of this orphan disease, and the fact that only 4% of the CF population carries a G551D mutation, there were a large number of clinical trial sites, with few subjects enrolled at each site. Study 102 included 161 subjects enrolled at 65 sites, with only 105 subjects who had complete data to 48 weeks located at 31 sites with at least one subject per treatment group. The remaining 56 subjects were split among 30 centers that had one of the two treatment groups with no subjects enrolled. Study 103B had a total of 24 centers that enrolled 52 patients; only 12 centers had subjects from both treatment groups complete to 48 weeks, comprising 33 subjects of the total 52. For Study 102, 62% of subjects were from the US, 26% were European, and 12% were from Australia. For Study 103B, 52% were US, 21% were EU, and 27% were Australian.

Site # (Name, Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
011 - University of Minnesota 420 Delaware St, SE, MMC276 Minneapolis, MN 55455 Phone: 612-624-0999 Fax: 612-625-2174 PI for 102: Joanne Billings billi001@umn.edu	Study 102	N= 5	22% improvement in FEV1 for Study 102, second-largest enroller
045 - Children’s Hospital Boston 300 Longwell Ave, Hunnewell 2 Boston, MA 02115 Phone: 617-355-1900 Fax: 617-730-0373 ahmet.uluer@tch.harvard.edu PI for 102: Ahmet Uluer PI for 103: Ahmet Uluer	Study 102 Study 103	N=5 N=2	Largest enroller of patients

III. Site Selection/Rationale

There were a large number of sites with few subjects at each site, which is to be expected for this disease and indication; CF affects about 30,000 patients in the US, and about 60,000 worldwide, and the G551D allele is only present in approximately 4% of this population. There was one center (Children’s Hospital of Boston) that completed 5 subjects in Study 102, and 2 in Study 103B, for a total of 7 subjects in the ITT database. All other sites had fewer subjects, and a significant number of sites enrolled only one subject. As a result, the sites selected above were based primarily the relatively high number of enrollees (site 045) or better than average efficacy (site 011). There were no deaths in any study, and there is no suspicion of scientific misconduct.

Because the majority of subjects in these studies were in the US, and efficacy results do not differ between US and that from Europe and Australia, we do not think that international audit is warranted.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- ☒ Enrollment of large numbers of study subjects
- ☒ High treatment responders: (greater than 20% improvement in primary endpoint)
- ☒ Significant primary efficacy results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ☐ Other (specify):

International Inspections:

Not Requested.

IV. Tables of Specific Data to be Verified (if applicable)

Verify the data associated with the primary endpoint, FEV1.

Should you require any additional information, please contact Miranda Raggio at 301-796-2109 or Kim Witzmann at 301-796-5266.

Concurrence: (as needed)

A. *Durmowicz, MD*__ Medical Team Leader

K. *Witzmann, MD*____ Medical Reviewer

_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

Completed by Miranda Raggio/11-22-11

Initialed by Sandy Barnes/11-22-11

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/s/

MIRANDA B RAGGIO
11/22/2011

*For voluminous study endpoint submissions (e.g. PRO “dossier” or content validity documentation greater than 50 pages), SEALD requests 60 days after receiving the background/briefing package document to complete the review.

Cleared by C. Jackson/11-4-11 Finalized by M. Raggio/11-4-11

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13 Pages of Draft
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MIRANDA B RAGGIO
11/04/2011