

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213137Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: November 19, 2019

To: Katie Chon, PharmD, RPh, Regulatory Project Manager, Division of Hematology Products (DHP)
Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Oxbryta (voxelotor) tablets, for oral use

NDA: 213137

In response to DHP's consult request dated July 2, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for Oxbryta.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Katie Chon) on November 7, 2019, and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on November 15, 2019.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 26, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

19 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROBERT L NGUYEN
11/19/2019 04:30:54 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: November 14, 2019

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

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

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Ruth Mayrosh, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Robert Nguyen, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): OXBRYTA (voxelotor)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 213137

Applicant: Global Blood Therapeutics, Inc.

1 INTRODUCTION

On June 26, 2019, Global Blood Therapeutics, Inc. submitted for the Agency's review the final portion of a rolling review for original New Drug Application (NDA) 213137 for OXBRYTA (voxelotor) tablets. The proposed indication for OXBRYTA (voxelotor) tablets is for the treatment of sickle cell disease in adult (b) (4) patients.

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 Hematology Products (DHP) on July 2, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for OXBRYTA (voxelotor) tablets.

2 MATERIAL REVIEWED

- Draft OXBRYTA (voxelotor) tablets PPI received on June 26, 2019, and received by DMPP and OPDP on November 7, 2019.
- Draft OXBRYTA (voxelotor) tablets Prescribing Information (PI) received on June 26, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 7, 2019.

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. We reformatted the PPI document using the Arial font, size 10.

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)

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.

3 Pages of Draft Labeling have been Withheld in Full as b4 9cCI/
TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RUTH I MAYROSH
11/14/2019 01:47:32 PM

ROBERT L NGUYEN
11/14/2019 02:35:11 PM

BARBARA A FULLER
11/15/2019 08:27:25 AM

LASHAWN M GRIFFITHS
11/15/2019 08:37:47 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum: November 4, 2019
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 213137
Product Name and Strength: Oxbryta (voxelotor) tablets, 500 mg
Applicant/Sponsor Name: Global Blood Therapeutics
FDA Received Date: October 25, 2019
OSE RCM #: 2019-1369-1
DMEPA Safety Evaluator: Stephanie DeGraw, PharmD
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Global Blood Therapeutics submitted a revised container label for Oxbryta (voxelotor) on October 25, 2019 (Appendix A). The revisions are in response to recommendations that we made during a previous label and labeling review.^a We reviewed the revised label to determine if it is acceptable from a medication error perspective.

2 CONCLUSION

We note that all previous recommendations were accepted and implemented. DMEPA concludes the revised container label is acceptable from a medication error perspective. We have no additional recommendations at this time.

^a DeGraw, S. Label and Labeling Review for Oxbryta (voxelotor) NDA 213137. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 24. RCM No.: 2019-1369.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON OCTOBER 25, 2019

Container Label



This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STEPHANIE L DEGRAW
11/04/2019 11:23:17 AM

HINA S MEHTA
11/06/2019 10:08:48 AM

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 24, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 213137
Product Name and Strength:	Oxbryta (voxelotor) tablets, 500 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Global Blood Therapeutics
FDA Received Date:	March 29, 2019, June 26, 2019, July 11, 2019, and July 22, 2019
OSE RCM #:	2019-1369
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1. REASON FOR REVIEW

Global Blood Therapeutics submitted NDA 213137 Oxbryta (voxelotor) tablets on March 29, 2019 as part of a rolling submission. Oxbryta is a hemoglobin S polymerization inhibitor proposed for the treatment of sickle cell disease in adult (b) (4) patients. We evaluated the proposed container label and Prescribing Information (PI) for areas of vulnerability that could lead to medication errors.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

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 post-market safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label and PI for Oxbryta to identify deficiencies that may lead to medication errors and other areas of improvement.

Our review of the proposed PI identified numbers greater than or equal to 1,000 expressed without a comma. In addition, we identified areas in the PI and container label that can be modified to improve the clarity of the information presented.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI and labels can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for the Division in Section 4.1 and recommendations for Global Blood Therapeutics in Section 4.2 below.

3. To ensure consistency with the Prescribing Information, revise (b) (4) to read "Dosage: see prescribing information".
4. As currently presented, the format for the expiration date is (b) (4), which is vulnerable to misinterpretation. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date.

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Oxbryta received on July 11, 2019, from Global Blood Therapeutics.

Table 2. Relevant Product Information for Oxbryta	
Initial Approval Date	N/A
Active Ingredient	voxelotor
Indication	Treatment of sickle cell disease in adult (b) (4) patients
Route of Administration	Oral
Dosage Form	Tablets
Strength	500 mg
Dose and Frequency	1,500 mg (3 tablets) once daily with or without food 1,000 mg (2 tablets) once daily with or without food in patients with hepatic impairment
How Supplied	90-count round HDPE bottle with a white child-resistant, (b) (4)
Storage	Store at or below 30°C (86°F).

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of Failure Mode and Effects Analysis,^a along with post-market medication error data, we reviewed the following Oxbryta labels and labeling submitted by Global Blood Therapeutics:

- Container Label received on July 22, 2019
- Prescribing Information (no image shown) received on July 11, 2019
<\\cdsesub1\evsprod\nda213137\0007\m1\us\uspi-clean.docx>

G.2 Labels and Labeling

Container Label



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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STEPHANIE L DEGRAW
09/24/2019 11:47:35 AM

HINA S MEHTA
09/27/2019 10:27:50 AM

CLINICAL INSPECTION SUMMARY

Date	September 11, 2019
From	Anthony Orenca M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Patricia O’Neal, M.D., Medical Officer Rosanna Setse, M.D., Ph.D., Medical Officer Tanya Wroblewski, M.D., Clinical Team Leader Ann Farrell, M.D., Director Wonme (Katie) Chon, Pharm.D., R.Ph., Project Manager Division of Hematology Products
NDA	213137
Applicant	Global Blood Therapeutics, Inc. (GBT)
Drug	Voxelotor
NME	Yes
Division Classification	Sickle hemoglobin (HbS) polymerization inhibitor
Proposed Indication	Treatment of Sickle Cell Disease (b) (4) Adults
Consultation Request Date	July 16, 2019
Summary Goal Date	October 25, 2019 (Breakthrough Therapy Priority Review)
Action Goal Date	November 25, 2019
PDUFA Date	February 25, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical sites and the sponsor site were selected for inspection in NDA 213137 Study GBT440-031.

The clinical data from Dr. Maureen Achebe’s site (Site 01025) and Dr. David Diuguid’s site (Site 01010), as reported by the sponsor to the NDA, are considered reliable.

Based on preliminary inspection report, the data from Dr. Anne Marsh’s site (Site 01104) are also considered reliable.

The inspection of the sponsor’s site found no significant deficiencies. In general, the sponsor maintained adequate oversight of the clinical trial and appeared to be in compliance with Good Clinical Practices.

Overall, the study appears to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending Establishment Inspection Reports.

II. BACKGROUND

Voxelotor (formerly GBT440), is a small-molecule sickle hemoglobin (HbS) polymerization inhibitor being developed by Global Blood Therapeutics, Inc. for the treatment of adults (b) (4) with sickle cell disease. Voxelotor was granted breakthrough designation on January 3, 2018. Voxelotor is intended to be administered orally once daily.

Voxelotor binds covalently and reversibly via a Schiff-base to the N-terminal valine of one of the α -chains of hemoglobin. Voxelotor's mechanism of action specifically targets the underlying mechanism of the disease by increasing the affinity of hemoglobin for oxygen and stabilizing hemoglobin in the oxyhemoglobin state thereby inhibiting polymerization of HbS in red blood cells.

A single study, GBT-440-031, will form part of the basis for the regulatory decision-making process for this application.

Study GBT-440-031

Study GBT-440-031 is a double-blind, randomized, placebo-controlled, multicenter study of subjects aged 12 to 65 years with Sickle Cell Disease (The disease complex included HbSS, HbSC, HbS β thalassemia, or other sickle cell syndrome variants). The study is being conducted in 3 groups. The purpose of Group 1 was to evaluate the safety and efficacy of voxelotor (900 mg and 1500 mg) compared with placebo and select the voxelotor dose(s) for further study in Group 3. The key purpose of Group 2 was to form the basis for the primary analysis of the study to establish the efficacy and safety of voxelotor in combination with Group 1. As of the data cutoff date of 31 October 2018, no subjects have been enrolled in Group 3. The study is ongoing.

The primary study objective was to assess the effect of voxelotor compared with placebo on improvement in hemoglobin in adults and adolescents with sickle cell disease.

The primary efficacy endpoint was hemoglobin response at Week 24. Hemoglobin response was based on the difference between the average value of hemoglobin levels at Week 20 and Week 24 and baseline hemoglobin level. A subject was considered a hemoglobin responder, if the hemoglobin level was greater than one unit.

The study subjects were screened at 60 study centers in United States, United Kingdom, Lebanon, Jamaica, Canada, Turkey, France, Italy, Netherlands, Egypt, Kenya, and Oman. There were 370 subjects [(Group 1 = 60; Group 2 = up to 180; Group 3 = up to 195), including 50 adolescents] planned to be recruited. For efficacy analyses component, a total of 274 study subjects [(Group 1 = 62; Group 2 = 212), including 46 adolescents] were analyzed. The first subject first visited on December 13, 2016. The data cutoff point was October 31, 2018.

III. RESULTS (by site):

1. Maureen Achebe, M.D., Site #01025

Brigham and Women's Hospital
75 Francis Street
Boston, MA 02115

Inspection dates: August 14 to 23, 2019

A total of 12 subjects were screened, including two subjects rescreened, and 10 patients were enrolled and randomized. Two subjects who received treatment discontinued after randomization due to adverse events. Out of the remaining eight randomized subjects in the treatment phase, four study subjects completed the study and subsequently continued into an open label study.

Source documents for 10 enrolled and randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings for study eligibility, informed consent form documentation, primary study endpoint assessment, adverse events, and serious adverse event reporting. Records review of these subjects indicated that the eligibility criteria for enrollment were met.

Source documents for the raw data used to assess the primary efficacy endpoint were verifiable at the study site. There was no under-reporting of adverse events. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

2. David Diuguid, M.D. Site #01010

Herbert Irving Comprehensive Cancer Center
161 Fort Washington Ave.
NY, NY 10032

Inspection dates: July 29 to August 2, 2019

A total of 13 subjects were screened and 7 subjects were enrolled and randomized. Three discontinued from the study: two patients withdrew consent, and one patient developed an adverse event and withdrew from further participation.

For this inspection, a complete review of regulatory documentation at the study site was performed. Source records for all subjects enrolled at the site were reviewed. The records reviewed included medical records, regulatory binder documents, source data worksheets, informed consent forms, monitoring follow-up reports, and pharmacy records.

Source documents for 7 enrolled and randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings for eligibility, adverse events, and serious adverse event reporting. Source documents for the primary efficacy raw data endpoint were verifiable at the study site.

There were no limitations during conduct of the clinical site inspection.

At the conclusion of the inspection, a Form FDA 483 was issued for inadequate or inaccurate case histories. Specifically, for several study subjects (Subjects [REDACTED]^{(b) (6)}), not all concomitant medications were recorded in the electronic case report forms (eCRFs). In addition, Subject [REDACTED]^{(b) (6)} reported headaches during Week 36 follow-up visit on [REDACTED]^{(b) (6)}. This was not reported as either a pre-existing condition or as an adverse event in the eCRF. These observations were study protocol deviations that had not been previously reported.

In Dr. Diuguid's response to Form 483 dated August 21, 2019, he stated that the site has completed review of all patients' concomitant medications, and research staff has entered these medications and the adverse event of headache into the subjects' e-CRFs on August 20, 2019. The study site planned the following corrective actions: (1) a clinic research manager will conduct monthly quality assurance reviews for data entry and verification, and (2) two study coordinators will monitor the study electronic data capture system to verify accurate and complete entry.

The Form FDA 483 (List of Inspectional Observations) was shared with the Division of Hematology Products (DHP).

Although the above observations are regulatory violations, the findings were found not significant for this clinical investigation and would unlikely affect the overall reliability of safety and efficacy data of the study. In general, this clinical site appeared to be in compliance with Good Clinical Practice.

3. Anne Marsh, M.D. Site #01014

747 52nd Street
Oakland, CA 94609

Inspection dates: August 26 to 30, 2019

A total of 10 subjects were screened and 7 patients were enrolled and randomized. Seven subjects completed study treatment.

The inspection evaluated the following documents: source records, screening and enrollment logs, physician clinical notes, eligibility criteria, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also reviewed.

Source documents for 7 enrolled and randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings for study eligibility, informed consent form documentation, primary study endpoint assessment, adverse events, and serious adverse event reporting. Records review of these subjects indicated that the eligibility criteria for enrollment were met.

Source documents for the raw data used to assess the primary efficacy endpoint were verifiable at the study site. There was no under-reporting of adverse events. There were no limitations during the conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

4. Global Blood Therapeutics, Inc. (GBT)

171 Oyster Point Blvd., Suite 300
South San Francisco, CA 94080

Inspection dates: August 1 to 12, 2019

This inspection evaluated compliance with the sponsor's responsibilities concerning the conduct of Study GBT-440-031. The inspection included review of organizational charts, vendor list, vendor oversight, transfer of obligations, investigator agreements, financial disclosures, monitoring plans, monitoring reports, monitor qualifications, safety reports, adverse events, protocol deviations, and standard operating procedures. Interim Site Visit Monitoring Reports for Study GBT-440-031 were selected and reviewed. No underreporting of significant adverse events to the Agency was noted.

A Form FDA 483 was issued at the end of the study for inaccurate and complete records. Specifically, (1) for six lot numbers of the investigational product, a caution safety label to this investigational drug was not attached, and (2) lack of adequate records covering quantity of products received from four study sites (Sites 01062, 01039, 05002, and 01045). While considered regulatory deficiencies, return of unused products from Dr. Diuguid's clinical site to the sponsor does not have an impact on this clinical study investigation's efficacy and safety assessments.

In the sponsor's August 27, 2019 response, the firm (1) clarified that investigational drug product lot numbers incorporate a booklet label affixed to the top of the blister card (primary package) with lot number, expiry date, kit number, subject ID and investigator name, including a booklet label page with the cautionary investigational drug label page, per 21CFR312.6(a); and (2) stated that investigational sites supervised by sponsor list kit numbers, and whether or not the return kit is unused or used. However, the firm will create tracking forms to be completed when returning drug products to reflect the quantity of dosage form units, in addition to the quantity of containers returned.

Despite the above regulatory deficiencies that were not considered significant, the sponsor oversight and monitoring of the trial was considered to be acceptable. In general, the sponsor appeared to be in compliance with Good Clinical Practice.

{See appended electronic signature page}

Anthony Orenca, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANTHONY J ORENCIA
09/11/2019 07:53:08 PM

MIN LU
09/12/2019 08:15:37 AM

KASSA AYALEW
09/12/2019 02:59:02 PM

DIVISION OF HEMATOLOGY PRODUCTS

Associate Director for Labeling Review of the Prescribing Information

Product Title	TRADENAME (voxelotor)
Applicant	Global Blood Therapeutics, Inc.
Application/Supplement Number	NDA 213137
Type of Application/Submission ¹	NME
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s) (if applicable)	Treatment of sickle cell disease in adult (b) (4) patients
Approved Indication(s) (if applicable)	tba
Date FDA Received Application	06/26/19
Review Classification (Priority/Standard)	Priority
Action Goal Date	02/26/20 (Internal Goal Date: 11/25/19)
Review Date	09/09/2019
Reviewer	Virginia E. Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements²
- Is consistent with labeling guidance recommendations³ and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

The applicant is seeking approval for voxelotor for the treatment of sickle cell disease in adult (b) (4) patients. This review is being completed between the first and second labeling meetings. Not all disciplines have reviewed the USPI at this time. ADL recommendations provided in this review (e.g., recommended edits and comments regarding parts of PI) are preliminary and pending discussion with other review team members for this product.

In the attached PI, ADL comments (in balloons) are labeled with my initials “KV”. This review includes a high-level summary of the rationale for major changes to the PI as compared with the applicant’s draft PI and currently approved PI.

¹ Examples include: Original Biologics License Application (BLA), New Molecular Entity (NME) NDA, Original NDA, NDA Efficacy Supplement, 505(b)(2) New Drug Application (NDA), New Chemical Entity (NCE) NDA, NDA Prior Approval Labeling Supplement, NDA CBE-0 Labeling Supplement

² See [January 2006 Physician Labeling Rule](#); 21 CFR [201.56](#) and [201.57](#); and [December 2014 Pregnancy and Lactation Labeling Rule](#) (the PLLR amended the PLR regulations). For applications with labeling in non-PLR “old” format, see 21 CFR [201.56\(e\)](#) and [201.80](#).

³ See [PLR Requirements for PI](#) website for PLR labeling guidances.

20 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VIRGINIA E KWITKOWSKI
09/09/2019 10:17:54 AM

Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA 213137
Submission Number	0003
Submission Date	6/26/2019
Date Consult Received	7/2/2019
Clinical Division	DHP

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 under IND-121691 dated 02/23/2019 in DARRTS ([link](#))
- Sponsor's clinical study report # GBT440-0115 (SN0003; [link](#))
- Investigator's brochure ver. 6.0 (SN0010; [link](#))
- Sponsor's cardiac safety report (SN0003; [link](#))
- Sponsor's propose product label (SN0007; [link](#)); and
- Highlights of clinical pharmacology and cardiac safety (SN0003; [link](#)).

1 SUMMARY

No significant QTc prolongation effect of voxelotor 1500 mg once daily was detected in this QT assessment.

The effect of voxelotor was evaluated in thorough QT study in healthy adult subjects (Study # GBT440-0115). The highest dose evaluated was 1500 mg (once daily for 14 days), which covers the supra-therapeutic exposure scenario (section 3.1). The data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that voxelotor is associated with significant QTc prolonging effect (refer to section 4.5) – see Table 1 for overall results. The findings of this analysis are further supported by the available nonclinical data (section 3.1) and central tendency analysis (section 4.3) and categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs on $\Delta\Delta\text{QTcF}$ (FDA Analysis)

ECG parameter	Treatment	Treatment Duration	Concentration (ng/mL)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
QTc	Voxelotor 1500 mg once daily	Day 1	2278.9	3.3	(1.5, 5.1)
QTc	Voxelotor 1500 mg once daily	Day 4	15430.2	4.6	(2.4, 6.7)
QTc	Voxelotor 1500 mg once daily	Day 14	21839.5	5.2	(2.5, 7.8)

* orally administered as once daily dose for 14 days

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 to the label submitted to SDN008 (link) from the QT-IRT. Our changes are highlighted ([addition](#), [deletion](#)). Each section is followed by a rationale for the changes made. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At plasma concentrations approximately (b) (4) 2-fold above therapeutic concentrations, (b) (4) does not prolong QT interval to any clinically relevant extent.

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

The sponsor is developing voxelotor for the treatment of sickle cell disease in adult (b) (4) patients as monotherapy or in combination with hydroxyurea. Voxelotor (b) (4) MW: 337.4 Da) is a hemoglobin S polymerization inhibitor that binds to hemoglobin S and exhibits its dose-dependent inhibition by increasing the affinity of Hb for oxygen. The product is formulated as immediate-release film-coated tablet (500 mg). The maximum proposed therapeutic dose is 1500 mg to be administered orally once daily (with or without food). At steady-state, peak concentration of 12.6 (CV: 24.8%) µg/mL are expected with 1500 mg once daily dosing in subjects with sickle cell disease (Pop-PK Report).

Following oral absorption, voxelotor is predominantly distributed into red blood cells to its preferential binding to hemoglobin (blood-to-plasma ratio is 15:1). Since hemoglobin and hematocrit values are lower in patients, exposures of voxelotor in subjects with sickle cell disease are typically lower (~2-fold) than those observed in healthy subjects at the same dose (Study # GBT440-031). Lower hemoglobin, faster RBC turnover, lower albumin levels can affect the blood-to-plasma partitioning and elimination half-life. Voxelotor is extensively metabolized and excreted via urine (35%; <1% unchanged) and feces (63%; 33% unchanged) (Study # GBT440-002). Higher exposures (45% increase in C_{max}; 93% increase in AUC) were observed in subjects with severe hepatic impairment (Study # GBT440-0112). It exhibits positive food effect (~95% increase in C_{max} with a high-fat meal; Study # GBT440-005). Higher exposures were also observed in certain genotypes (HbSC; ~40% higher C_{max,ss}). The highest single dose studied in healthy subjects was 2800 mg (Study # GBT440-001) and the highest multiple dose studied in healthy subjects

was 1800 mg (Study GBT440-0115; $C_{max,ss}$: 26.3 $\mu\text{g/mL}$). Considering hERG IC_{50} is $>10 \mu\text{M}$, the peak concentrations of 12.6 $\mu\text{g/mL}$ (99 to 99.8% binding) offers 26 to 133-fold margin.

Previously, the QT-IRT reviewed the sponsor's substitution request for thorough QT study under IND-121691. The sponsor submitted concentration-QT analysis based on PK/EGC data collected in their Phase-1 single ascending dose (100-2800 mg) /multiple ascending dose study (GBT440-001). However, the exposure margin available from this study was not found to be adequate to waive the requirements positive control for assay sensitivity. It was recommended that the sponsor conducts dedicated thorough QT study (Dt: 08/03/2016).

The sponsor proposed a 2-Part study assessing safety of higher doses (1200, 1500, and 1800 mg) using multiple ascending doses in Part A. Followed by the Part B, as thorough QT study in healthy subjects. The QT-IRT reviewed the sponsor's study protocol for this dedicated QT study. In general, the study design was acceptable to the QT-IRT and the response to the sponsor included general advice to the sponsor such as adequacy of dose selection, exposure-response modeling, and data submission (Dt: 03/09/2018).

Subsequently, the sponsor provided revised protocol with altered PK sampling scheme as the steady levels were expected to reach earlier at higher dose levels than previously planned. The protocol also included clarification on the ECG assessment in Part B (Day 4 instead of Day 10). These changes proposed by the sponsor were acceptable to the QT-IRT (Dt: 07/20/2018).

Recently, the sponsor completed this multiple-dose, randomized, double-blind, placebo-controlled, active-comparator, parallel study using a multiple ascending dose run-in phase (Study # GBT440-0115). In this 2-Part study, the sponsor evaluated safety of voxelotor in three sequential cohorts (1200, 1500, and 1800 mg or matching placebo; once daily for 14 days) using double-blind study in healthy subjects ($n=24$; 6 active + 2 placebo per dose level). On Days 1 through 12, study drug was administered following a standardized breakfast. On Days 13 and 14, study drug was administered following a high-fat breakfast. The sponsor decided to utilize 1500 mg as suprathapeutic dose for Part B.

Part B was a double-blind, randomized, placebo and positive-controlled, double-dummy, parallel group, multiple dose thorough QT study with a nested crossover comparison between moxifloxacin and placebo. Subjects ($n=72$) were randomized (2:1:1) to receive voxelotor 1500 mg once daily for 14 days (Cohort 1: voxelotor), or moxifloxacin placebo and 400 mg oral moxifloxacin in a nested cross-over manner (2A: moxifloxacin on Day 1 and placebo on Day 15; or 2B: placebo on Day 1 and moxifloxacin on Day 15). Study drug was administered following an overnight fast on Days 1 and 15, with a standardized breakfast on Days 2 through 12, and a high-fat breakfast on Days 13 and 14.

PK samples were collected on Days 1, 4, and 14 (predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose) for determination of voxelotor; and Day 1 and Day 15 (predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose) for determination of moxifloxacin. Time-matched ECG were extracted on Days -1, 1, 4, and 14 at the following times: predose (-1), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. PK and ECG assessments were performed at Days 4 and 14 in Part B to correspond to voxelotor plasma therapeutic

(approximately 12 µg/mL) and suprathereapeutic (approximately 24 µg/mL) concentrations, respectively.

3.2 SPONSOR'S RESULTS

3.2.1 Central Tendency Analysis

The statistical reviewer used a different statistical model in central tendency analysis from the sponsor. The trend of time-profile of QTcF in the reviewer's analysis is similar to sponsor. The largest upper limit of 90% CI of $\Delta\Delta$ QTcF exceeded 10 ms on Day 4 and Day 14. However, the study, which has 36 subjects on each of two cohorts, was designed primarily for concentration QTc analysis not central tendency analysis. 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- $\Delta\Delta$ QTc slope and the lower bound of the 90% CI of the predicted effect at geomean C_{max} above 5 ms. Assay sensitivity was also demonstrated in the by-time point analysis with mean $\Delta\Delta$ QTcF on moxifloxacin of 14.9, 15.3, and 14.2 ms at 2, 3, and 4 h, respectively, with all lower bounds of the 2-sided 90% CI above 5 ms at these time points.

The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.5.1 for additional details.

3.2.1.1.1 QT bias assessment

No QT bias assessment was conducted by the sponsor.

3.2.2 Categorical Analysis

None of the subjects had absolute QTcF > 450 ms or a change from baseline in QTcF >60 ms. The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.4 for additional details.

3.2.3 Safety Analysis

There were no deaths or SAEs reported. Headache, diarrhea, and nausea were the most commonly reported AEs and were Grades 1 to 2 in severity.

In Part A, 2 subjects (1 subject receiving voxelotor 1200 mg and 1 subject receiving voxelotor 1800 mg) were discontinued from study drug administration and the study due to nonserious TEAEs of pollakiuria and acute sinusitis.

In Part B, 3 subjects receiving voxelotor 1500 mg were discontinued from study drug administration and the study due to nonserious TEAEs of rash maculo-papular, rash and vomiting.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study. One subject receiving single dose voxelotor 1500 mg in Part A experienced syncope (grade 2).*

3.2.4 Exposure-Response Analysis

The sponsor performed PK/PD analysis to explore the relationship between plasma concentration of voxelotor and Δ QTcF (change from baseline in QTcF) using a linear mixed-effects approach.

The sponsor's model included Δ QTcF as dependent variable, time-matched plasma concentration as a continuous covariate, treatment and time as categorical factors, and a random intercept and slope per subject. The slope (i.e., the regression parameter for the concentration of voxelotor) and the treatment effect-specific intercept (defined as the difference between active and placebo) were estimated together with 2-sided 90% CI.

For the assessment of the ECG effect of voxelotor versus placebo, the time term incorporated into the models (both by-time point analysis and concentration-response analysis [or assay sensitivity]) included the single pre-dose time point and all post-dose time points on Days 10 and 14, and Days 1 and 15 for active versus placebo and moxifloxacin versus placebo, respectively. The predicted effect and its 2-sided 90% CI for placebo corrected change from baseline ($\Delta\Delta$)QTcF (i.e., the product with the slope estimate + treatment effect-specific intercept) at geometric mean peak concentrations were obtained.

The sponsor's analysis indicated dose- or concentration-dependent effect of voxelotor on $\Delta\Delta$ QTcF on Days 4 and 14. The sponsor's model predicted $\Delta\Delta$ QTcF for the peak voxelotor concentrations on Day 4 (geomean: 15254.3 ng/mL; 90%CI: 14076, 16532; corresponds to therapeutic concentrations) was 3.86 (90%CI: 1.43, 6.29) ms and predicted $\Delta\Delta$ QTcF for the peak voxelotor concentrations on Day 14 (geomean: 21508 ng/mL; 90%CI: 20081, 23036; corresponds to supra-therapeutic concentrations) was 4.53 (90%CI: 1.61, 7.45) ms. The sponsor analysis indicates that QT effects ($\Delta\Delta$ QTcF) above 10 ms can be excluded at voxelotor plasma concentration of $\leq 30,000$ ng/mL.

The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.5 and 4.3.1.1 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 (i.e., mean < 10 bpm) were observed (see Sections 4.3.2).

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

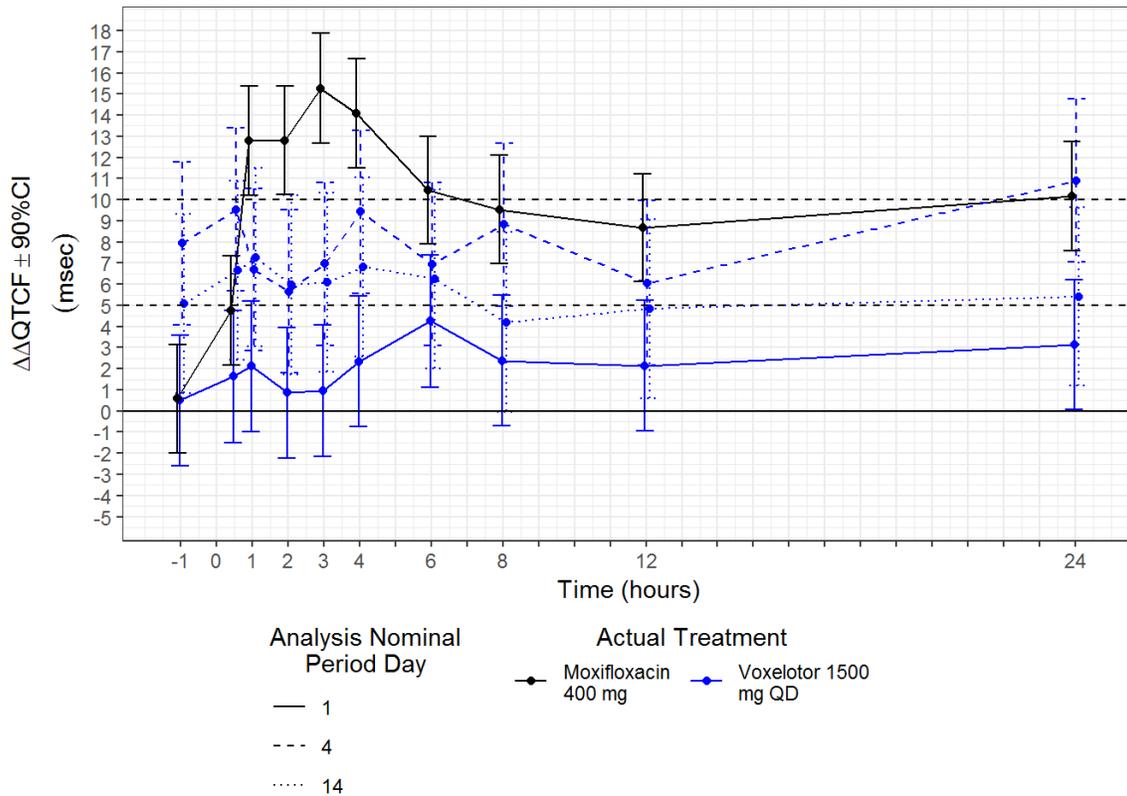
4.3 CENTRAL TENDENCY ANALYSIS

4.3.1 QTc

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes time, actual treatment, time-by-actual treatment interaction as fixed effects. Baseline values are also included in the model as a covariate.

The following figure displays the time profile of $\Delta\Delta$ QTcF for different treatment groups. There were 36 subjects received voxelotor at Day 1 (1 drop-out at Day 4; 3 drop-outs at Day 14), and there were 36 subjects received Moxifloxacin 400 mg.

Figure 1: Mean and 90% CI $\Delta\Delta$ QTcF Time Course (unadjusted CIs).

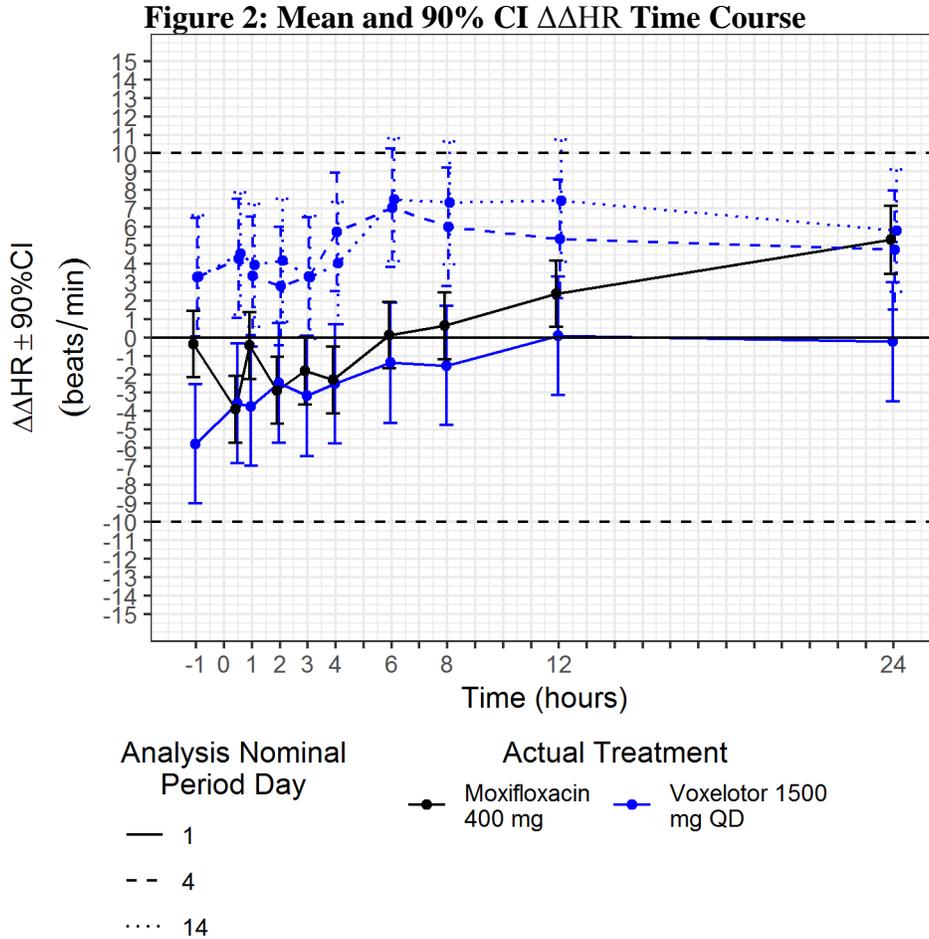


4.3.1.1 Assay sensitivity

The statistical reviewer used the linear mixed-effects model described in section 4.3.1 with sequence and period as additional fixed effects to analyze moxifloxacin and placebo data. The results are presented in Figure 1. The largest lower bound of the unadjusted 90% confidence interval is 12.7 ms for drug moxifloxacin 400 mg. By considering Bonferroni multiple endpoint adjustment, the largest lower bound is 11.7 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study. The time profile of moxifloxacin is consistent with ascending, peak, and descending phase of historical moxifloxacin profile. Overall, assay sensitivity was demonstrated in this study.

4.3.2 HR

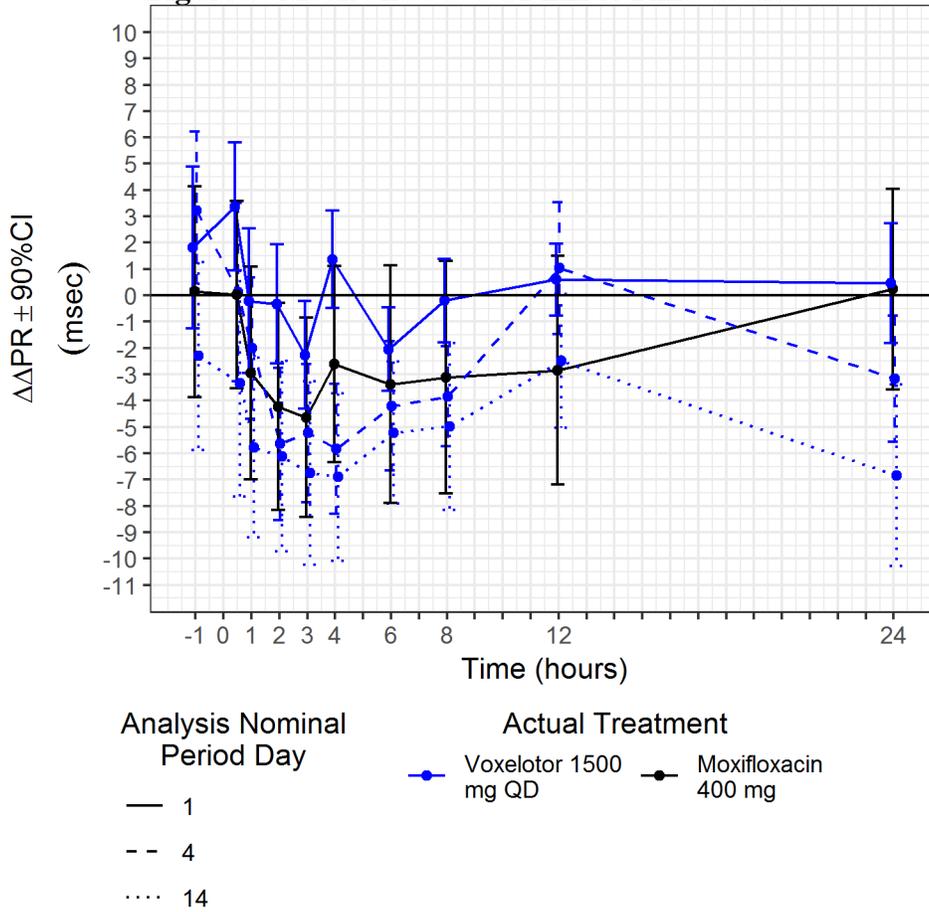
The same statistical analysis was performed based on HR (Figure 2). The largest upper limits of 90% CI for the HR mean differences between voxelotor 1500 mg QD and placebo and placebo at Day 1, 4, and 14 are 3.3 bpm, 10.3 bpm and 10.8 bpm, respectively.



4.3.3 PR

The 90% CIs for PR interval are calculated using descriptive approach (Figure 3). Since the structure of observed PR intervals varies over time, the descriptive approach could yield more robust results. The largest upper limits of 90% CI for the PR mean differences between voxelotor 1500 mg QD and placebo (assuming mean PR after receiving placebo is fixed) at Day 1, 4, and 14 are 5.8 ms, 6.2 ms and 1.3 ms, respectively.

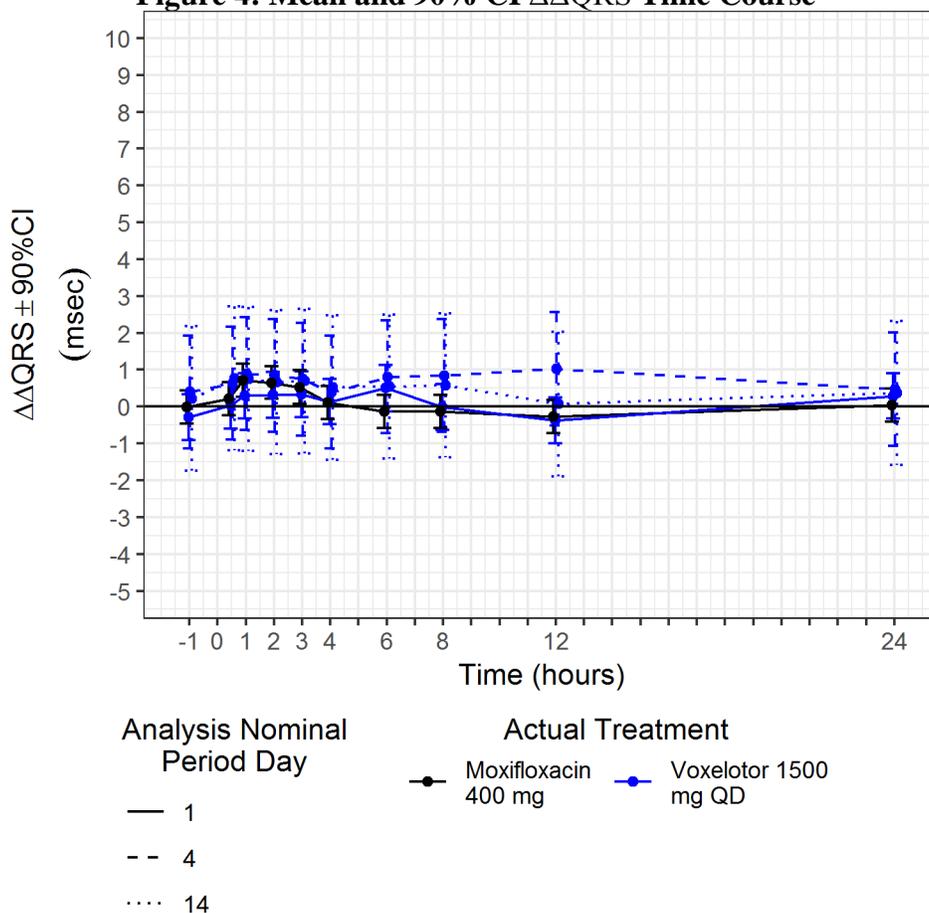
Figure 3: Mean and 90% CI $\Delta\Delta$ PR Time Course



4.3.4 QRS

The same statistical analysis was performed based on QRS interval (Figure 4). The largest upper limits of 90% CI for the QRS mean differences between voxelotor 1500 mg QD and placebo and placebo at Day 1, 4, and 14 are 1.1 ms, 2.6 ms and 2.7 ms, respectively.

Figure 4: Mean and 90% CI $\Delta\Delta$ QRS Time Course



4.4 CATEGORICAL ANALYSIS

4.4.1 QTc

No subject's QTcF was above 450 ms. No subject's change from baseline was above 60 ms.

4.4.2 PR

There are no subjects who experienced PR interval greater than 220 ms in voxelotor 1500 mg QD groups on Day 1, 4 and 14.

4.4.3 QRS

There are no subjects who experienced QRS interval greater than 120 ms and >25% increase from baseline.

4.4.4 HR

The outlier analysis results for HR are presented in Table 2. One subject receiving placebo experienced HR>100 at day 4. The subject had baseline HR<100.

Table 2: Categorical Analysis for HR

Analysis Nominal Period Day	Actual Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
1.000	Voxelotor 1500 mg QD	36	343	36 (100.0%)	343 (100.0%)	0 (0%)	0 (0%)
1.000	Placebo	18	178	18 (100.0%)	178 (100.0%)	0 (0%)	0 (0%)
4.000	Voxelotor 1500 mg QD	35	337	35 (100.0%)	337 (100.0%)	0 (0%)	0 (0%)
4.000	Placebo	36	353	35 (97.2%)	352 (99.7%)	1 (2.8%)	1 (0.3%)
14.000	Voxelotor 1500 mg QD	32	306	32 (100.0%)	306 (100.0%)	0 (0%)	0 (0%)
14.000	Placebo	36	357	36 (100.0%)	357 (100.0%)	0 (0%)	0 (0%)

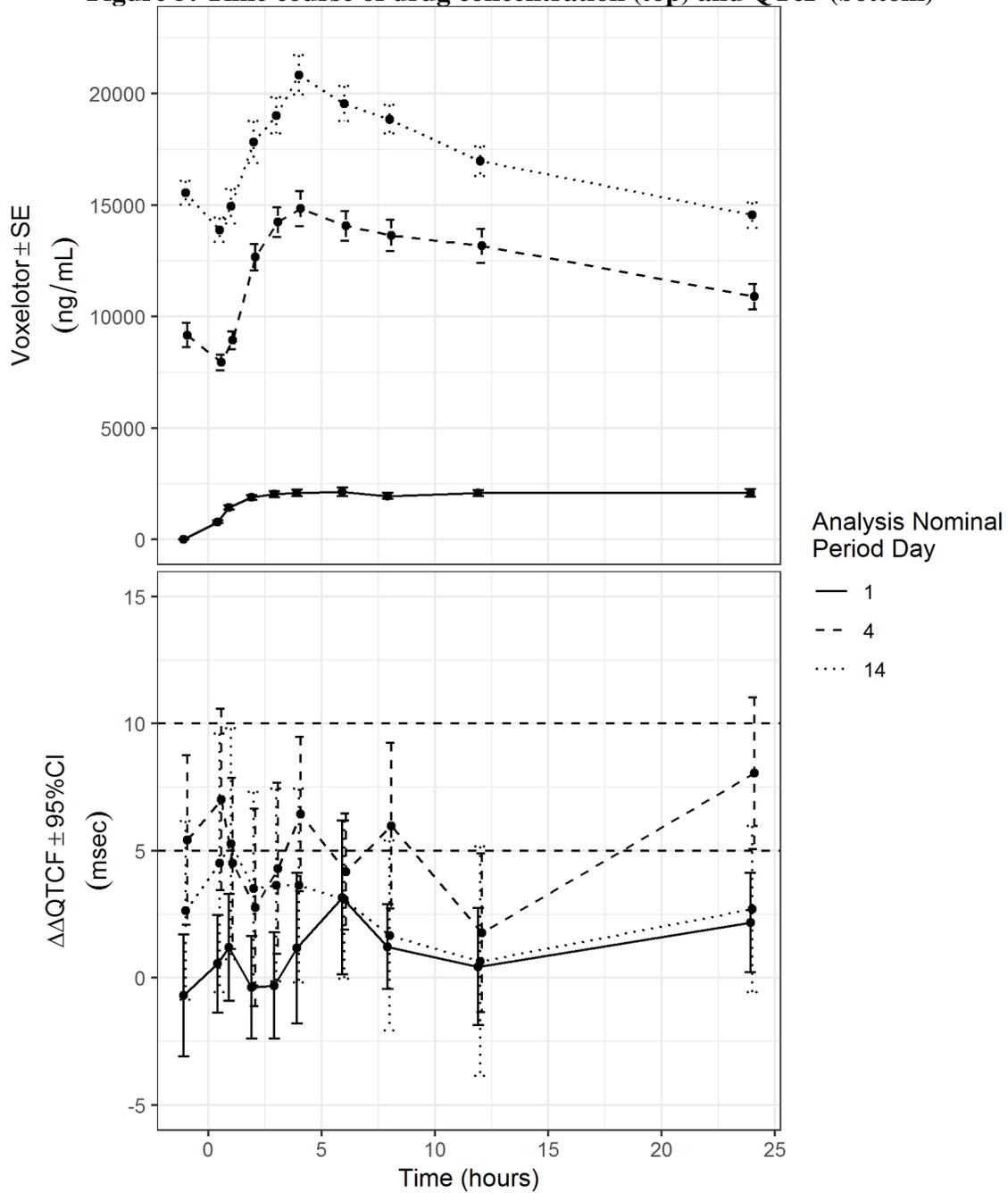
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between Δ QTcF and voxelotor concentration.

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.

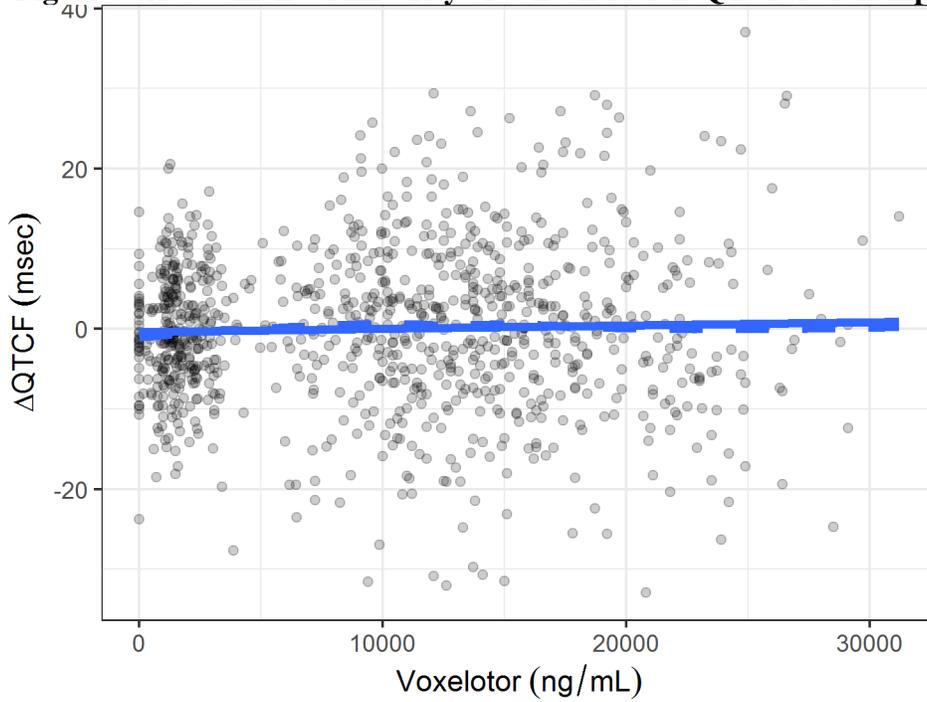
An evaluation of the time-course of drug concentration and changes in Δ QTcF is shown in Figure 5, which shows an absence of significant hysteresis. The maximum change in heart rate is ~10 bpm on Day 4 (corresponds to therapeutic concentrations) and ~11 bpm on Day 14 (corresponds to suprathreshold concentrations) (4.3.2).

Figure 5: Time course of drug concentration (top) and QTcF (bottom)



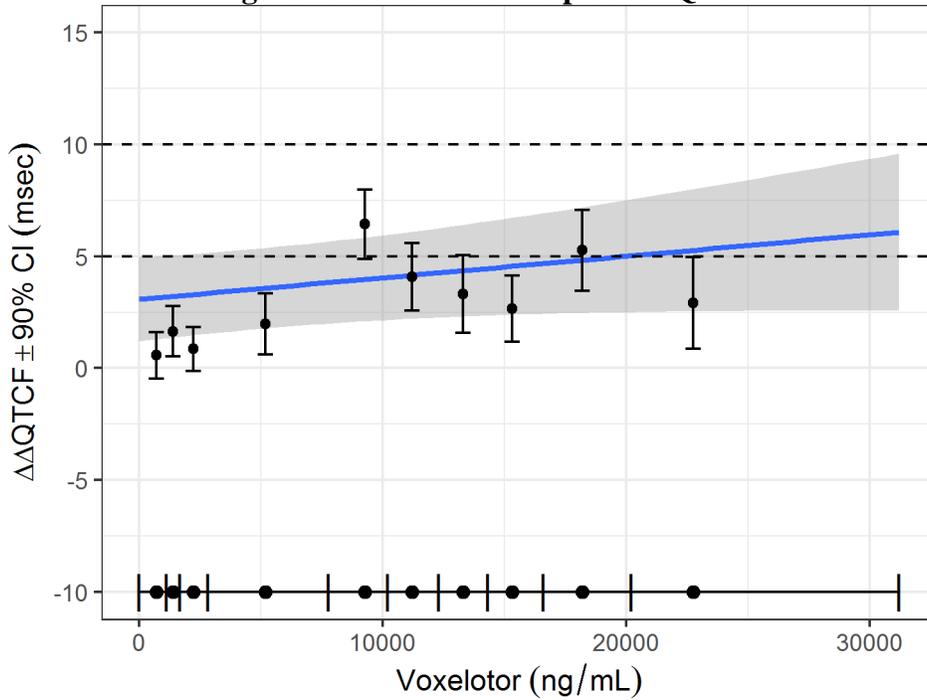
After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between voxelotor concentration and $\Delta\Delta\text{QTcF}$ was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between voxelotor concentration and $\Delta\Delta\text{QTcF}$ and supports the use of a linear model.

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 provide in Table 1.

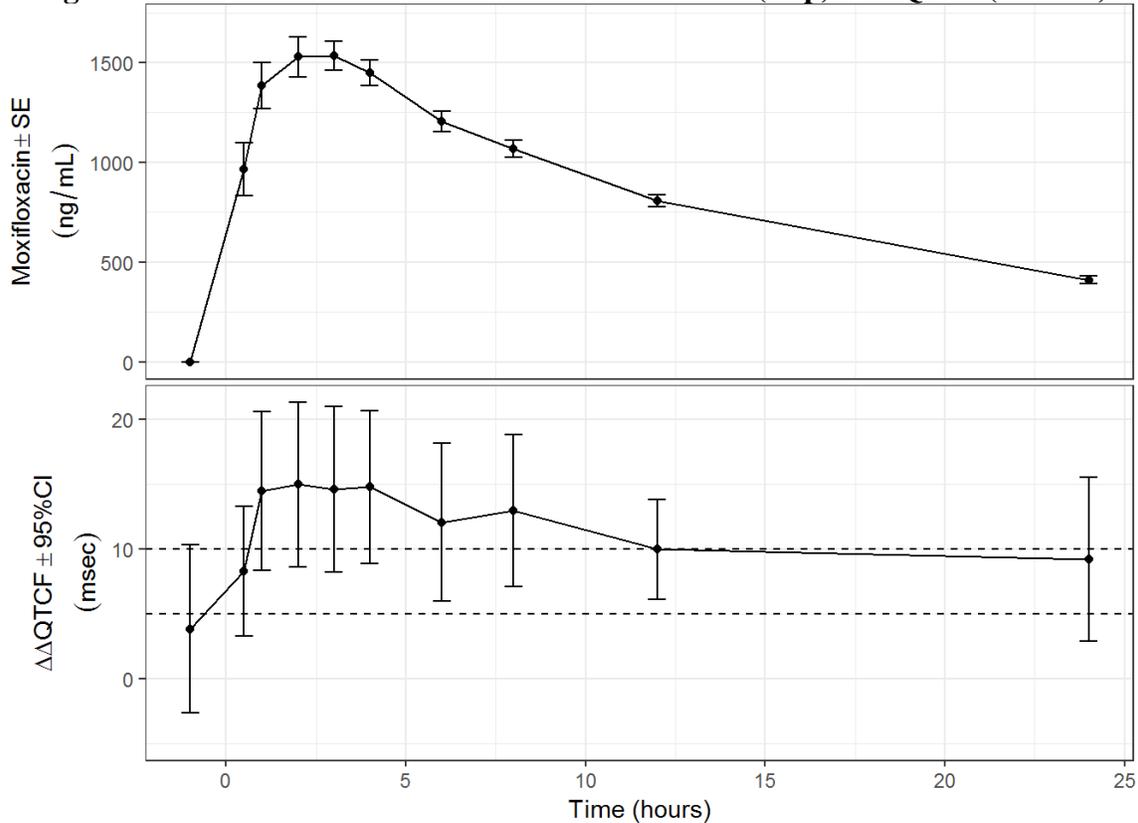
Figure 7: Goodness-of-fit plot for QTc



4.5.1 Assay sensitivity

To demonstrate assay sensitivity, the sponsor included oral moxifloxacin 400 mg as a positive control to detect small increases from baseline for QTcF in this study. The PK profile in the moxifloxacin group are generally consistent with the ascending, peak, and descending phases of historical data (Figure 8).

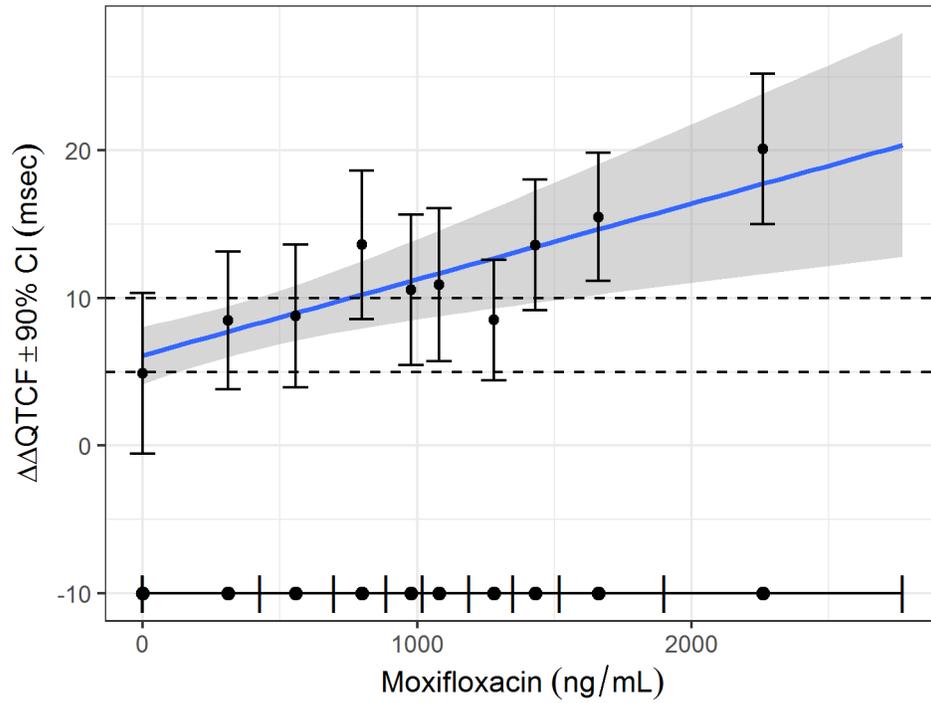
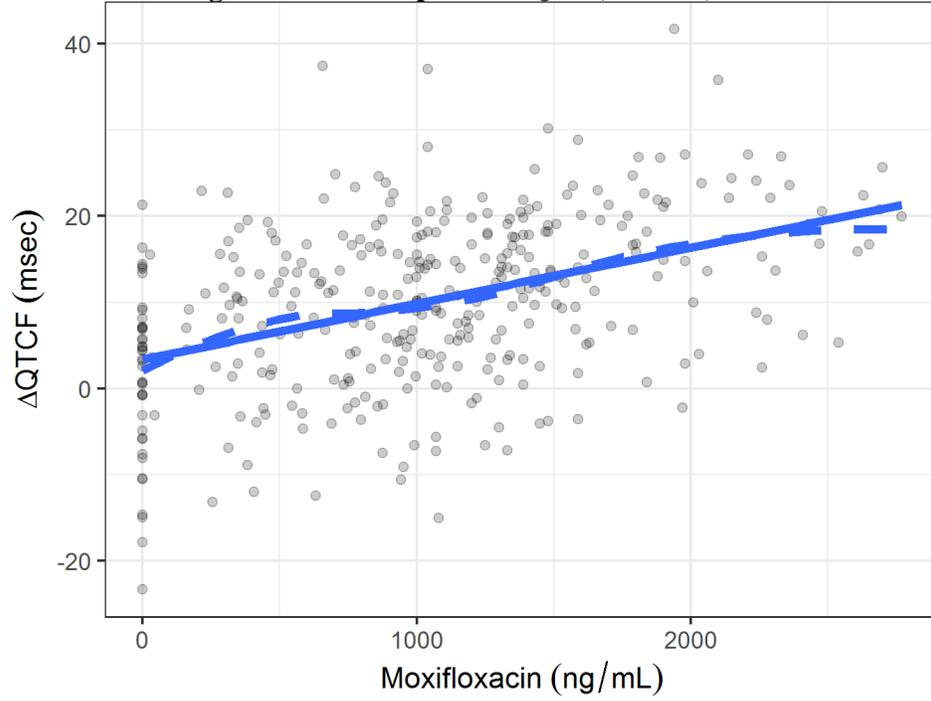
Figure 8: Time course of moxifloxacin concentration (Top) and QTcF (Bottom)



Concentration-response analysis of moxifloxacin data indicated a positive slope in the relationship between ΔQTcF and the plasma concentration of moxifloxacin (Figure 9). The lower limit of the two-sided 90% confidence interval at the observed mean peak concentrations of moxifloxacin is above 5 ms. Therefore, assay sensitivity is established.

Assay sensitivity was also established using central tendency analysis. Please see section 4.3.1.1 for additional details.

Figure 9: Assessment of linearity of concentration-QTc relationship (Top) and goodness-of-fit plot for QTc (Bottom) of moxifloxacin



This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GIRISH K BENDE
08/23/2019 10:12:58 AM

YU YI HSU
08/23/2019 10:15:30 AM

DEVI KOZELI on behalf of DALONG HUANG
08/23/2019 11:22:07 AM
Signing on behalf of Patrick as he is on leave

MOHAMMAD A RAHMAN
08/23/2019 02:06:37 PM

MICHAEL Y LI
08/23/2019 03:23:07 PM

LARS JOHANNESSEN
08/23/2019 03:36:23 PM

CHRISTINE E GARNETT
08/25/2019 09:16:13 PM