

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212273Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: September 30, 2019

To: Courtney McGuire, Clinical Reviewer
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Angela Ramsey, Regulatory Project Manager, DPARP

From: Kyle Snyder, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for Trikafta™ (Elexacaftor, tezacaftor and ivacaftor) tablets; (ivacaftor) tablets, co-packaged for oral use

NDA: 212273

In response to DPARP's consult request dated August 2, 2019, OPDP has reviewed the proposed prescribing information (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for Trikafta™ (Elexacaftor, tezacaftor and ivacaftor) tablets; (ivacaftor) tablets, co-packaged for oral use.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DPARP on September 26, 2019. Comments on the proposed PI are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed on the proposed PPI, and comments will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DPARP on September 26, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

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/s/

KYLE SNYDER
09/30/2019 02:15:08 PM

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

PATIENT LABELING REVIEW

Date: September 30, 2019

To: Sally Seymour, MD
Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

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

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Maria Nguyen, MSHS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kyle Snyder, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): TRIKAFTA (elexacaftor/tezacaftor/ivacaftor) tablets;
(ivacaftor) tablets

Dosage Form and Route: elexacaftor/tezacaftor/ivacaftor tablets, for oral use; co-packaged with ivacaftor tablets, for oral use

Application Type/Number: NDA 212273

Applicant: Vertex Pharmaceuticals, Incorporated

1 INTRODUCTION

On July 19, 2019, Vertex Pharmaceuticals, Incorporated submitted for the Agency's review an original New Drug Application (NDA) 212273 for TRIKAFTA (elexacaftor/tezacaftor/ivacaftor) tablets; (ivacaftor) tablets, for oral use. The proposed indication for TRIKAFTA (elexacaftor/tezacaftor/ivacaftor) tablets; (ivacaftor) tablets, for oral use is for the treatment of cystic fibrosis (CF) in people aged 12 years and older who have at least one (b) (4) F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on July 19, 2019, and August 2, 2019, for DMPP and OPDP, respectively, to review the Applicant's proposed Patient Package Insert (PPI) for TRIKAFTA (elexacaftor/tezacaftor/ivacaftor) tablets; (ivacaftor) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft TRIKAFTA (elexacaftor/tezacaftor/ivacaftor) tablets; (ivacaftor) tablets, for oral use PPI received on July 19, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 26, 2019.
- Draft TRIKAFTA (elexacaftor/tezacaftor/ivacaftor) tablets; (ivacaftor) tablets, for oral use Prescribing Information (PI) received on July 19, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 26, 2019.
- Approved SYMDEKO (tezacaftor/ivacaftor) tablets; (ivacaftor) tablets, for oral use comparator labeling dated February 12, 2018.
- Approved KALYDECO (ivacaftor) tablets, for oral use comparator labeling dated January 31, 2012.

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.

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 APFont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- 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 is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP 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/

MARIA T NGUYEN
09/30/2019 03:39:49 PM
DMPP-OPDP review of TRIDAFTA NDA 212273 PPI

KYLE SNYDER
09/30/2019 03:42:37 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 16, 2019
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 212273
Product Name and Strength:	Trikafta (elexacaftor/ tezacaftor/ivacaftor) Tablets, 100 mg/50 mg/75 mg and 150 mg of ivacaftor
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Vertex Pharmaceuticals Inc
FDA Received Date:	July 19, 2019
OSE RCM #:	2019-1545
DMEPA Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Trikafta (elexacaftor/ tezacaftor/ivacaftor; ivacaftor) Tablets, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the proposed Trikafta prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D -N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted container labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	The Highlights and Dosage Administration section lack readability	Important dosage information may be overlooked	Consider displaying the usual adult dosing be displayed in bulleted or table format. For example: Adults and pediatric patients aged 12 years and older:

Table 2. Identified Issues and Recommendations for Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			• Morning dose: two elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg tablets • Evening dose: one ivacaftor 150 mg tablet Morning and evening doses should be taken approximately 12 hours apart with fat-containing food.

Table 3. Identified Issues and Recommendations for Vertex Pharmaceuticals Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The instructions for use in the (b) (4) and blue box on the label and labeling do not include the drug name nor account for possible dose modifications in special patient populations	Omitting the drug name and notice of potential patient specific dosing modifications from the product dosing instructions may lead to wrong drug and dosing administration error	Under Morning (2 tablets) revise "Take 2 orange tablets marked with "T100"" to "Take 2 orange (elexacaftor/ tezacaftor/ivacaftor) tablets marked with "T100" or as directed by your healthcare provider" Under Evening (1 Tablet) revise "Take 1 light blue tablet marked with "V 150"" to "Take 1 light blue (ivacaftor) tablet marked with "V 150" or as directed by your healthcare provider"
2.	The proprietary name and established names lack prominence on primary display panel (PDP)	The proprietary and established names may be overlooked and/or misinterpreted leading to potential medication errors	Increase the prominence of the proprietary and established names. Ensure that the established name is at least ½ the size of the proprietary name and in accordance with 21 CFR 201.10(g)(2). If additional space is needed, consider decreasing the size and/or boldness of the graphic located in the top third of the PDP as it further detracts the readers attention from more important product information.

Table 3. Identified Issues and Recommendations for Vertex Pharmaceuticals Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	The daily dose statement is not inclusive of patients that require dose modifications	Due to dose modifications in specific populations, (b) (4) (b) (4)	Remove the statement (b) (4) and replace with "Recommended Dosage: See prescribing information"
4.	The net quantity should include the total quantity of units per carton and container	(b) (4) this statement may add unnecessary clutter to the label and labeling	Delete (b) (4) from the net quantity statement on the carton and container. For example: Carton and Container should state: Carton: 84 tablets 4-wallets (each containing 14 tablets of elexacafator/tezafactor/ivacaftor and 7 tabs of ivacaftor) Container: 1-wallet (containing 14 tablets of elexacafator/tezafactor/ivacaftor and 7 tabs of ivacaftor)
Container Label(s)			
1.	The strength statement per tablet is omitted. As currently presented the strength statement may be easily misunderstood	The product strength should describe the milligram amount of drug per single unit so that there is no confusion as to how much product is contained in each single unit tablet as compared to the total contents of the entire blister card ^a	Revise the strength presentation to read: elexacafator/tezafactor/ivacaftor 100 mg/50 mg/75 mg per tablet and ivacaftor 150 mg per tablet

^a FDA Guidance for Industry, Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors <https://www.fda.gov/media/85879/download>

Table 3. Identified Issues and Recommendations for Vertex Pharmaceuticals Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling			
1.	The usual dose statement on the side panel of the carton is currently presented as: (b) (4)	The usual dosage statement should meet 21 CFR 201.55 and maintain consistency with the Prescribing Information	Revise the Usual Dosage statement to read: "Recommended Dosage: See prescribing information"

4 CONCLUSION

Our evaluation of the proposed Trikafta container labels and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Vertex Pharmaceuticals Inc so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Trikafta that Vertex Pharmaceuticals Inc submitted on July 19, 2019.

Table 4. Relevant Product Information for Trikafta	
Initial Approval Date	N/A
Active Ingredient	elexacaftor/tezacaftor/ivacaftor
Indication	treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the CFTR gene. If the patient's genotype is unknown, confirm the presence of at least one F508del mutation using a genotyping assay.
Route of Administration	Oral
Dosage Form	Tablet
Strength	100 mg elexacaftor, 50 mg tezacaftor, 75 mg ivacaftor fixed dose combination tablets and 150 mg ivacaftor tablets
Dose and Frequency	- Adults and pediatric patients aged 12 years and older: two tablets (each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) in the morning and one tablet (containing ivacaftor 150 mg) in the evening, approximately 12 hours apart. TRIKAFTA should be taken with fat-containing food. - Reduce dose in patients with moderate hepatic impairment. Not recommended in patients with severe hepatic impairment. - Reduce dose when co-administered with drugs that are moderate or strong CYP3A inhibitors.
How Supplied	84-count tablet (b) (4) (4 (b) (4) wallets, each (b) (4)
Storage	Store at 20°C -25°C (68°F -77°F); excursions permitted to 15°C -30°C (59°F -86°F) [see USP Controlled Room Temperature].
Container Closure	Closure system for VX-445 drug substance are commercially available. VX-445 drug substance is packaged (b) (4) [REDACTED]

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Trikafta labels and labeling submitted by Vertex Pharmaceuticals Inc.

- Container label(s) received on July 19, 2019
- Carton labeling received on July 19, 2019
- Prescribing Information (Image not shown) received on July 19, 2019

F.2 Label and Labeling Images

Container label(s)



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

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/s/

LISSA C OWENS
09/16/2019 11:13:57 AM

IDALIA E RYCHLIK
09/16/2019 11:59:57 AM

Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA 212273
Submission Number	# 0001
Submission Date	7/19/2019
Date Consult Received	7/30/2019
Clinical Division	DPARP

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

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT review dated 07/02/2018 under IND-132547 in DARRTS ([link](#));
- Sponsor's proposed product label (SN0001 / SDN001; [link](#))
- Sponsor's clinical study report # VX18-445-009 (SN0001 / SDN001; [link](#));
- Sponsor's E-R analysis report # O372 (SN0001 / SDN001; [link](#));
- Investigator's brochure under IND-132547 (SN0120; [link](#)); and
- Highlights of clinical pharmacology and cardiac safety under IND-132547 ([link](#)).

1 SUMMARY

No significant QTc prolongation effect of elexacaftor (a component of a fixed dose combination of elexacaftor, tezacaftor, and ivacaftor; Trikafta) was detected in this QT assessment.

The effect of elexacaftor (VX-445) was evaluated in randomized, single center, double-blind, placebo- and active-controlled, thorough QT/QTc study in healthy subjects (Study # VX18-445-009). The highest dose evaluated was 400 mg once daily which offers 2-fold margin over therapeutic exposure. The data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that elexacaftor is associated with significant QTc prolonging effect (refer to section 4.5) – see Table 1 for overall results.

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Concentration (ng/mL)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
QTc	VX-445 200 mg*	9,762.5	-1.5	(-3.7 to 0.7)
QTc	VX-445 400 mg*	20,442.7	-2.6	(-5.0 to -0.3)

*once daily dosing for seven days under fed conditions (200 mg: Day 2 to 8; and 400 mg: Day 9 to 15)

The findings of this analysis are further supported by the available nonclinical data (section 3.1), central tendency analysis (section 4.3) and categorical analysis (section 4.4). Assay sensitivity was established using concentration-response analysis of moxifloxacin data which indicated a positive slope in the relationship between ΔQTcF and the plasma concentration of moxifloxacin.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 PROPOSED LABEL

Below are proposed edits from the QT-IRT to the label submitted to SN0001 ([link](#)). Our changes are highlighted ([addition](#), [deletion](#)). This is a suggestion only and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At doses up to 2 times the maximum recommended dose of elexacaftor and 3 times the maximum recommended dose of tezacaftor and ivacaftor, the QT/QTc interval in healthy subjects was not prolonged to any clinically relevant extent.

(b) (4)

We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.

3 SPONSOR’S SUBMISSION

3.1 OVERVIEW

Vertex Pharmaceuticals Inc. is developing fixed dose combination of elexacaftor, tezacaftor, and ivacaftor (Trikafta) for the treatment of cystic fibrosis in patients (age ≥ 12 years; who have at least one F508del mutation in the CFTR gene). Cystic fibrosis is an autosomal recessive disease believed to be caused by reduced function of the CFTR protein due to mutations in the CFTR gene. Elexacaftor and tezacaftor are expected to bind to different sites on the CFTR protein and offer additive effect in facilitating the cellular processing and trafficking of F508del CFTR. Ivacaftor is believed to be a potentiator (increase probability of channel opening) of the CFTR protein at the cell surface.

Previously approved co-pack product (Symdeko, NDA-210491; 2018) by the same sponsor has dosing recommendations of one fixed-dose combination tablet containing tezacaftor 100 mg and ivacaftor 150 mg in the morning; with one tablet containing ivacaftor 150 mg in the evening. The QT effect of tezacaftor and ivacaftor were evaluated in separate studies and are described in the product label as below:

At a dose 3 times the maximum approved recommended dose, tezacaftor does not prolong the QT interval to any clinically relevant extent. In a separate study of ivacaftor evaluating doses up to 3 times the maximum approved recommended dose, ivacaftor does not prolong the QT interval to any clinically relevant extent.

The triple combination product is formulated as immediate-release film coated tablets containing 100 mg of elexacaftor (VX-445; MW: 597.66 g/mol), 50 mg of tezacaftor (MW: 520.50 g/mol), and 75 mg of ivacaftor (MW: 392.49 g/mol). The proposed therapeutic dose is twice daily administration of tablets containing elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg (morning and evening) under fed (fat-containing food) condition. The peak concentration of 8.66 ± 2.05 $\mu\text{g/mL}$, 6.77 ± 1.47 $\mu\text{g/mL}$, and 1.24 ± 0.34 $\mu\text{g/mL}$ are expected for elexacaftor (Racc: 3.6), tezacaftor (Racc: 2.8) and ivacaftor (Racc: 4.7) at steady-state with twice daily dosing (elexacaftor 200 mg and tezacaftor 100 mg once daily and ivacaftor 150 mg twice daily).

Initially, the sponsor submitted concentration-QT analysis using First-In-Human study (Study # 445-001, Part A). The highest dose evaluated in this study (360 mg single dose) resulted in a peak concentration of ~ 8 $\mu\text{g/mL}$. However, the sponsor did not demonstrate that the doses used in the study would offer a sufficiently high multiple of the clinically relevant exposure to waive the need for a separate positive control for assay sensitivity (Dt: 04/24/2018). Subsequently, the sponsor submitted thorough QT study protocol which was reviewed by the QT-IRT. The proposed study design and analysis plan were acceptable to the QT-IRT and general comments on data submission and analysis were provided to the sponsor (Dt: 07/02/2018).

Recently, the sponsor completed this randomized, single center, double-blind, placebo- and active-controlled, thorough QT/QTc study in healthy subjects (Study # VX18-445-009). The study utilized a parallel design with nested crossover groups for moxifloxacin and placebo. Subjects (n=64) were randomized (2:1:1 ratio to Groups 1, 2A, or 2B) and received a total of 16 days study drug treatment under the fed condition.

- *Group 1 received moxifloxacin-matching placebo on Day 1, therapeutic dose of VX-445 200 mg once daily from Day 2 to Day 8 (n=32), supratherapeutic dose of VX-445 400 mg qd from Day 9 to Day 15 (n=31), and moxifloxacin-matching placebo on Day 16.*
- *Group 2A received a single dose of moxifloxacin on Day 1, VX-445-matching placebo from Day 2 to Day 15, and moxifloxacin-matching placebo on Day 16.*
- *Group 2B received moxifloxacin-matching placebo on Day 1, VX-445-matching placebo from Day 2 to Day 15, and a single dose of moxifloxacin on Day 16.*

A total of 64 subjects were enrolled and 62 subjects completed study drug treatment and 63 subjects completed the study. The peak concentrations of 20.9 (CV: 22.8%) $\mu\text{g/mL}$ and 8.49 (CV: 31.9%) $\mu\text{g/mL}$ were observed for VX-445 and M23-445, respectively, following 400-mg once daily doses. The median T_{max} was ~ 5 hours for VX-445 and 10 to 12 hours for M23-445 following both 200-mg and 400-mg once daily dosing.

Concomitant administration with itraconazole (a strong CYP3A inhibitor) increases exposures of VX-445 (AUC by 2.8-fold). Although PK VX-445 is not evaluated in subjects with hepatic impairment, it is expected to increase exposures of VX-445. Reduced dose is recommended in patients with moderate hepatic impairment and with concomitant administration of moderate to strong inhibitors of CYP3A. Based on hERG assay, IC₅₀ of >30 μM offers more than 200-fold margin at therapeutic concentrations (17 μM ; 99% bound). The sponsor claims that there were no VX-445-related effects on QT interval as

observed in the cardiovascular dog studies or the GLP 28-day and 9-month toxicity studies in dogs.

3.2 SPONSOR'S RESULTS

3.2.1 Central tendency analysis

VX-445 excluded the 10 ms threshold at the therapeutic and suprathreshold dose levels in FDA reviewer's supportive central tendency analysis on TQT study VX18-8445-009. The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin with a positive concentration- $\Delta\Delta\text{QTc}$ slope and the lower bound of the 90% CI of the predicted effect at geometric C_{max} above 5 ms.

Assay sensitivity was also established by the moxifloxacin arm in the supportive by-time analysis. The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.5.1 and 4.3 for additional details.

3.2.1.1.1 QT bias assessment

Assay sensitivity was established using moxifloxacin control arm; therefore, no QT bias assessment was conducted.

3.2.2 Categorical Analysis

No subject had $\text{QTcF} > 450$ ms or a change from baseline in QTcF (ΔQTcF) > 30 ms for VX-445 and placebo. The results of the reviewer's analysis are the same as the sponsor's results for QTcF and ΔQTcF . Please see section 4.4 for additional details.

3.2.3 Safety Analysis

There were no deaths, serious AEs, life-threatening AEs, or AEs that led to study drug interruption.

Two subjects had AEs that led to study drug discontinuation. One subject in the VX-445 group discontinued due to a mild AE of rash generalized that resolved after drug discontinuation. One subject in the placebo/moxifloxacin group (Group 2B) discontinued due to a severe AE of blood creatine phosphokinase increased.

There were no clinically relevant findings in laboratory values, vital signs, physical examinations, or ECGs.

3.2.4 Exposure-Response Analysis

With the intent to exclude an effect > 10 ms at clinically relevant plasma concentrations, the sponsor performed PK/PD analysis evaluating the relationship between plasma concentration of VX-445 (and its metabolite, M23-445) and ΔQTcF (change from baseline in QTcF) using a linear mixed-effects approach.

The sponsor's model included ΔQTcF as dependent variable, time-matched plasma concentration (of VX-445, and its metabolite, M23-445) as a continuous covariate, treatment (active = 1 or placebo = 0) and time (i.e., actual post-baseline time point) as categorical factors, and a random intercept and slope per subject. The slope (i.e., the regression parameter for the concentration) and the treatment effect-specific intercept (defined as the difference between active and placebo) were estimated together with 2-sided 90% CI. The predicted effect and its 2-sided 90% CI for placebo corrected change from baseline QTcF ($\Delta\Delta\text{QTcF}$) at geometric mean peak concentrations were obtained (i.e., the product with the slope estimate + treatment effect-specific intercept).

The sponsor evaluated 1) VX-445 and M23-445 with interaction, 2) VX-445 and M23-445 without interaction, and 3) only M23-445. The sponsor's analysis did not indicate significant relationship (estimated slope 0.00010 ms/ng/mL) between plasma concentration of VX-445 and M23-445 on $\Delta\Delta\text{QTcF}$. The sponsor's final model using M23-445 predicted $\Delta\Delta\text{QTcF}$ for the peak concentrations on Day 8 with 200 mg once daily dosing (geomean: 2986.3 ng/mL; 90%CI: 2718.95, 3280.03; corresponds to therapeutic concentrations) was -1.07 (90%CI: -3.51, 1.37) ms and predicted $\Delta\Delta\text{QTcF}$ for the peak concentrations on Day 15 with 400 mg once daily dosing (geomean: 8054.9 ng/mL; 90%CI: 7265.66, 8929.98; corresponds to supra-therapeutic concentrations) was -3.10 (90%CI: -6.22, 0.02) ms. The sponsor's C-QT analysis indicate that a QTcF effect above 10 ms for both VX-445 and M23-445 can be excluded up to a VX-445 plasma concentration of approximately 32.7 $\mu\text{g/mL}$ and a M23-445 plasma concentration of approximately 14.0 $\mu\text{g/mL}$.

The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.5 for additional details.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases or decreases in heart rate were observed (i.e., absolute mean change in HR was <10 bpm; see Sections 4.3.2 and 4.5).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT bias assessment

Not applicable.

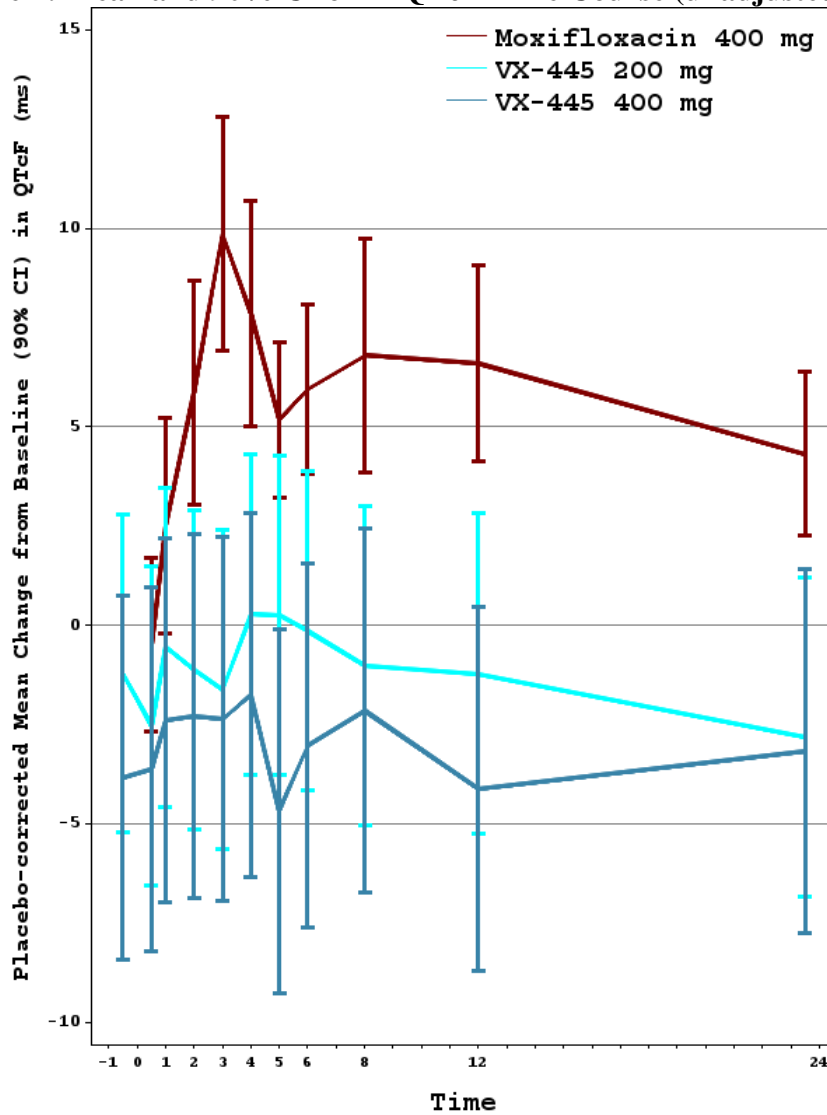
4.3 CENTRAL TENDENCY ANALYSIS

4.3.1 QTc

The statistical reviewer used repeated measures mixed model to analyze the ΔQTcF effect of VX-445. The model includes treatment, time point, and treatment by time point as fixed effects and subject as a random effect. Baseline values are also included in the model as a

covariate. The following figure displays the time profile of $\Delta\Delta\text{QTcF}$ for different treatment groups.

Figure 1: Mean and 90% CI of $\Delta\Delta\text{QTcF}$ Time Course (unadjusted CIs)



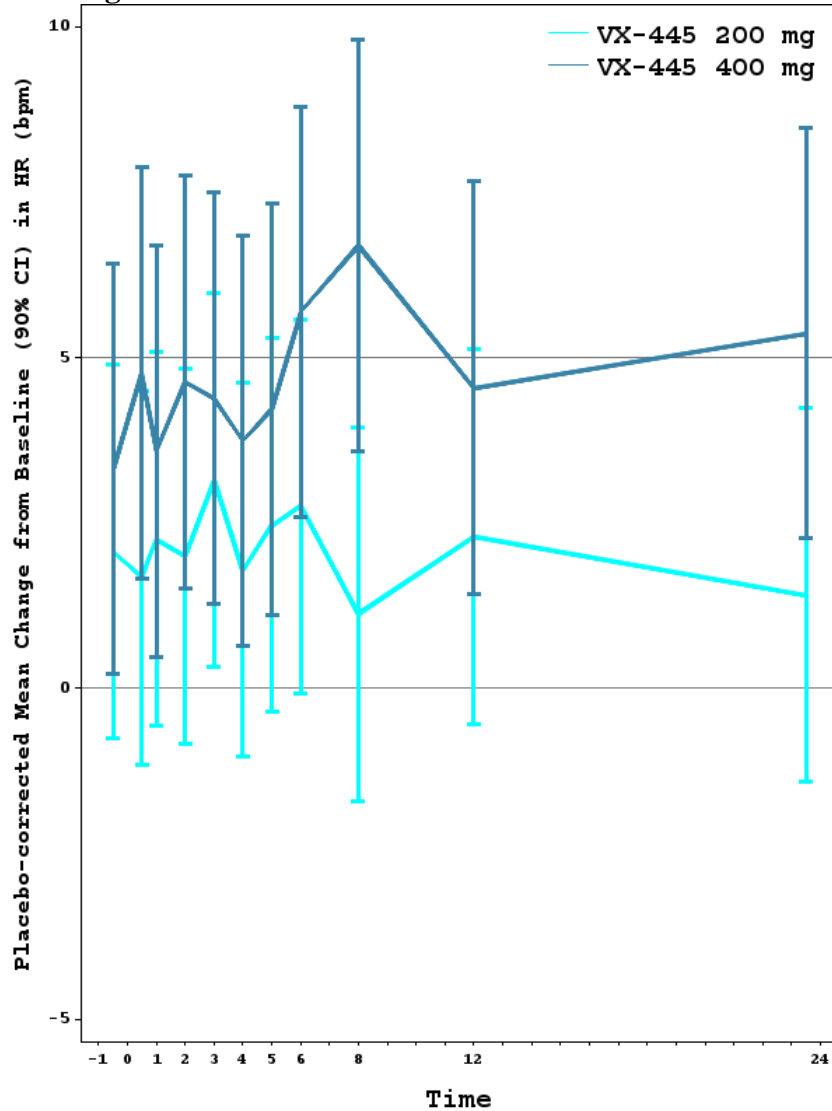
4.3.1.1 Assay sensitivity

The primary method for assay sensitivity was exposure response. Please see section 4.5.1 for details. Assay sensitivity was confirmed to be established in the supportive by-time analysis. The reviewer's central tendency analysis for moxifloxacin is shown in the above Figure 1. The statistical reviewer conducted central tendency analysis for assay sensitivity separately. Mixed model appropriate for crossover design was used in the assessment of assay sensitivity; the model includes sequence, period, treatment, time point, and treatment by time point as fixed effects and subject as a random effect. Baseline values are also included as a covariate.

4.3.2 HR

The same statistical analysis used for VX-445 was performed based on HR (Figure 2). At the studied doses, no clinically relevant increase in heart rate was found for VX-445.

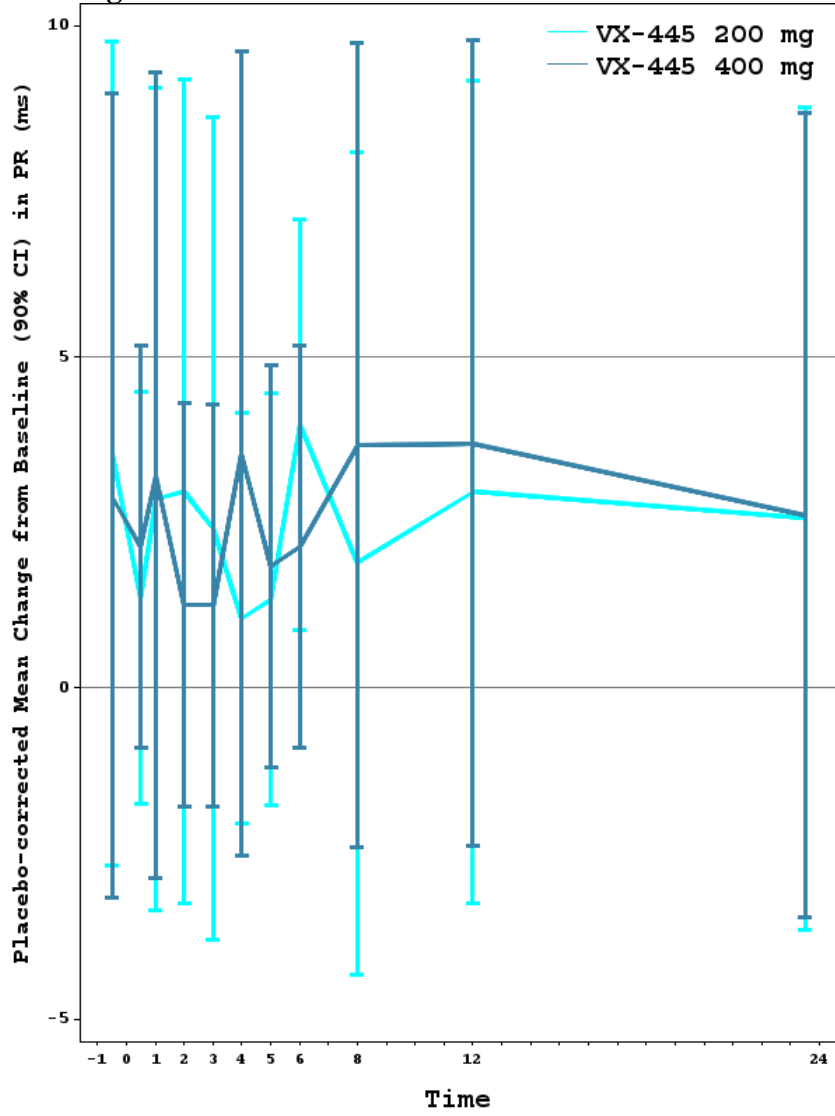
Figure 2: Mean and 90% CI of Δ HR Timecourse



4.3.3 PR

The same statistical analysis used for VX-445 was performed based on PR interval (Figure 3).

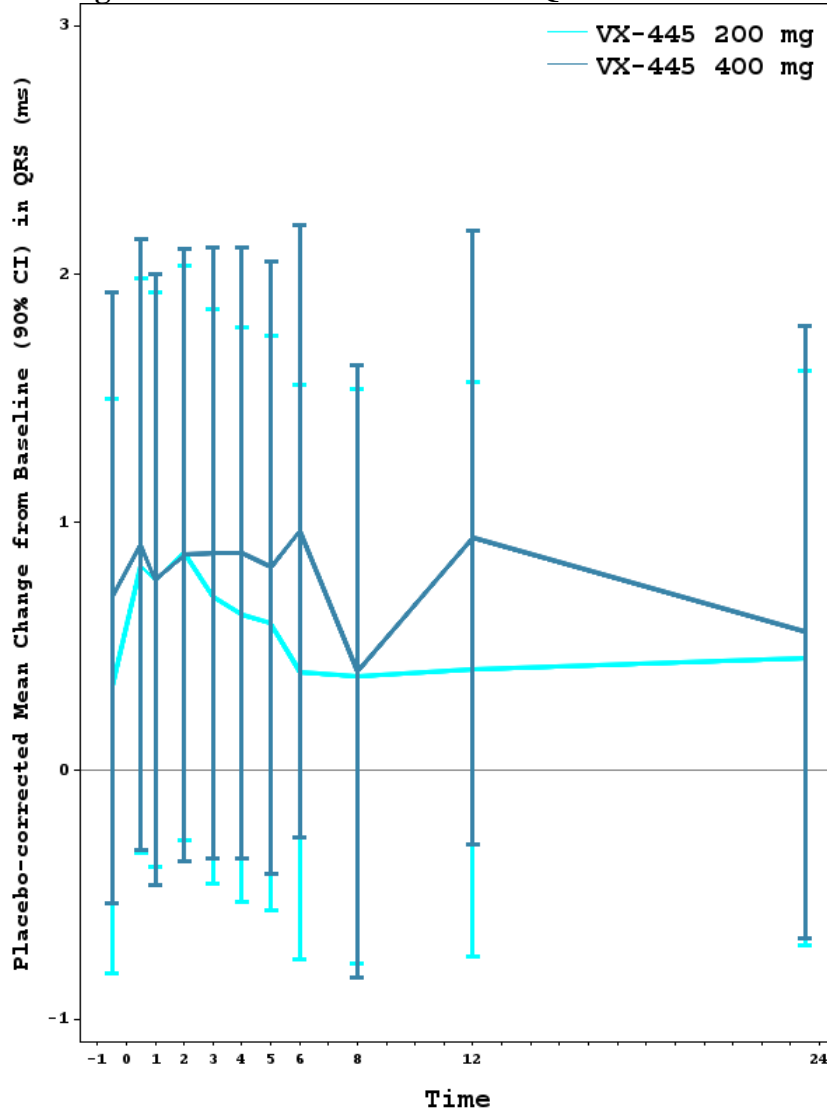
Figure 3: Mean and 90% CI of $\Delta\Delta$ PR Timecourse



4.3.4 QRS

The same statistical analysis used for VX-445 was performed based on QRS interval (Figure 4).

Figure 4: Mean and 90% CI of $\Delta\Delta$ QRS Timecourse



4.4 CATEGORICAL ANALYSIS

4.4.1 QTc

The reviewer conducted categorical analysis for the primary part, i.e., only data from Days -1, 8, and 15 for VX-445 (Group 1) and pooled placebo (Group 2A and Group 2B) were included in the categorical analysis. None of the subjects had QTcF >450 ms or Δ QTcF >30 ms for VX-445 or placebo. The findings are the same as the sponsor's results.

4.4.2 PR

All subjects' PR values were $\leq$ 220 ms.

4.4.3 QRS

No subject had QRS >120 ms with an increase from baseline in QRS >25% in the primary part of the study.

4.4.4 HR

No subject had HR >100 bpm or HR $\leq$ 45 bpm while taking VX-445.

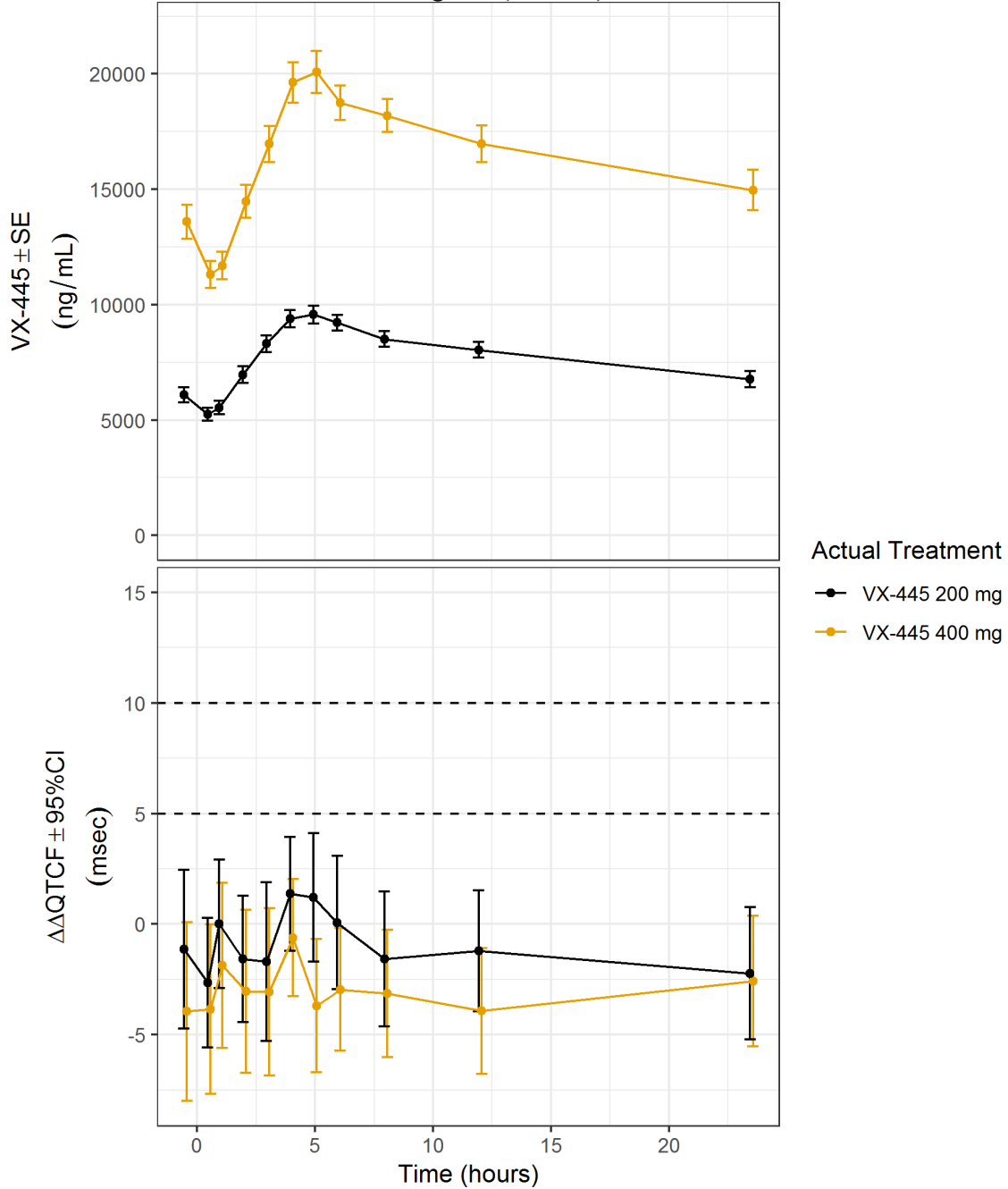
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between Δ QTcF and plasma concentration of VX-445 (n=32) and its metabolite M23-445 (n=30).

Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and Δ QTcF and 3) presence of non-linear relationship.

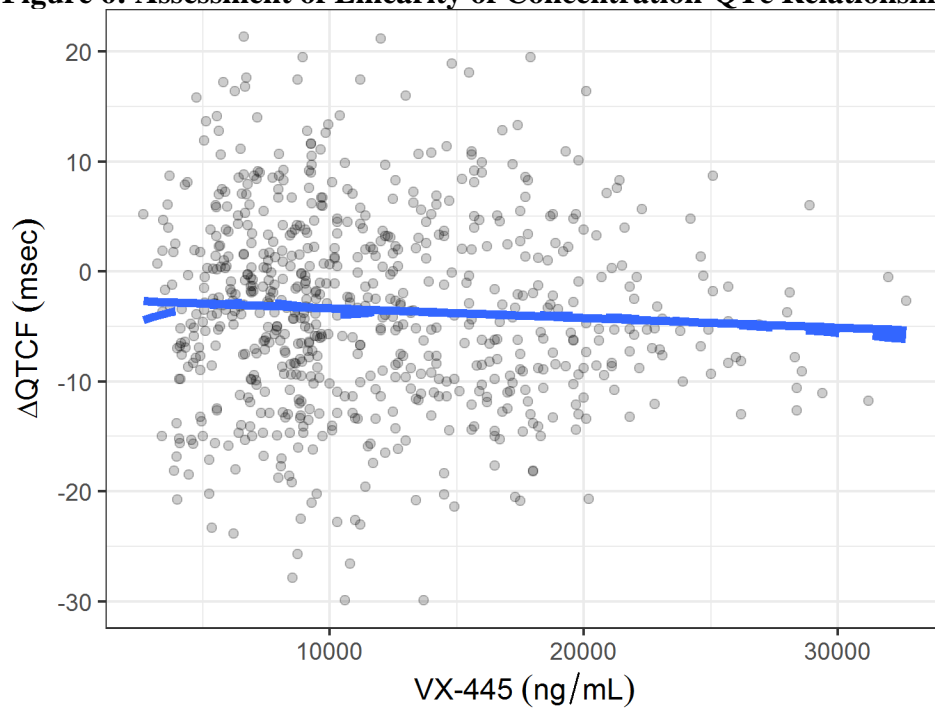
An evaluation of the time-course of drug concentration and changes in $\Delta\Delta$ HR and $\Delta\Delta$ QTcF is shown in Figure 5, which do not appear to show significant hysteresis. No significant increases or decreases in heart rate were observed. The maximum change in heart rate was 3.1 bpm at 200 mg dose and 6.7 bpm at 400 mg dose (see section 4.3.2 and 4.4.4).

Figure 5: Time Course of Drug Concentration (top), Heart Rate (middle) and QTcF (bottom)



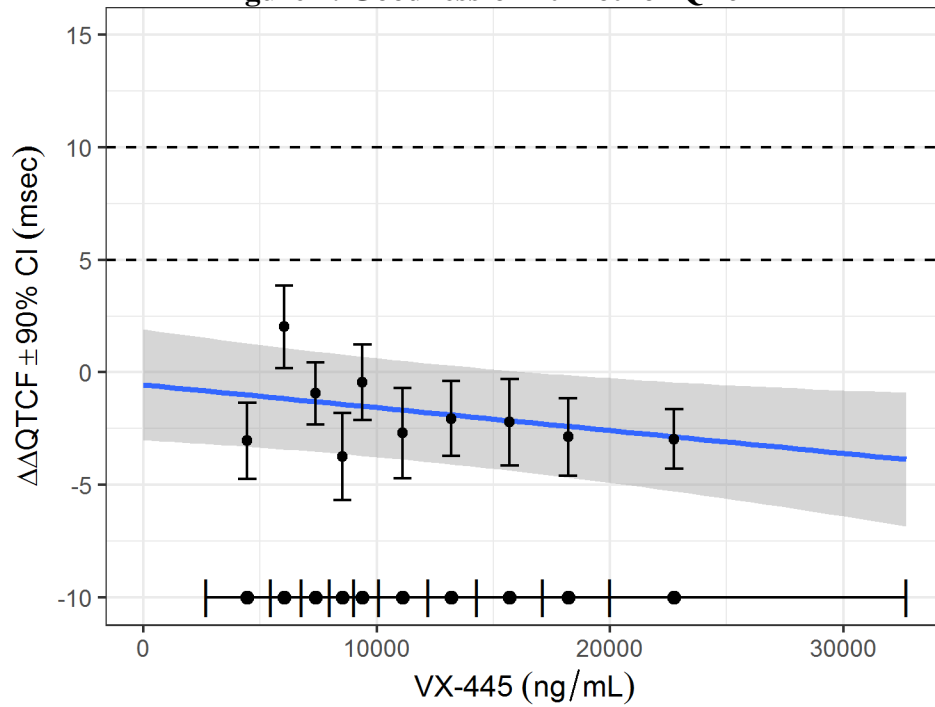
After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between drug concentration and Δ QTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between VX-445 concentration and Δ QTcF and supports the use of a linear model. Similar observations were also made for metabolite (Data not shown).

Figure 6: Assessment of Linearity of Concentration-QTc Relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provided in Table 1.

Figure 7: Goodness-of-fit Plot for QTc



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