CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213756Orig1s000

OTHER REVIEW(S)

Clinical Inspection Summary

Date	March 30, 2020
From	Michele Fedowitz, M.D. Yang-Min (Max) Ning, MD, PhD. Kassa Ayalew, M.D., M.P.H. Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Denise Casey, M.D. Suzanne Demko, P.A.-C. Sharon Sickafuse, RPM Harpreet Singh, M.D. Division of Oncology 2 (DO2) Office of Oncologic Diseases (OOD)
NDA #	213756
Applicant	AstraZeneca Pharmaceuticals LP
Drug	Selumetinib
NME (Yes/No)	Yes
Therapeutic Classification	Inhibitor of mitogen-activated protein kinase 1
Proposed Indication	For the treatment of pediatric patients, aged 3 years and above, with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas
Consultation Request Date	October 4, 2019
Summary Goal Date	April 1, 2020
Action Goal Date	May 13, 2020
PDUFA Date	May 13, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from an open-label, single-arm trial (the SPRINT study, NCT01362803) were submitted to the Agency in support of a New Drug Application (NDA) for selumetinib for the above proposed indication. Two clinical investigators, Drs. Michael Fisher (Site PA076) and Brigitte Widemann (Site NCI-POB), and the study sponsor were selected for clinical inspections.

The inspections verified the submitted clinical data with source records at these two clinical investigator sites. The study sponsor inspection found that this trial was properly conducted as per the protocol, with no significant regulatory violations identified.

Based on the results of these inspections, the data generated by the two clinical investigator sites which were submitted by the study sponsor appear reliable and are acceptable in support of this NDA for the proposed indication.

II. BACKGROUND

AstraZeneca Pharmaceuticals LP, the Applicant for this NDA, seeks regular approval of selumetinib for use in pediatric patients of ≥3 years who have symptomatic and inoperable neurofibromatosis type 1 (NF1)-related plexiform neurofibromas (PN). To support the proposed indication, the Applicant submitted clinical data from Stratum 1 of the SPRINT study (NCT01362803) titled "A Phase I/II Study of the Mitogen Activated Protein Kinase 1 Inhibitor Selumetinib in Children with Neurofibromatosis Type 1 and Inoperable Plexiform Neurofibromas". The sponsor for this study is Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI).

The SPRINT study was an open-label, single-arm, multi-center trial of selumetinib in subjects with NF-1 and inoperable PN. Inoperable PN was defined as a PN that could not be surgically completely resected without risk for substantial morbidity due to proximity to vital structures, invasiveness, or high vascularity of the PN. The study had two strata: Stratum 1 was designed to enroll subjects who already had PN-related morbidity (e.g., disfigurement, motor dysfunction, pain, visual impairment, etc.) and Stratum 2 to enroll subjects who had no significant clinical morbidity but with potential for significant clinical PN-related morbidity at the time of enrolment. Subjects (≥ 2 and ≤18 years) were required to be able to swallow intact capsules. Note that the current application is based on the clinical data of Stratum 1.

The primary endpoint of this study was the confirmed partial or complete response rate [objective response rate (ORR)] in subjects with PN-related morbidity using centrally read 3D magnetic resonance imaging (MRI) volumetric analysis.

Study subjects were to be given selumetinib at 25 mg/m^2 (BSA), twice daily on a continuous dosing schedule (a cycle of 28 days). Study treatment was to be discontinued if subjects were no longer deriving clinical benefit, experienced unacceptable toxicity, PN progression, or at the discretion of the investigator. Responses in target PN lesions were assessed with volumetric MRI analysis at baseline and prior to initiation of Cycles 5, 9, 13, 17, 21, 25, and thereafter every 6 cycles. All volumetric MRI scans were sent to the NCI Pediatric Oncology Branch (NCI-POB) for a central evaluation. Responses were evaluated and determined per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria.

From 8/12/2015 through 8/22/2016, the study enrolled 50 subjects into Stratum 1 from four study sites in the U.S. only. Fifty percent of subjects were from the site NCI-POB. The data cutoff date for the analyses reported in this NDA was June 29, 2018.

Two participating clinical investigators (CI), Drs. Michael Fisher (Site PA076) and Brigitte Wideman (Site NCI-POB) were selected for inspection since the two investigator sites enrolled a relatively high number of subjects among the four study sites. The NCI-POB site was associated with the highest response rate of 78% in Stratum 1. CTEP/NCI was selected for

clinical inspection because it served as the study sponsor and has held the trial master file for the current application. The previous inspection of CTEP, conducted in 2014, reported regulatory violations including "Failure to obtain signed 1572" and "Failure to maintain records of disclosable financial interests paid to investigators by sponsors".

III. RESULTS

1. **Dr. Michael Fisher (CI Site PA076)**
   Colket Translational Research Building -10th Floor
   3501 Civic Center Blvd
   Philadelphia, PA 19104

   This clinical investigator was inspected on December 2-5, 2019 as a data audit for the SPRINT study. This was the first FDA inspection for this investigator.

   The investigator site screened 11 subjects and enrolled 10 into Stratum 1 of this study. As of the data cutoff date, eight subjects remained on study treatment and two subjects were discontinued from study treatment due to no tumor response (Subject (b) (6)) and adverse event (Subject (b) (6) who developed acute renal injury). At the time of the inspection, 7 subjects continued receiving study treatment, with one subject (Subject (b) (6)) discontinued on (b) (6) (after the data cutoff date) at the investigator's discretion.

   All subjects' source records were reviewed and compared with the Applicant's submitted data listings for the site. The reviewed records included the informed consents signed by the parent/guardian, eligibility criteria, progress notes, vital signs, adverse events, concomitant medication logs, volumetric MRI scans performed and reports, echocardiograms (ECHO), electrocardiograms (ECGs), laboratory reports, and study-related questionnaires and dosing diaries. The inspection also reviewed the documents related to the conduct and oversight of this study at the site, including the Investigator's Brochure, IRB's approval of the study protocol/amendments and informed consent form, training records, signed Form FDA 1572s, financial disclosures, conflict of interest statements, enrollment log, investigational drug accountability, data entry into electronic case report forms, study monitoring log, deidentification of subjects' personal information before the electronic submission of MRI scans to the central NCI review, and study record retentions.

   The inspection found no regulatory violations at the site. The submitted data listings were verifiable with the reviewed source records and there were no significant discrepancies identified. There was no observation of underreporting of adverse events. For Subject (b) (6), a data point discrepancy was noted at Cycle 25 (dated (b) (6)) in the questionnaire "Plexiform Neurofibroma Symptom Checklist Phase 2." The line listing answer for Number 10 was "a lot" and the source document answer was "some". This discrepancy was investigated by the

site during the inspection and found to be likely attributed to a clerical error.

No Form FDA 483 was issued to Dr. Fisher at the conclusion of the inspection.

2. Dr. Brigitte Widemann (CI Site NCI-POB)

National Cancer Institute
Pediatric Oncology Branch
(NCI-POB)
10 Center Drive, Room 1-3750
Bethesda, MD 20892-1104

This investigator was inspected from October 28 through November 1, 2019 as a data audit for the SPRINT study. This was the first FDA clinical inspection of Dr. Widemann.

This investigator site screened 36 patients and enrolled 27 for Stratum 1 of the study. As of the data cutoff date, 6/29/2018, 20 subjects remained on study treatment. Seven subjects were discontinued from study treatment, including two subjects ((b) (6) and (b) (6)) discontinued due to adverse events, two subjects ((b) (6) and (b) (6)) due to disease progression, one ((b) (6)) due to a protocol violation, one ((b) (6)) discontinued at the investigator's discretion, and one ((b) (6)) secondary to completion of study treatment. Four subjects had discontinued treatment since the data cutoff date: one ((b) (6)) due to intercurrent illness, two ((b) (6) and (b) (6)) due to the investigator's decision, and one ((b) (6)) due to disease progression.

Subjects' source records were reviewed and compared with the Applicant's submitted data listings for the site. All subject records were reviewed for the informed consents signed by the parent/guardian and eligibility criteria. The reviewed source records included electronic progress notes and orders, MRI scans, primary endpoint source data, and adverse event reports.

The inspection also reviewed the documents related to the conduct and oversight of this study at the site, including the IRB's approval of the study protocol/amendments and informed consent form, training records, signed Form FDA 1572s, financial disclosures, conflict of interest statements, subject screening and enrollment log, study monitoring log, investigational drug accountability records, and investigational drug return form.

The primary endpoint data was verifiable with source records and there was no underreporting of adverse events. At the close of this inspection, no Form FDA-483 was issued to Dr. Widemann.

Key discussion items included: 1) Protocol deviations involved 2 subjects whose consent was not obtained properly, with child's assent but not signed by the parent; 2) Inadequate documentation of study drug accountability; 3) Incomplete financial disclosures of a key sub-investigator during her participation in the study.

Reviewer's Comments: These discussion items did not appear to alter the reported clinical data from this site, nor put study subjects at undue risk.

3. Cancer Therapy Evaluation Program (CTEP) at NCI (Study Sponsor)
National Cancer Institute
9000 Rockville Pike
Bethesda, MD 20892

This study sponsor was inspected on January 6 through January 10, 2020 to evaluate its conduct and management of the SPRINT study. This was the third FDA inspection of CTEP. The previous inspections were conducted on 10/24/16 – 11/15/16 and 6/16/14 - 7/17/14, respectively. For each inspection, the final compliance classification was Voluntary Action Indicated (VAI).

Source documents were reviewed, including the NCI/CTEP organizational chart, standard operating procedures, test article accountability records, site training program plan and training records, form FDA-1572 and financial disclosure forms, the study site audit/monitoring plan and site audit/monitoring plans and report, and review of safety plan and monitoring.

At the close of the inspection, no form FDA-483 was issued. Two key items discussed with the CTEP management during and at the closing meeting included:

1. Documentation of IND safety reports not being provided in writing to 3 of the 4 clinical investigator sites. In response to this finding, CTEP provided a memo (Exhibit #60 of the inspection) showing that the adverse event (Grade 4 creatinine increased and hyperuricemia) was communicated to the participating sites. The event which occurred on November 9, 2016 was communicated and updated during routine safety conference calls held on December 7, 2016, January 4, 2017, and February 1, 2017 (when the subject came off treatment). The memo also showed that the adverse event was reported to FDA Division of Oncology 2 on January 26, 2017.

2. Central documentation was not readily available at the time of inspection to clearly show that the investigator's brochure was electronically provided to all 4 CI sites prior to the study initiation. CTEP explained that access to the Investigator Brochure was kept on a password-protected site and access to this site was to be sent electronically to each investigator via email sent to investigators (Exhibit #61 of the inspection). These notification emails have been currently archived.

Reviewer's comments: The above discussion items do not appear to affect the reported data from the study sponsor. Of note, the investigator brochure that was documented and reviewed in the inspection of Dr. Fisher's site **(***CI Site PA076) at Children's Hospital of Philadelphia appears to support the CTEP's memo regarding the process of distributing Investigator's Brochure for the inspected study.*

{See appended electronic signature page}

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cc:

Central Doc. Rm. NDA 213756
Review Division /Division Director/
Review Division /Project Manager/
Review Division/Cross Discipline Team Lead/
Review Division/Clinical Reviewer/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Acting Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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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:	March 10, 2020
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 213756
Product Name and Strength:	Koselugo (selumetinib) Capsules, 10 mg and 25 mg
Applicant Name:	AstraZeneca Pharmaceuticals LP
OSE RCM #:	2019-1637-1
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on February 28, 2020 for Koselugo. Division of Oncology 2 (DO2) requested that we review the revised container labels for Koselugo (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Our review of the revised container labels found the Applicant implemented all of our recommendations. In addition, we note the Applicant has updated the "Manufactured for… by…" information that appears on the container labels. We have no additional recommendations at this time.

[a] Stewart J. Label and Labeling Review for Koselugo (NDA 213756). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 12. RCM No.: 2019-1637.

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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: February 27, 2020

To: Sharon Sickafuse, MS, Regulatory Project Manager, Division of Oncology 2 (DO2)

Stacy Shord, Associate Director for Labeling

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 TRADENAME (selumetinib) capsules, for oral use

NDA: 213756

In response to DO2's consult request dated September 17, 2019, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for the original NDA submission for selumetinib.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DO2 (Sharon Sickafuse) on February 13, 2020, 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 February 26, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 13, 2019, and our comments are provided below.

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

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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:	February 26, 2020
To:	Sharon Sickafuse **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Robert Nguyen, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TRADENAME (selumetinib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 213756
Applicant:	AstraZeneca Pharmaceuticals, LP

1 INTRODUCTION

On September 13, 2019, AstraZeneca Pharmaceuticals, LP submitted for the Agency's review a New Drug Application (NDA) 213756 for TRADENAME (selumetinib) capsules. The propsed indication is for the treatment of pediatric patients aged 3 years and above, with neurofibromatosis-1 (NF1) and symptomatic, inoperable plexiform neurofibroma (PN).

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 Oncology Products 2 (DOP2) on September 18, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (selumetinib) capsules.

2 MATERIAL REVIEWED

- Draft TRADENAME (selumetinib) capsules PPI received on September 13, 2019, and received by DMPP and OPDP on February 13, 2020.
- Draft TRADENAME (selumetinib) capsules Prescribing Information (PI) received on September 13, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 13, 2020.

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 APHont 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)

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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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:	February 12, 2020
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 213756
Product Name, Dosage Form, and Strength:	Koselugo (selumetinib) Capsules, 10 mg and 25 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	AstraZeneca Pharmaceuticals LP
FDA Received Date:	September 13, 2019 and December 4, 2019
OSE RCM #:	2019-1637
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

This review responds to a request from DOP2 to review the proposed container labels, Patient Information, and prescribing information (PI) submitted for Koselugo (selumetinib) Capsules for areas of vulnerability that may 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 or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container labels, Patient Information, and PI for Koselugo (selumetinib) to identify deficiencies that may lead to medication errors and other areas of improvement. We identified areas in the PI and container labels that can be modified to improve the clarity of the information presented.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Patient Information did not identify areas of vulnerability that may lead to medication errors. However, we conclude that the proposed PI and container label can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of the product. We provide recommendations for the division in Section 4.1 and recommendations for AstraZeneca Pharmaceuticals LP in Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. General
    a. Replace "TRADENAME" with the conditionally acceptable proprietary name "Koselugo" wherever it appears.
    b. We defer to OPQ for the determination of the established name and the correct strength expression.
    c. To ensure stability, the proposed Koselugo product should be dispensed in its original container with the desiccant. However, for dosage requiring multiple strengths (i.e., 35 mg and 45 mg), it will be necessary for pharmacies to dispense a quantity less than a full bottle (e.g., cash payers, vacation supply, or an emergency supply until patients can see the doctor for a new prescription). Further, hospital pharmacies may repackage Koselugo capsules into unit-dose blister packs because drugs are routinely dispensed in unit-doses in the usual hospital setting. We ask the Review Team to consider asking the Applicant to supply Koselugo in unit-dose blister packs to ensure the safe and effective use of this product. So as not hold up treatment options for oncology patients, Koselugo unit-dose blister packs may be introduced after approval of this NDA.
2. Dosage and Administration Section
    a. In Section 2.2 *Administration*, consider revising the statement "Do not take an additional dose…" to read "If vomiting occurs after Koselugo administration, do not take an additional dose, but continue with the next scheduled dose." to lead with the issue then the action.

4.2 RECOMMENDATIONS FOR ASTRAZENECA PHARMACEUTICALS LP

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Commercial Labels & Professional Sample Labels)

1. Replace "TRADENAME" with the conditionally acceptable proprietary name "Koselugo" wherever it appears.
2. As currently presented, the established name reads (b) (4) Revise the established name to read "(selumetinib)".
3. To reduce clutter on the principal display panel, remove the statement (b) (4)
4. Revise the statement (b) (4) to read "Recommended dosage: See Prescribing Information".

5. To reduce clutter on the side panel, remove the statement [redacted] (b) (4)

B. Commercial Container Labels

1. We note the expiration date format as shown by the placeholder is MMYYYY. Clarify if the expiration date format will be numerical characters only. To minimize confusion and reduce the risk for deteriorated drug medication errors, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends 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. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

C. Professional Sample Container Labels

1. Relocate the statement "Professional Sample-Not For Sale" to the principal display panel (PDP) (e.g., relocate to the PDP beneath the NDC number).
2. As currently presented, the format for the expiration date is not defined. See recommendation B2 above.
3. Consider providing a blank open space on the label so the provider of the drug sample can write or affix a label with the patient name and specific instructions for use.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Koselugo received on December 4, 2019 from AstraZeneca Pharmaceuticals LP.

Table 2. Relevant Product Information for Koselugo	
Initial Approval Date	N/A
Active Ingredient	selumetinib
Indication	For the treatment of pediatric patients aged 3 years and above, with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN).
Route of Administration	Oral
Dosage Form	Capsules
Strength	10 mg and 25 mg
Dose and Frequency	The recommended dose is 25 mg/m^2 taken orally twice daily, every 12 hours. For patients with moderate hepatic impairment, the recommended dose is 20 mg/m^2 orally twice daily. Take at least 2 hours before or at least 1 hour after a meal. Dosing is individualized based on BSA (mg/m2) and rounded to the nearest achievable 5 mg or 10 mg dose (up to a maximum single dose of 50 mg).
How Supplied	Bottles of 60 capsules.
Storage	Store at 25° C (77°F); excursions permitted to 15° to 30° C (59°F to 86°F).
Container Closure	75 mL, white, induction-sealed, HDPE bottles with (b) (4) closures

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Koselugo labels and labeling submitted by AstraZeneca Pharmaceuticals LP.

- Container labels received on September 13, 2019
- Professional Sample Container Labels received on September 13, 2019
- Prescribing Information (Image not shown) received on December 4, 2019, available from \\cdsesub1\evsprod\nda213756\0020\m1\us\annotated-draft-label.docx

- Patient Information (Image not shown) received on December 4, 2019, available from \\cdsesub1\evsprod\nda213756\0020\m1\us\annotated-draft-label-patient-information.docx

G.2 Label and Labeling Images

Commercial Configurations

Container Label- 10 mg; 60 count

(b) (4)

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

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Consultation Review

Submission	NDA 213756
Submission Number	001
Submission Date	7/26/2019
Date Consult Received	9/18/2019
Drug Name	Selumetinib
Indication	NF-1 related plexiform neurofibroma
Therapeutic dose	25 mg/m^2 of body surface area; twice daily
Clinical Division	DOP2

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 dated 9/18/2019 regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT review under IND (b) (4) dated 03/17/2014 in DARRTS (link);
- Sponsor's clinical study report # D1532C00071 (SN0001; link);
- Investigator's brochure Ed.19 under IND- (b) (4) (SN1027; link);
- Sponsor's propose product label (SN0004; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0004, Appendix B; link).

1 SUMMARY

No significant QTc prolongation effect of selumetinib was detected in this QT assessment.

The effect of selumetinib was evaluated in a thorough QT study (Study # D1532C00071). This was a Phase 1, double-blind, placebo- and positive-controlled, randomized, three-period, crossover study assessing the effects of single oral dose selumetinib (75 mg) on QTc interval compared to placebo in male healthy subjects (n=54). The highest dose that was evaluated was 75 mg single, which is the maximum tolerated dose and covers the maximum therapeutic exposure scenario (moderate hepatic impairment & drug interaction, section 3.1). The data were analyzed using by time analysis as the primary analysis, which did not suggest that selumetinib is associated with large mean increases in the QTc interval (refer to section 4.3) – see Table 1 for overall results.

The findings of this analysis are further supported by the available nonclinical data (sections 3.1.2), exposure-response analysis (section 4.5) and categorical analysis (section 4.4). For assay sensitivity, the sponsor included oral moxifloxacin 400 mg as a positive control. Assay sensitivity was established using the by-time analysis.

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

ECG parameter	Treatment	Time	ΔΔQTcF	90% CI
QTc	Selumetinib 75 mg	1.5 h	1.0	(-0.7 to 2.7)

For further details on the FDA analysis please see section 4.

At the proposed therapeutic dose of 25 mg/m^2 twice daily in pediatric patients (3 to ≤ 18 years old), the peak concentration of ~800 (%CV: 52) ng/mL (Racc: ~1.1-fold) are expected at the steady-state. The maximum tolerated dose is 25 mg/m^2 in pediatric population (75 mg b.i.d. in adults).

The peak concentrations are expected to be doubled in subjects with severe hepatic impairment (Cmax: 1.98-fold) compared to subjects with normal hepatic function. The sponsor proposes dose reduction (20 mg/m^2 twice daily) in patients with moderate hepatic impairment and it is not recommended for use in patients with severe hepatic impairment. Concomitant administration of selumetinib with CYP3A4 or CYP2C19 inhibitors is expected to result in increased selumetinib exposures (Cmax: ~1.25-fold). In the current study, the peak concentrations of ~1240 ng/mL and ~330 ng/mL were observed for selumetinib and its N-desmethyl metabolite, respectively.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to the QT-IRT (SN0004; link). 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

(b) (4)

At a dose 1.5 times the maximum recommended dose, <TRADENAME> does not prolong the 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

3.1.1 Clinical

AstraZeneca Pharmaceuticals is developing selumetinib (AZD6244, ARRY-142886, sulfate salt; MW: 555.76) for the treatment of pediatric patients aged 3 years and above, with neurofibromatosis type 1 and symptomatic, inoperable plexiform neurofibromas. Selumetinib is an allosteric inhibitor of mitogen activated protein kinase that is non-competitive with respect to adenosine triphosphate. N-desmethyl selumetinib (a pharmacologically active metabolite; ~7% of parent) was identified to be approximately 3- to 5-fold more active than the selumetinib parent compound. The amide metabolite is up to 50-fold less active than selumetinib. Dosing is individualized based on body surface area and rounded to the nearest achievable 5 mg or 10 mg dose (up to a maximum single dose of 50 mg). The proposed dose is 25 mg/m^2 of body surface area to be administered orally twice daily. The product is available as immediate-release capsule formulation containing 10 and 25 mg of selumetinib. At the proposed dose of 25 mg/m^2 twice daily in pediatric patients (3 to ≤ 18 years old), the peak concentration of ~800 (%CV: 52) ng/mL (Racc:1.1-fold) are expected at the steady-state. The maximum tolerated dose is 25 mg/m^2 in pediatrics (75 mg b.i.d. in adults).

The QT-IRT reviewed the QT assessment proposal previously (DARRTS: 03/17/2014). It was a Phase 1, double-blind, placebo- and positive-controlled, randomized, three-period, crossover study to assess the effects of single oral dose selumetinib (75 mg) on QTc interval compared to placebo, using moxifloxacin (400 mg Avelox; open-label) as a positive control using a double-dummy technique, in healthy male subjects (n=54) aged 18 to 45 years (Study # D1532C00071). The primary objective of this study was to assess the effect of a single dose of selumetinib (75 mg) on the change in time-matched QT interval corrected according to Fridericia's formula (QTcF) interval compared to placebo using by-time analysis.

Previously, the selected dose was found to be reasonable as there was no significant accumulation at 75 mg b.i.d. dosing. However, it was highlighted that the selected dose may not cover the worst-case scenario associated with intrinsic and extrinsic factors. Highest exposure scenario predicted to be subjects with hepatic impairment or concomitant potent CYP3A4 inhibitor. Concomitant administration of selumetinib with CYP3A4 or CYP2C19 inhibitors is expected to result in increased selumetinib exposures (Cmax: ~1.25-fold). In the current study, the peak concentrations of ~1240 ng/mL and ~330 ng/mL were observed for selumetinib and its N-desmethyl metabolite, respectively. The peak concentrations are expected to be doubled in subjects with severe hepatic impairment (Cmax: ~1.98-fold) compared to subjects with normal hepatic function. The sponsor

proposes dose reduction (20 mg/m^2 twice daily) in patients with moderate hepatic impairment and it is not recommended for use in patients with severe hepatic impairment.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to highlights of clinical pharmacology and cardiac safety.

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

Selumetinib 75 mg excluded the 10 msec threshold for ΔΔQTcF.

Reviewer's comment: *FDA reviewer's analysis results for ΔΔQTcF, ΔΔHR, ΔΔPR, and ΔΔQRS are similar to the sponsor's results.*

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm.

Reviewer's comment*: Both FDA reviewer's analysis and sponsor's analysis show that the assay sensitivity was established by the moxifloxacin arm.*

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the FDA reviewer's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline, HR (<45 or >100 bpm), PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline).

Reviewer's comment*: Sponsor's analysis and FDA analysis for QTcF and HR are same. The sponsor used different categories for PR and QRS. So exact comparison was not possible.*

3.2.3 Exposure-Response Analysis

The sponsor planned a PK-PD analysis to investigate the relationship of QTc change with PK exposure only if there were clinically relevant changes in QTc. The sponsor performed graphical analyses to explore the relationship between the placebo-corrected change from baseline in QTc intervals and plasma concentrations of selumetinib in the present study. The sponsor's analyses did not indicate a significant relationship between QTcF and plasma concentrations of selumetinib suggesting an absence of significant QTc prolongation.

Reviewer's comment: *The conclusion of the FDA reviewer's analysis is similar to the sponsor's conclusion. Please see section 4.5 for FDA reviewer's exposure-response analysis.*

3.2.4 Cardiac Safety Analysis

There were no deaths or discontinuations of investigational product due to an AE were reported for any volunteer in the study. Volunteer (b) (6) reported an SAE (hemorrhoids) after placebo. There were no cardiac AEs.

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.*

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 large increases or decreases in heart rate (i.e. |mean| < 10 bpm) were observed (see Section 0).

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 BY-TIME ANALYSIS

The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG. The statistical reviewer used linear mixed model to analyze the drug effect by time for each biomarker (ΔQTcF, ΔHR , ΔPR, ΔQRS) independently. The model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The model also includes subject as a random effect and compound symmetry covariance matrix to explain the associated between repeated measures within period.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTc for different treatment groups. The maximum ΔΔQTc values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of ΔΔQTcF Timecourse (unadjusted CIs).

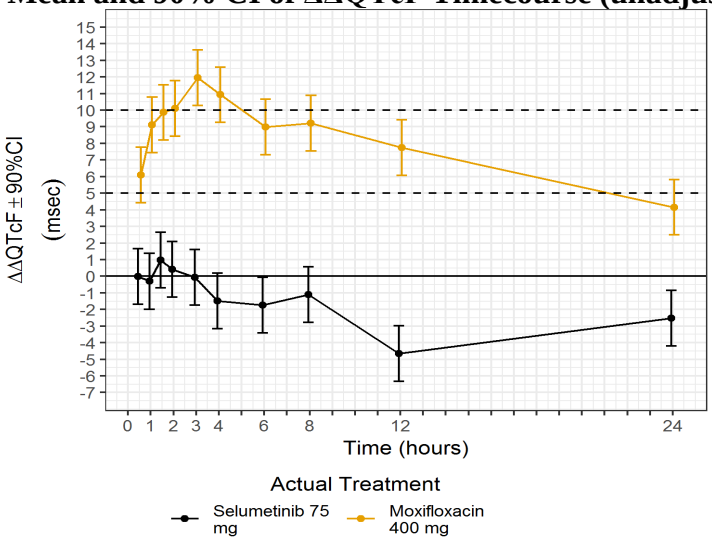


Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTc

Actual Treatment	Time (hours)	ΔΔQTcF (msec)	90.0% CI (msec)
Selumetinib 75 mg	1.5	1.0	(-0.7 to 2.7)

4.3.1.1 Assay Sensitivity

FDA reviewer used the same model for assay sensitivity and the primary model. The time-course of changes in ΔΔQTc is shown in Figure 1 and shows the expected time-profile with a mean effect of > 5 msec after Bonferroni adjustment for 4 time points (Table 3).

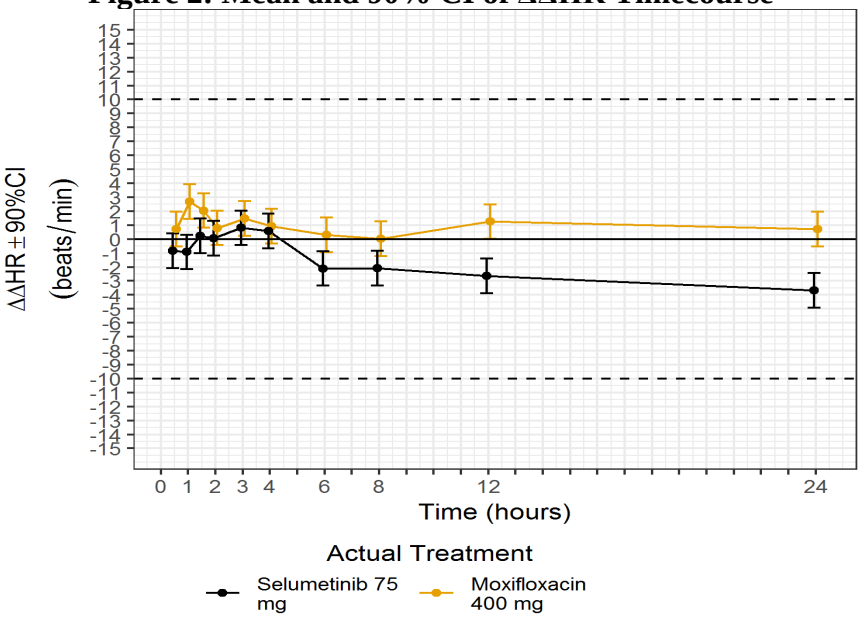
Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTc

Actual Treatment	Time (hours)	ΔΔQTcF (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	3.000	11.9	(9.7 to 14.2)

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

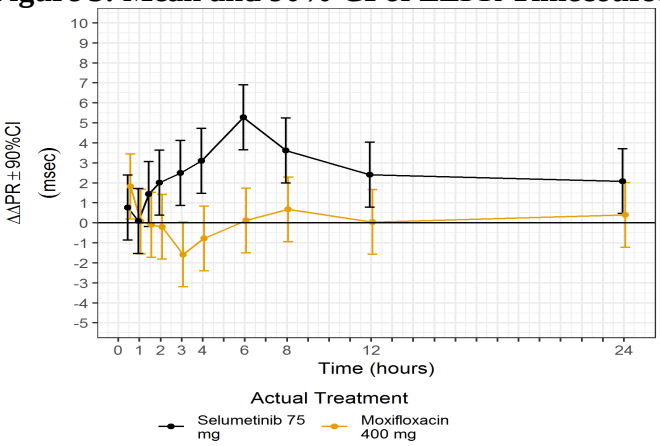
Figure 2: Mean and 90% CI of ΔΔHR Timecourse



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

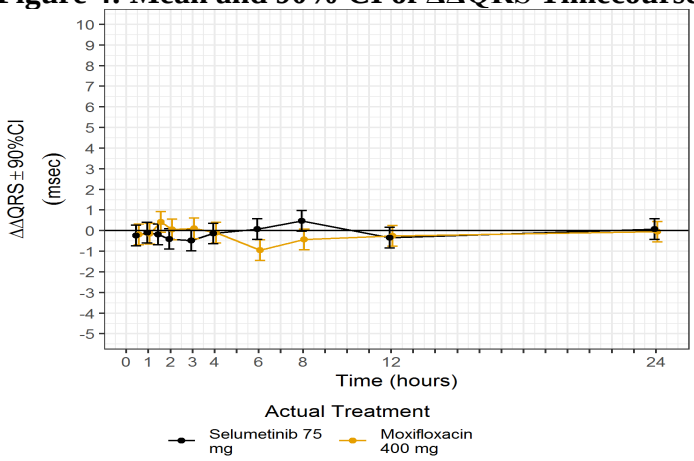
Figure 3: Mean and 90% CI of ΔΔPR Timecourse



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Timecourse



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs. Categorical analyses were performed for QTc, ΔQTC, HR, PR and QRS. If a category is omitted that means that no subjects had values in that category.

4.4.1 QTc

None of the subjects experienced QTc value and **Δ**QTcF value greater than 450 msec and 30 msec, respectively.

4.4.2 HR

None of the subjects experienced HR greater than 100 bpm.

4.4.3 PR

There were no subjects who experienced PR greater than 220 msec and an increase from baseline above 25%.

4.4.4 QRS

None of the subjects experienced QRS greater than 120 msec.

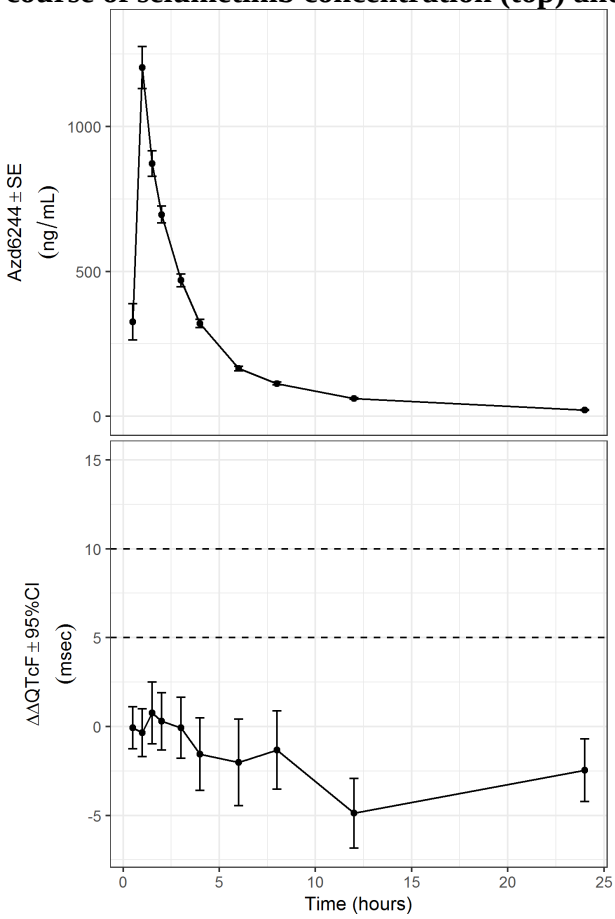
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between plasma selumetinib concentration and ΔQTcF. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK. A total of 54 healthy subjects were randomized in this study, of which 48 subjects completed the treatments and 47 subjects completed the study.

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 ΔQTcF and 3) presence of non-linear relationship.

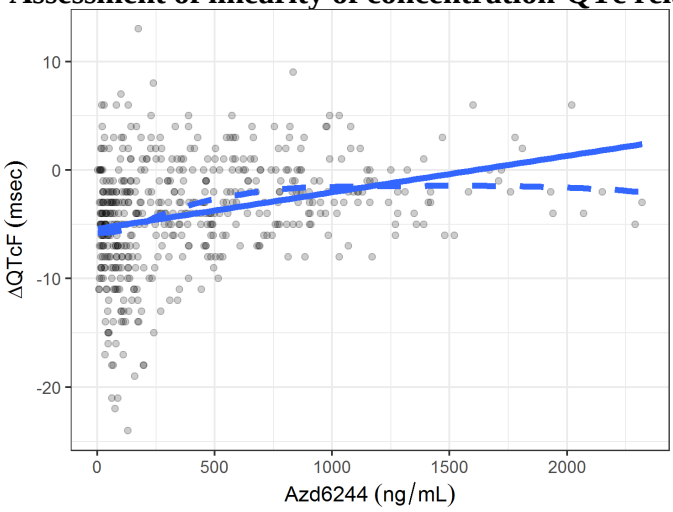
An evaluation of the time-course of selumetinib concentration and changes in ΔΔQTcF is shown in Figure 5, which do not appear to show significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which suggests an absence of significant ΔΔHR changes.

Figure 5: Time course of selumetinib concentration (top) and QTc (bottom)



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between selumetinib concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between selumetinib concentration and ΔQTcF and supports the use of a linear model.

Figure 6: Assessment of linearity of concentration-QTc relationship

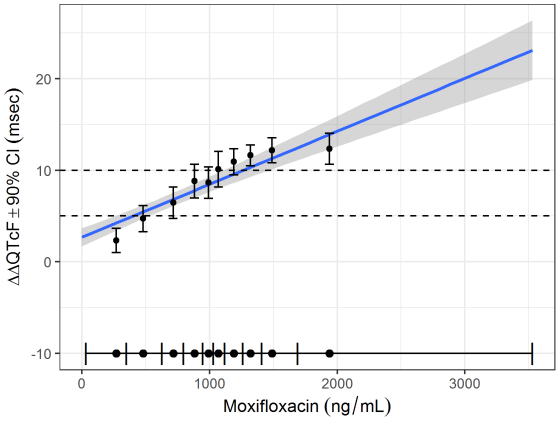


4.5.1.1 Assay sensitivity

Assay sensitivity was established using by time analysis. Please see section 0 for additional details.

Moxifloxacin plasma concentrations were determined up to 48 hours following oral administration of 400 mg moxifloxacin. The PK profile in the moxifloxacin group are generally consistent with the ascending, peak, and descending phases of historical data (data not shown). Concentration-response analysis of moxifloxacin data indicated a positive slope in the relationship between ΔQTcF and the plasma concentration of moxifloxacin (Figure 7). Assay sensitivity was established as the lower limit of the two-sided 90% confidence interval for the ΔΔQTcF at the observed mean peak concentrations of moxifloxacin was greater than 5 ms (data not shown).

Figure 7: Goodness-of-fit plot for QTc (Moxifloxacin)



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