CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215310Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	September 7, 2021
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 215310
Product Name and Strength:	Exkivity (mobocertinib) capsule, 40 mg
Applicant/Sponsor Name:	Takeda Pharmaceuticals USA, Inc
OSE RCM #:	2021-292-1
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on August 9, 2021 for Exkivity. Division of Oncology 2 (DO2) requested that we review the revised container labels for Exkivity (Appendix A) to determine if they are 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

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Mahmoud, S. Label and Labeling Review for Exkivity (NDA 215310). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 July 16. RCM No.: 2021-292.

APPENDIX A. IMAGES OF LABELS RECEIVED ON AUGUST 9, 2021

Container labels

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/s/

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ASHLEIGH V LOWERY
09/08/2021 10:53:25 AM

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

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

Memorandum

Date: 08/09/21

To: Jacqueline Glen, Regulatory Project Manager, DO2

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for EXKIVITY™ (mobocertinib), for oral use

NDA: 215310

In response to DO2's consult request dated March 15, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for EXKIVITY™ (mobocertinib), for oral use (Exkivity).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling accessed in SharePoint on July 30, 2021 and are provided below.

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 August 5, 2021

Carton and Container Labeling: OPDP has reviewed the proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 26, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at rachael.conklin@fda.hhs.gov.

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/s/

RACHAEL E CONKLIN
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Clinical Inspection Summary

Date	August 4, 2021
From	Lee Pai-Scherf, MD Karen Bleich, MD Kassa Ayalew, MD, MPH Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Elizabeth Duke, MD Nicole Drezner, MD Harpreet Singh, MD Division of Oncology 2/ Office of Oncologic Products
NDA #	215310
Applicant	Takeda Pharmaceuticals USA, Inc.
Drug	Mobocertinib (TAK-788, AP32788, EXKIVITY)
NME (Yes/No)	Yes
Therapeutic Classification	Tyrosine kinase inhibitor
Proposed Indication(s)	(b) (4)
Consultation Request Date	March 29, 2021
Summary Goal Date	July 26, 2021 (extended to August 6, 2021)
Action Goal Date	August 28, 2021
PDUFA Date	October 26, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study AP32788-15-101 were submitted to the Agency in support of a New Drug Application (NDA 215310) for mobocertinib for the above proposed indication. Two clinical investigators (Dr. Lyudmila Bazhenova, site #58248 and Dr. Pasi Janne, site #58008) were selected for clinical inspection, as well as (b) (4) contract research organization (CRO).

The inspections revealed no significant findings at the clinical investigator sites and the CRO site. Based on the results of these inspections, the Study AP32788-15-101 overall appears to have been conducted adequately and the data generated by the inspected clinical investigators and the (b) (4) CRO appear acceptable in support of the proposed indication in the NDA.

II. BACKGROUND

Takeda Pharmaceuticals, Inc. seeks approval for mobocertinib (b) (4) Mobocertinib is a new molecular entity and was granted Breakthrough Therapy Designation for the proposed indication.

Clinical data from an ongoing, phase 1/2, 3-part (dose escalation, expansion, and extension) study of mobocertinib in subjects with NSCLC (Study AP32788-15-101) was submitted to support this NDA.

The application includes safety data from 325 subjects enrolled in Study 101 who received at least 1 dose of mobocertinib. The efficacy population consists of 114 subjects with EGFR exon 20 insertion mutation positive metastatic NSCLC previously treated with platinum-based chemotherapy who received mobocertinib at a dose of 160 mg orally, once daily. The primary efficacy endpoint to support the proposed indication is objective response rate, as assessed by a blinded independent review committee (BIRC).

The first subject was enrolled on June 8, 2016 and the NDA data cutoff date is May 29, 2020. At the time of the data cutoff, the study was being conducted at 70 study centers in US, Europe, and Asia. Twenty nine out of the 96 subjects enrolled in the extension cohort were enrolled in 14 US sites.

Two clinical investigators were identified for inspection by DO2 and OSI: Dr. Lyudmila Bazhenova (site #58248) and Dr. Pasi Janne (site #58008). Clinical site selection used a risk-based approach, taking into consideration the total number of subjects enrolled and safety and efficacy parameters. OSI's Clinical Investigators Site Selection Tool (CISST) was utilized to assist with site selection. In addition, (b) (4) and for evaluation of the primary efficacy endpoint of a larger number of subjects.

III. RESULTS (by site):

1. **Dr. Lyudmila Bazhenova (site # 58248)**
   UC San Diego health
   3855 Health Sciences Drive, MC 0987, Room 2026
   La Jolla, CA 92093
   United States

   Inspection dates: 05/24 – 05/27/2021

Dr. Bazhenova was inspected as a surveillance inspection for Study AP32788-15-101. This was the first inspection of this clinical investigator.

At the time of the inspection, the clinical investigator had screened 16 subjects and enrolled 12 subjects. Nine subjects were enrolled and treated prior to the NDA data cut-off date of May 29, 2020. Of the 9 subjects, 2 were alive and in follow-up and 7 had died. Three subjects were enrolled after the data cut-off date and were alive, on treatment.

Source documents for all 9 subjects enrolled prior to the NDA data cut-off date were audited. All subjects signed informed consent form. There was no underreporting of SAEs or significant protocol deviations.

Radiographic scans and related investigator's assessment to determine the primary efficacy endpoint of ORR and key secondary endpoint of DOR were verified and were performed according to protocol. All imaging examinations performed on study subjects were submitted for central review.

Other documents reviewed during the inspection include, financial disclosure, training records, delegation of authority log, investigational drug accountability, case report forms, monitoring records, and the IRB communications. No regulatory violations were observed.

2. Dr. Pasi Janne (site # 58008)
Dana-Farber Cancer Institute
450 Brookline Avenue, LG1B14
Boston, MA 2215
USA United States

Inspection dates: 06/14 – 06/21/2021

Dr. Janne was inspected as a surveillance inspection for Study AP32788-15-101. Previous inspections of Dr. Janne conducted on 05/05/2016 and 08/07/2015 revealed no significant findings.

At the time of the inspection, the site had screened 34 subjects and enrolled 26 subjects: 9 in the escalation part, 11 in the expansion cohort part and 6 in the study extension. Of the 26 subjects enrolled in the study, 4 subjects are alive and continue to be followed and 22 are off study.

Source documents for the 26 subjects enrolled in the study were reviewed. All subjects met protocol specified inclusion and exclusion criteria and signed informed consent. There was no underreporting of AEs or SAEs or significant protocol deviations.

One discrepancy was noted between source records for Subject (b) (6) and the independent review committee (IRC) reading records submitted to the NDA. The subject had baseline imaging (CT and MRI) performed on (b) (6) (day -8). On (b) (6) (day 31), the subject had unscheduled CT imaging which was interpreted as partial response by IRC. On (b) (6) (day 42) the subject had an unscheduled MRI of the CNS that was read by the investigator as progressive disease (PD). In the submitted subject level data listing, the last

IRC read date for this subject is (b) (6) (PR), and the disposition for this subject is "withdrawal by subject" on (b) (6)

Following the inspection, an information request was sent to the sponsor to obtain the IRC interpretation of the (b) (6) MRI. Based on the Sponsor's response to OSI's information request, both the (b) (6) CT and the (b) (6) MRI of the brain were grouped under the Unscheduled Visit date of (b) (6). The overall disease assessment by IRC for this visit was partial response (PR) based on the CT of (b) (6) and the MRI of (b) (6)

Reviewer's comment: The grouping of the central interpretations of the CT performed on (b) (6) and the MRI performed on (b) (6) is acceptable and explains the absence of a central read dated (b) (6) in the subject level data listing. We note the discrepancy between the central read of the MRI (stable disease) and the investigator's read of the MRI (progressive disease), which is not uncommon. In light of the sponsor's response, there is no discrepancy between the source records and submitted imaging interpretation records for this subject.

There were no discrepancies or issues with the imaging process when compared to the information submitted to the NDA. There were no scans at the site that were not submitted for central review.

Other documents reviewed during the inspection included but were not limited to financial disclosure forms, IRB approvals and documentation, delegation log, monitoring log, electronic case report forms, and test article control records. No discrepancies or regulatory violations were observed.

(b) (4)

(b) (4) was inspected as data audit and surveillance inspection for Study AP32788-15-101. This CRO has been previously inspected on (b) (4) all without significant findings.

The inspection included the review of the following records: (b) (4) statement of work and change orders with the Sponsor, standard operating procedures (SOPs), imaging process flow charts, site imaging manuals, independent review charter, software validation summary reports, independent reader qualification forms, financial disclosures and training records.

For Study AP32788-15-101, the radiographic images were either couriered directly from the clinical site to (b) (4) document management team or electronically uploaded into the RAVE imaging system. Once (b) (4) received the images, they were logged and deidentified and checked by a specialist for quality control. When all images are ready for review, they are transmitted to the RAVE imaging EDC which is accessible to the Readers for assessment.

Two Readers were randomly designated to each imaging study and blinded to each other's assessment. If both assessments did not yield the same assessment response, an adjudicator, blinded to the previous reads, was assigned to read the images and determine the final assessment.

To verify the submitted imaging data, 30 subjects were randomly selected at various study cycles for review from the 114 subjects included in the efficacy population.
The firm followed all procedures for contracted study related activities.

{See appended electronic signature page}

Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Karen Bleich, M.D.
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

CC:

DARRTS: NDA 214665
Review Division /Project Manager/Jacqueline Glen
OSI/Database PM/Dana Walters
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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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:	August 4, 2021
To:	Jacqueline Glen, MS Regulatory Project Manager **Division of Oncology 2 (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rachael Conklin, MS, RN Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	EXKIVITY (mobocertinib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 215310
Applicant:	Takeda Pharmaceuticals USA, Inc.

1 INTRODUCTION

On February 26, 2021, Takeda Pharmaceuticals USA, Inc. submitted for the Agency's review an original New Drug Application (NDA) 215310 for EXKIVITY (mobocertinib) capsules. The proposed indication for EXKIVITY (mobocertinib) capsules is for the treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive metastatic non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have received prior platinum-based chemotherapy.

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 2 (DO2) on March 15, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for EXKIVITY (mobocertinib) capsules.

2 MATERIAL REVIEWED

- Draft EXKIVITY (mobocertinib) capsules PPI received on February 26, 2021, and received by DMPP and OPDP on July 27, 2021.
- Draft EXKIVITY (mobocertinib) capsules Prescribing Information (PI) received on February 26, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 27, 2021.

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. 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.

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LASHAWN M GRIFFITHS
08/05/2021 01:49:52 PM

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

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

Date of This Review:	July 16, 2021
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 215310
Product Name, Dosage Form, and Strength:	Exkivity (mobocertinib) capsule, 40 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Takeda Pharmaceuticals USA, Inc
FDA Received Date:	April 28, 2021
OSE RCM #:	2021-292
DMEPA Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the approval process for Exkivity (mobocertinib) capsule, the Division of Oncology 2 (DO2) requested that we review the proposed Exkivity Prescribing Information (PI) and container labels 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 Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
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 reviewed the proposed PI and container labels and determined that they may be improved to ensure safe product use.

4 CONCLUSION & RECOMMENDATIONS

The proposed PI and container label may be improved to ensure safe product use. We provide specific recommendations in Sections 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 2 (DO2)

We recommend the following for the Prescribing Information (PI):

A. Section 16 (How Supplied/Storage and Handling)
    1. Revise the storage statement for clarity and to make it consistent with container label- "Store EXKIVITY at room temperature. (b) (4)

4.2 RECOMMENDATIONS FOR TAKEDA PHARMACEUTICALS USA, INC

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

A. Container labels
    1. As presented, the product strength (40 mg) lacks prominence. Increase the prominence of the product strength (e.g., font size, bolding) to reduce the risk of medication errors.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Exkivity received on April 28, 2021 from Takeda Pharmaceuticals USA, Inc.

Table 2. Relevant Product Information for Exkivity	
Initial Approval Date	N/A
Active Ingredient	mobocertinib
Indication	(b) (4)
Route of Administration	Oral
Dosage Form	capsule
Strength	40 mg
Dose and Frequency	160 mg orally once daily at approximately the same time, with or without food.
How Supplied	40 mg gelatin capsules: white, size 2, imprinted with “MB788” on the cap and “40mg” on the body in black ink. Bottle of 90 capsules (b) (4) Bottle of 120 capsules
Storage	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 27, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, mobocertinib. Our search identified no previous reviews.

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 Exkivity labels and labeling submitted by Takeda Pharmaceuticals USA, Inc.

- Container label received on April 28, 2021
- Prescribing Information (Image not shown) received on April 28, 2021, available from \\CDSESUB1\evsprod\nda215310\0016\m1\us\annotated-draft-label-exkivity-uspi-dn-000340017.doc

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

G.2 Label and Labeling Images

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/s/

SALI MAHMOUD
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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 215310
Submission Number	002 (New NDA)
Submission Date	2/26/2021
Date Consult Received	3/15/2021
Drug Name	EXKIVITY (Mobocertinib, TAK-788)
Indication	(b) (4)
Therapeutic dose	160 mg QD
Clinical Division	DO2

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 3/15/2021 regarding the sponsor's QT evaluation report. We reviewed the following materials:

- Previous IRT review dated 05/28/2020 (link) in DARRTS (IND126721);
- QT analysis report for Mobocertinib (Submission 0002; link);
- Cardiac Safety Report (Submission 0002; link);
- Proposed label (Submission 0002; link);
- Investigator's brochure (Submission 0002; link); and
- Highlights of clinical pharmacology and cardiac safety (Submission 0002; link).

1 SUMMARY

At therapeutic doses (160 mg QD) of mobocertinib, mean increases in the QTc interval of 23 msec (*UCL:* 26 msec) were detected in this QT assessment. The QT prolonging effect was concentration-dependent. 2.5% patients experienced QTc >500 msec, 13.5% patients experienced increases from baseline QTc >60 msec, and 1 patient experienced a serious adverse event of ventricular arrhythmia that was reported to be associated with Torsades de Pointes. The patient had several AEs of QT interval prolongation (including QTc >500 msec) and hypomagnesemia prior to the arrhythmia.

Mobocertinib was evaluated in an open-label study AP32788-15-101. The highest dose studied was 180 mg QD, which covered the highest therapeutic dose (160 mg QD). The data were analyzed using concentration-QTc analysis as the primary analysis, which showed that mobocertinib treatment is associated with significant QTc prolonging effect (section 4.5) – see Table 1 for overall results. The findings of this analysis are further supported by the central tendency analysis (section 4.3) and categorical analysis (section 4.4).

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

Treatment	Concentration	ΔQTCF	90% CI
Mobocertinib 160 mg QD	69.6 (ng/mL)	23.0	(20.5, 25.5)

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

Given the similar PK profiles and uncertainties in the underlying mechanism for the observed QT prolonging effect, individual contributions from mobocertinib or its two major metabolites on the QTc interval cannot be distinguished. The concentration-QTc analysis using combined molar concentration of mobocertinib and its two active metabolites as the exposure covariate also suggested a positive exposure-response relationship, and the predicted QTc increases are similar to that is shown in Table 1.

Co-administration with strong CYP3A4 inhibitor, itraconazole, resulted in 1.9-fold and 5.3-fold increase on the combined molar Cmax and AUC_{inf} of mobocertinib and its 2 active metabolites. The effect of severe renal impairment and the effect of moderate/severe hepatic impairment on mobocertinib PK are being evaluated in the ongoing studies.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

At therapeutic doses (160 mg QD), the mean increase in the PR interval was 12 msec (UCL: 15 msec). PR interval prolongation >220 msec occurred in 5% patients taking mobocertinib 160 mg QD. Because there were no clinical TEAEs of second or third degree AV block, we recommend including a description of PR prolongation in section 12.2 of the product label. Evaluation for heart block should contine in ongoing clinical trials.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

We recommend the Division consider including a box warning for QTc prolongation and Torsades de Pointes given that there was 1 event in this small safety database and patients with heart failure are at increased risk for torsades.

Below are proposed edits to the label submitted to Submission 0002 (link) from the IRT. Our changes are highlighted (addition, ~~deletion~~) for suggestions only and we defer final labeling decisions to the Division.

(b) (4) **QTc** (b) (4) **Prolongation** and Torsades de Pointes

(b) (4)

(b) (4)

12.2 Pharmacodynamics

Cardiac Electrophysiology

The largest mean increase in QTc was 23.0 msec (UCI: 25.5 msec) following administration of EXKIVITY 160 mg QD (b) (4)
The increase in QTc interval was concentration-dependent.

The largest mean increase in the PR interval was 12.4 msec (UCI: 15.0 msec). PR interval prolongation >220 msec occurred in 5% patients taking mobocertinib 160 mg QD.

(b) (4)

Reviewer's comments:

- *Because there was one subject who experienced a nonfatal torsade arrhythmia, we recommend that section (b) (4) explicitly lists this torsade case.*
- *We do not agree with only listing QT prolongation AEs in the section; instead, we described the % patients with QTc>500 msec or increase from baseline >60 msec.*
- *For our categorical analyses, we could only find ECG data for (b) (4) subjects. Therefore, our percentages are based on (b) (4) subjects (not (b) (4) subjects).*
- *We do not agree with the sponsor's concentration-QTc analysis method and the results. Therefore, our recommendations for section 12.2 are based on FDA's analysis of the data which follows the Scientific White Paper for concentration-QTc analysis. We proposed to report the reviewer's concentration-QTs analysis results which are also supported by the central tendency analysis.*

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Previously the IRT reviewed the QT assessment plan and concluded that study AP32788-15-101 (Part 1 and 2) appeared adequate to characterize the potential for TAK-788 to prolong the QTc interval at doses up to 160 mg QD for the oncology indication (IRT review under IND 126721 dated 05/28/2020 in DARRTS, link).

AP32788-15-101 is an open-label, multi-center, parallel study in patients with non-small cell lung cancer (NSCLC). It consists of a dose escalation phase (Part 1, up to 180 mg QD), an expansion phase (Part 2, 160 mg QD), and an extension phase (160 mg QD). In Part 1 and 2, time-matched PK/ECG data were collected on Cycle 1 Day 1 at predose and on Cycle 2 Day 1 at predose, 1, 2, 4, and 6 hours postdose. There are no major changes in the concentration-QTc analysis plan based on Part 1 and 2 of the study after the previous IRT review. The sponsor also included partial data from the extension phase in the cardiac safety report (labeled as from study TAK78801-788101).

The sponsor reported linear PK for the parent drug between 5-180 mg QD doses, in which Tmax was reported to be 4 hr postdose after the first dose and at steady state. The terminal elimination half was reported to be 20 hrs with minimal accumulation (AR: 1.06). In vitro studies indicated that metabolism of mobocertinib is primarily mediated by CYP3A4/5 to form 2 active metabolites, AP32960 and AP32914, which accounted for ~62% and ~7%, respectively at steady state. A DDI study showed significant impact on the combined molar exposure of mobocertinib and its 2 active metabolites in the presence of itraconazole (geometric mean ratio is 6.3 on AUC_{inf} and 2.9 on Cmax). Food, race, age, and sex do not appear to impact drug exposure. The effect of severe renal impairment and the effect of moderate and severe hepatic impairment on mobocertinib PK are being evaluated in the ongoing studies (TAK-788-1007 and TAK-788-1008).

3.1.2 Nonclinical Safety Pharmacology Assessments

Mobocertinib, AP32914, and AP32960 inhibited the hERG potassium channel in a concentration dependent manner with IC50 values of 10, 5.1, and 10 μM, respectively. … the safety margins are >11000-fold for mobocertinib, >28000-fold for AP32960, and >41000-fold for AP32914 calculated between the in vitro hERG IC50 values and the geometric mean Cycle 2 Day 1 unbound plasma $C_{max,ss}$ values in patients receiving a 160 mg QD mobocertinib dose. … there were no findings of QT prolongation in dog toxicity studies of up to 3 months in duration.

Reviewer's assessment: *The sponsor evaluated the effects of mobocertinib, AP32960, and AP32914 on hERG current, a surrogate for IKr that mediate membrane potential repolarization in cardiac myocytes. The non-GLP hERG study report (link) describes the potential effects of mobocertinib, AP32960, and AP32914 on hERG current using an automated patch clamp system in CHO cells. The hERG current was assessed at room temperature, using a step-step voltage protocol (from a holding potential of -80 mv to a depolarizing pulse of 20 mV for 2 second, followed by a repolarizing pulse to -40 mV for 1 second) that is different from the recommended hERG current protocol by the FDA*

(link). The reviewer does not expect protocol differences to impact hERG current pharmacology. The positive control (E-4031) inhibited hERG potassium current with an IC50 of 30 nM. No drug concentrations were verified in the study. The stability of hERG currents in control and after adding drug cannot be assessed from the report. Therefore, the hERG assay did not meet the best practice recommendations of the new draft ICH S7B Q&As 2.1 (link).

The IC50s for the inhibitory effect of mobocertinib, AP32960, and AP32914 on hERG potassium current were 10 µM, 5.1 µM and 10 M µM, respectively. The safety margins of mobocertinib, AP32960, and AP32914 against (inhibit) hERG are provided below:

Table 2. Safety Margin of mobocertinib, AP32960, and AP32914 on hERG Current

	Cmax (ng/mL)	Protein Binding	Free Cmax (ng/mL)	hERG IC50 (µM)	Mol Weight (g/mol)	Safety Margin (Ratio)
Mobocertinib	69.6	99%	0.696	10	703.8	10112x
AP32960	45.9	99%	0.459	5.1	571.68	6352x
AP32914	5.7	98.6%	0.07	10	571.68	80067x

Cmax was 69.6 ng/mL at 160 mg QD in this QT assessment. The calculation assumes that AP32960 and AP32914 accounted for ~66% and ~8%, respectively, of parent exposure at steady state.

In summary, the in vitro hERG assay did not meet the best practice considerations for an in vitro assay according to the new draft ICH S7B Q&A 2.1 (link). While the assay results showed mobocertinib, AP32960, and AP32914 have hERG safety margins of 10112x, 6352x and 80067x, suggesting mobocertinib, AP32960, and AP32914 may not have direct interactions with the hERG current, the limitations of the hERG assay outlined above may significantly impact these safety margins. In addition, the QTc prolongation observed in clinical studies could be due to indirect interactions with cardiac ion channels.

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

The primary analysis for mobocertinib was based on exposure-response analysis. Please see section 3.2.3 for additional details.

Reviewer's comment: *Sponsor provided descriptive statistics for mean QTcF change from baseline. Prolongation of QTcF and JTPc were observed. The reviewer's analyses show similar results. Please see section 4.3 for more details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline, HR (<45 or >100 beats/min), PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *In contrast to the sponsor's analysis, our categorical analysis is based on ECGs collected in all patients taking 160 mg QD dosing in order to inform the product labeling. Please see section 4.4 for more details.*

3.2.3 Exposure-Response Analysis

The sponsor used a nonlinear mixed effects modeling approach based on the likelihood ratio test with an additive error model to assess the concentration-QTcF relationship in NONMEM. The estimated weighted sum of mobocertinib, AP32960, and AP32914 plasma concentration was included as a predictor, and time were considered to be a confounder and included as a predictor. A demographic covariate effect was only found in the RR model where female sex was associated with a higher heart rate at baseline. The molar sum C_{max} after 160 mg mobocertinib QD based on non-compartmental analysis was 202 nM and the typical prediction corresponding to the molar sum C_{max} is 12.7 msec (95% CI: 8.7 - 16.8) msec for ΔQTcF.

Reviewer's comment: *We do not agree with the sponsor's analysis method because the effect of time on the QTc interval cannot be estimated with confidence in the absence of a placebo control.*

3.2.4 Cardiac Safety Analysis

Of the cardiac TEAEs (16.7%) a majority of the events were supraventricular arrythmias (7.3%) with the remaining events having a rate of <4% (≤3 patients each). Seven events of cardiac disorder were reported as ≥Grade 3; pericardial effusion (3.1%), ventricular arrhythmia (1%) and ventricular tachycardia. Serious events that were deemed potentially related to study dosing included cardiac failure, and ventricular tachycardia, reported in 1 patient each.

There were no TEAEs of QT prolonged that were deemed serious or led to study drug discontinuation, 2% to 4% of patients experienced a QT prolongation event that was Grade ≥3. One SAE of ventricular arrhythmia was reported to be associated with torsades de pointes and led to discontinuation of mobocertinib.

Table 3. Cardiac Disorders Treatment Emergent Adverse Events of Clinical Interest in Patients Who Have Received at Least 1 Dose of Mobocertinib at 160 mg QD

	Mobocertinib 160 mg QD N=256 n (%)				
Primary System Organ Class Preferred Term	TEAE	Related	Grd>=3	Serious	Discontinued
Subjects with at Least 1 Adverse Events	76 (30)	27 (11)	32 (13)	26 (10)	5 (2)
Respiratory, thoracic and mediastinal disorders	41 (16)	4 (2)	13 (5)	16 (6)	2 (<1)
Dyspnoea	41 (16)	4 (2)	13 (5)	16 (6)	2 (<1)
Cardiac disorders	19 (7)	8 (3)	9 (4)	8 (3)	3 (1)
Atrial fibrillation	4 (2)	1 (<1)	1 (<1)	1 (<1)	0
Palpitations	3 (1)	0	0	0	0
Cardiac failure	2 (<1)	1 (<1)	1 (<1)	1 (<1)	0
Sinus tachycardia	2 (<1)	1 (<1)	0	0	0
Acute myocardial infarction	1 (<1)	0	1 (<1)	1 (<1)	0
Cardiac arrest	1 (<1)	0	1 (<1)	1 (<1)	0
Cardiac failure congestive	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Cardiomyopathy	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Stress cardiomyopathy	1 (<1)	0	1 (<1)	0	0
Supraventricular extrasystoles	1 (<1)	1 (<1)	0	0	0
Ventricular arrhythmia	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Ventricular tachycardia	1 (<1)	1 (<1)	1 (<1)	1 (<1)	0
Investigations	20 (8)	16 (6)	6 (2)	1 (<1)	0
Electrocardiogram QT prolonged	17 (7)	15 (6)	5 (2)	0	0
Ejection fraction decreased	2 (<1)	1 (<1)	1 (<1)	1 (<1)	0
Troponin increased	1 (<1)	0	0	0	0
General disorders and administration site conditions	13 (5)	2 (<1)	5 (2)	3 (1)	0
Chest pain	9 (4)	1 (<1)	3 (1)	1 (<1)	0
Multiple organ dysfunction syndrome	2 (<1)	0	2 (<1)	2 (<1)	0
Oedema	2 (<1)	1 (<1)	0	0	0
Nervous system disorders	2 (<1)	0	2 (<1)	0	0
Syncope	2 (<1)	0	2 (<1)	0	0
Gastrointestinal disorders	1 (<1)	0	1 (<1)	1 (<1)	0
Ascites	1 (<1)	0	1 (<1)	1 (<1)	0
Psychiatric disorders	1 (<1)	0	0	0	0
Mental status changes	1 (<1)	0	0	0	0

Source: \\cdsesub1\evsprod\NDA215310\0002\m1\us\irt-highlight-clinpharm-cardiac-safety.pdf

Reviewer's comment: *Clinical adverse events consistent with proarrhythmia risk were observed in the clinical database. A graphic of the patient narrative for the ventricular arrhythmia (torsade case) case is presented in section 4.6. The patient had several AEs of QT interval prolongation (including QTc>500 msec) and hypomagnesemia prior to the arrhythmia.*

4 REVIEWERS' ASSESSMENT

In the reviewer's analyses, data from the dose escalation phase were pooled into two treatment groups: 1) Mobocertinib 5 to 80 mg QD or BID (2-5 patients at each dose level); and 2) Mobocertinib 120 to 180 mg QD (more than 2/3 of patients on 120 mg QD). Data from the dose expansion cohorts 1-7 were pooled into a new treatment group, Mobocertinib 160 mg QD E1-E7. The reviewer's categorical analysis included data from Part 1 and 2 of study 101, and pooled data from all patients receiving 160 mg QD doses in studies 101 (Part 1-3) and 1003.

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 beats/min) were observed (see section 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 BY TIME ANALYSIS

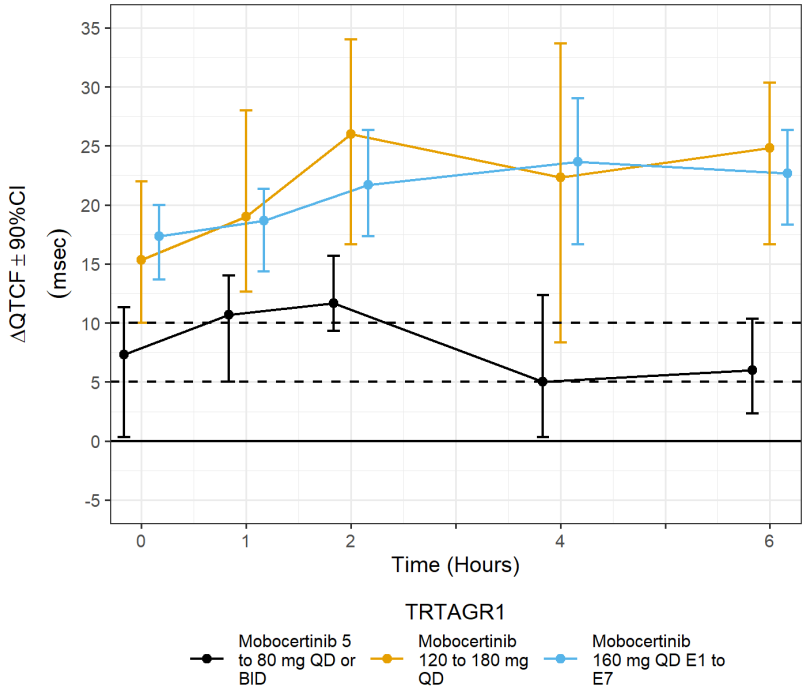
The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG at Cycle 2 Day 1 in study AP32788-15-101 (Part 1&2).

The statistical reviewer evaluated the ΔQTcF effect using nonparametric descriptive statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTc for different treatment groups.

Figure 1: Median and 90% CI of ΔQTcF Time Course (unadjusted CIs).



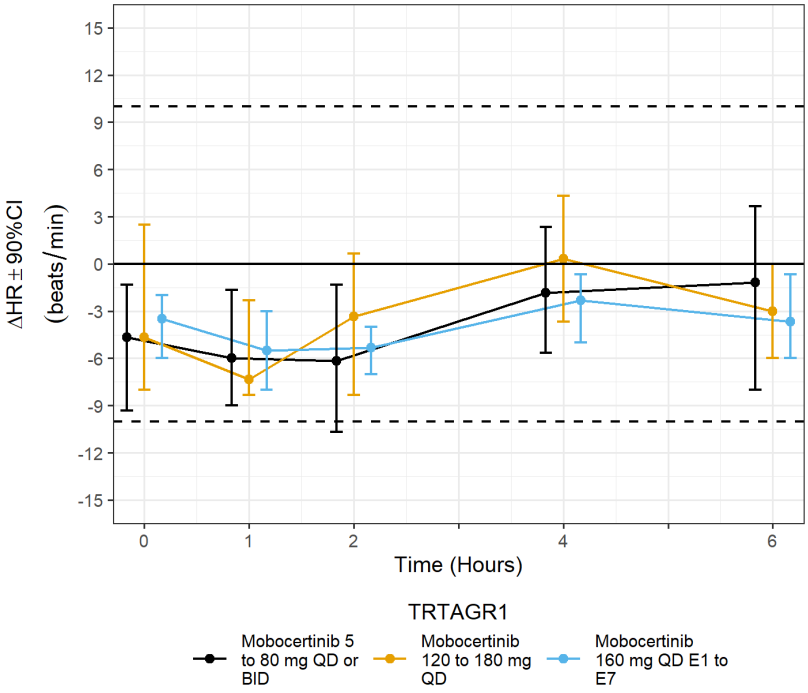
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

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

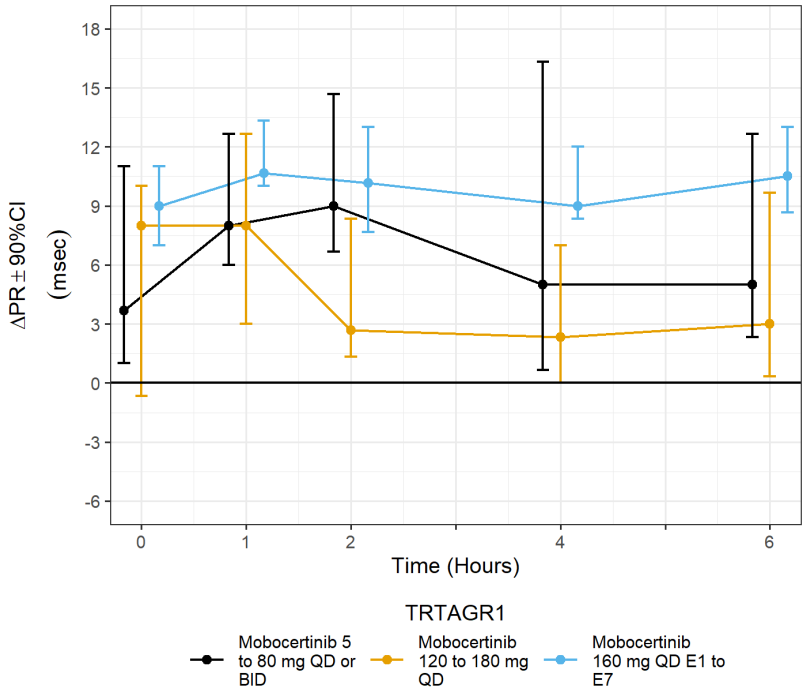
Figure 2: Median and 90% CI of ΔHR Time Course



4.3.3 PR

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

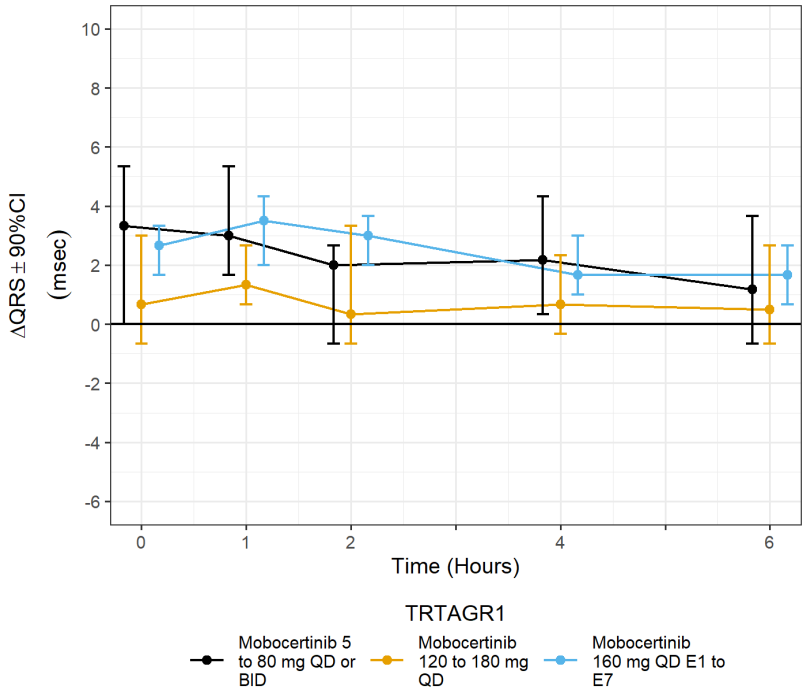
Figure 3: Median and 90% CI of ΔPR Time Course



4.3.4 QRS

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

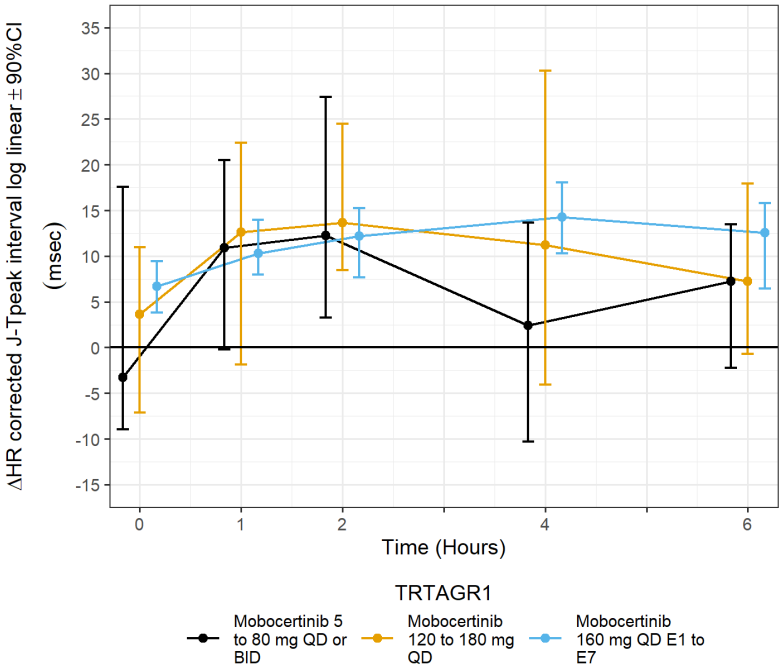
Figure 4: Median and 90% CI of ΔQRS Time Course



4.3.5 JTPc (JTPc = JTP / $RR^{0.58}$)

Figure 5 displays the time profile of ΔJTPc for different treatment groups.

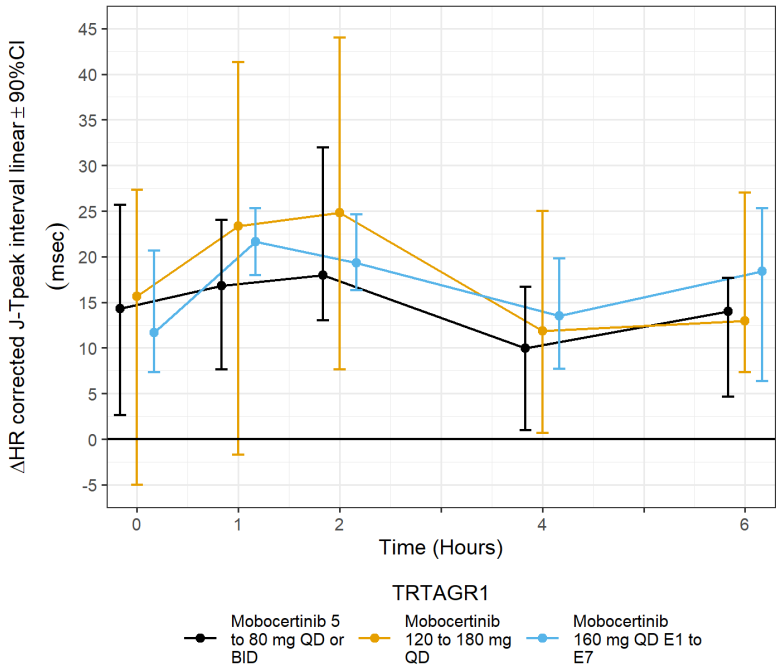
Figure 5: Median and 90% CI of ΔJTPc Time Course



4.3.6 JTPc (JTPc = JTP + 0.15(1-RR))

Figure 6 displays the time profile of ΔJTPc for different treatment groups.

Figure 6: Median and 90% CI of ΔJTPc Time Course



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.

4.4.1 QTc

Table 3 lists the number of subjects as well as the number of observations whose QTc values were ≤ 450 msec, between 450 and 480 msec, between 480 and 500 msec and greater than 500 msec with or without a change from baseline greater than 60 msec. There are 6 (out of 245) subjects who experienced QTcF above 500 msec after receiving mobocertinib 160 mg.

Table 3: Categorical Analysis for QTc (maximum)

TRTAGR1	Total (N)		450 < Value <= 480 msec		480 < Value <= 500 msec		Value > 500 msec & Δ < 60 msec		Value > 500 msec & Δ >= 60 msec	
	# Subj	# Obs	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Study Identifier AP32788-15-101 Part 1 and 2										
Mobocertin b 5 to 80 mg QD or BID	35	302	4 (11.4%)	10 (3.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mobocertin b 120 to 180 mg QD	33	474	10 (30.3%)	84 (17.7%)	0 (0%)	5 (1.1%)	0 (0%)	0 (0%)	1 (3.0%)	2 (0.4%)
Mobocertin b 160 mg QD E1 to E7	134	1569	37 (27.6%)	186 (11.9%)	4 (3.0%)	12 (0.8%)	0 (0%)	0 (0%)	2 (1.5%)	5 (0.3%)
Pooled AP32788-15-101 Part 1, 2 and 3 and Tak-788-1003										
Mobocertin b 160 mg (all)	245	2613	66 (26.9%)	336 (12.9%)	11 (4.5%)	39 (1.5%)	1 (0.4%)	5 (0.2%)	5 (2.0%)	9 (0.3%)

Table 4 lists the categorical analysis results for ΔQTcF (less than 30 msec, between 30 and 60 and greater than 60 msec). There are 33 (out of 245) subjects who experienced QTcF change from baseline above 60 msec after receiving mobocertinib 160 mg.

Table 4: Categorical Analysis for ΔQTcF (maximum)

TRTAGR1	Total (N)		Value <= 30 msec		30 msec < Value <= 60 msec		Value > 60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Study Identifier AP32788-15-101								
Mobocertin b 5 to 80 mg QD or BID	35	302	26 (74.3%)	275 (91.1%)	9 (25.7%)	27 (8.9%)	0 (0%)	0 (0%)
Mobocertin b 120 to 180 mg QD	33	474	14 (42.4%)	323 (68.1%)	15 (45.5%)	138 (29.1%)	4 (12.1%)	13 (2.7%)
Mobocertin b 160 mg QD E1 to E7	134	1569	65 (48.5%)	1180 (75.2%)	56 (41.8%)	345 (22.0%)	13 (9.7%)	44 (2.8%)
Pooled AP32788-15-101 Part 1, 2 and 3 and Tak-788-1003								
Mobocertin b 160 mg (all)	245	2613	111 (45.3%)	1958 (74.9%)	101 (41.2%)	558 (21.4%)	33 (13.5%)	97 (3.7%)

4.4.2 HR

Table 5 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min).

Table 5: Categorical Analysis for HR (maximum)

TRTAGR1	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Study Identifier AP32788-15-101						
Mobocertin b 5 to 80 mg QD or BID	36	325	28 (77.8%)	306 (94.2%)	8 (22.2%)	19 (5.8%)
Mobocertin b 120 to 180 mg QD	33	474	30 (90.9%)	463 (97.7%)	3 (9.1%)	11 (2.3%)
Mobocertin b 160 mg QD E1 to E7	134	1570	116 (86.6%)	1531 (97.5%)	18 (13.4%)	39 (2.5%)
Pooled AP32788-15-101 Part 1, 2 and 3 and Tak-788-1003						
Mobocertin b 160 mg (all)	245	2616	207 (84.5%)	2540 (97.1%)	38 (15.5%)	76 (2.9%)

4.4.3 PR

Table 6 lists the categorical analysis results for PR (less than 200 msec; between 200 and 220 msec and above 220 msec with and without 25% increase over baseline). There are 13 subjects (out of 243 subjects who provided PR data) experienced PR above 220 msec after receiving mobocertinib 160 mg.

Table 6: Categorical Analysis for PR

TRTAGR1	Total (N)		Value <= 220 msec		Value > 220 msec & Δ% < 25%		Value > 220 msec & Δ% >= 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Study Identifier AP32788-15-101								
Mobocertin b 5 to 80 mg QD or BID	35	302	34 (97.1%)	301 (99.7%)	1 (2.9%)	1 (0.3%)	0 (0%)	0 (0%)
Mobocertin b 120 to 180 mg QD	33	474	32 (97.0%)	472 (99.6%)	1 (3.0%)	2 (0.4%)	0 (0%)	0 (0%)
Mobocertin b 160 mg QD E1 to E7	132	1555	123 (93.2%)	1502 (96.6%)	5 (3.8%)	46 (3.0%)	4 (3.0%)	7 (0.5%)
Pooled AP32788-15-101 Part 1, 2 and 3 and Tak-788-1003								
Mobocertin b 160 mg (all)	243	2600	230 (94.7%)	2527 (97.2%)	6 (2.5%)	53 (2.0%)	7 (2.9%)	20 (0.8%)

4.4.4 QRS

Table 7 lists the categorical analysis results for QRS (less than 120 msec and above 120 msec with and without 25% increase over baseline). There are 15 (out of 245) subjects who experienced QRS above 120 msec after receiving mobocertinib 160 mg.

Table 7: Categorical Analysis for QRS

TRTAGR1	Total (N)		Value <= 120 msec		Value > 120 msec & Δ% < 25%		Value > 120 msec & Δ% >= 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Study Identifier AP32788-15-101								

TRTAGR1	Total (N)		Value <= 120 msec		Value > 120 msec & Δ% < 25%		Value > 120 msec & Δ% >= 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Mobocertin b 5 to 80 mg QD or BID	36	325	35 (97.2%)	317 (97.5%)	0 (0%)	6 (1.8%)	1 (2.8%)	2 (0.6%)
Mobocertin b 120 to 180 mg QD	33	474	31 (93.9%)	443 (93.5%)	1 (3.0%)	24 (5.1%)	1 (3.0%)	7 (1.5%)
Mobocertin b 160 mg QD E1 to E7	134	1570	129 (96.3%)	1536 (97.8%)	4 (3.0%)	33 (2.1%)	1 (0.7%)	1 (0.1%)
Pooled AP32788-15-101 Part 1, 2 and 3 and Tak-788-1003								
Mobocertin b 160 mg (all)	245	2615	230 (93.9%)	2513 (96.1%)	11 (4.5%)	90 (3.4%)	4 (1.6%)	12 (0.5%)

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

4.5.1 QTc

Prior to evaluating the relationship between drug-concentration and QTc using a linear model, the three key assumptions of the model needs to be evaluated using exploratory analysis: 1) presence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTc and 3) presence of non-linear relationship.

- Figure 2 shows the time-course of ΔHR, which shows an absence of significant ΔHR changes.
- Figure 7 evaluates the time-course of drug-concentration and ΔQTc and do not appear to show significant hysteresis. Because the PK profiles of mobocertinib and its metabolites (AP32960 and AP32914) are similar, individual concentrations from mobocertinib and its metabolites may not be distinguished. Considering uncertainties in the underlying mechanism for the observed QT prolonging effect (for example, the observation could have resulted from indirect effect on cardiac ion channels by TKI inhibitors), the reviewer used parent drug concentration (mobocertinib) in the reviewer's primary analysis, and used the combined molar concentration of mobocertinib and its two active metabolites in the supportive analyses.
- Figure 8 shows the relationship between drug concentration and ΔQTc. The figure suggests higher ΔQTc with increasing mobocertinib concentration and it shows deviation from linearity at the two ends of studied concentration range.

Figure 7: Time course of drug concentration and QTc

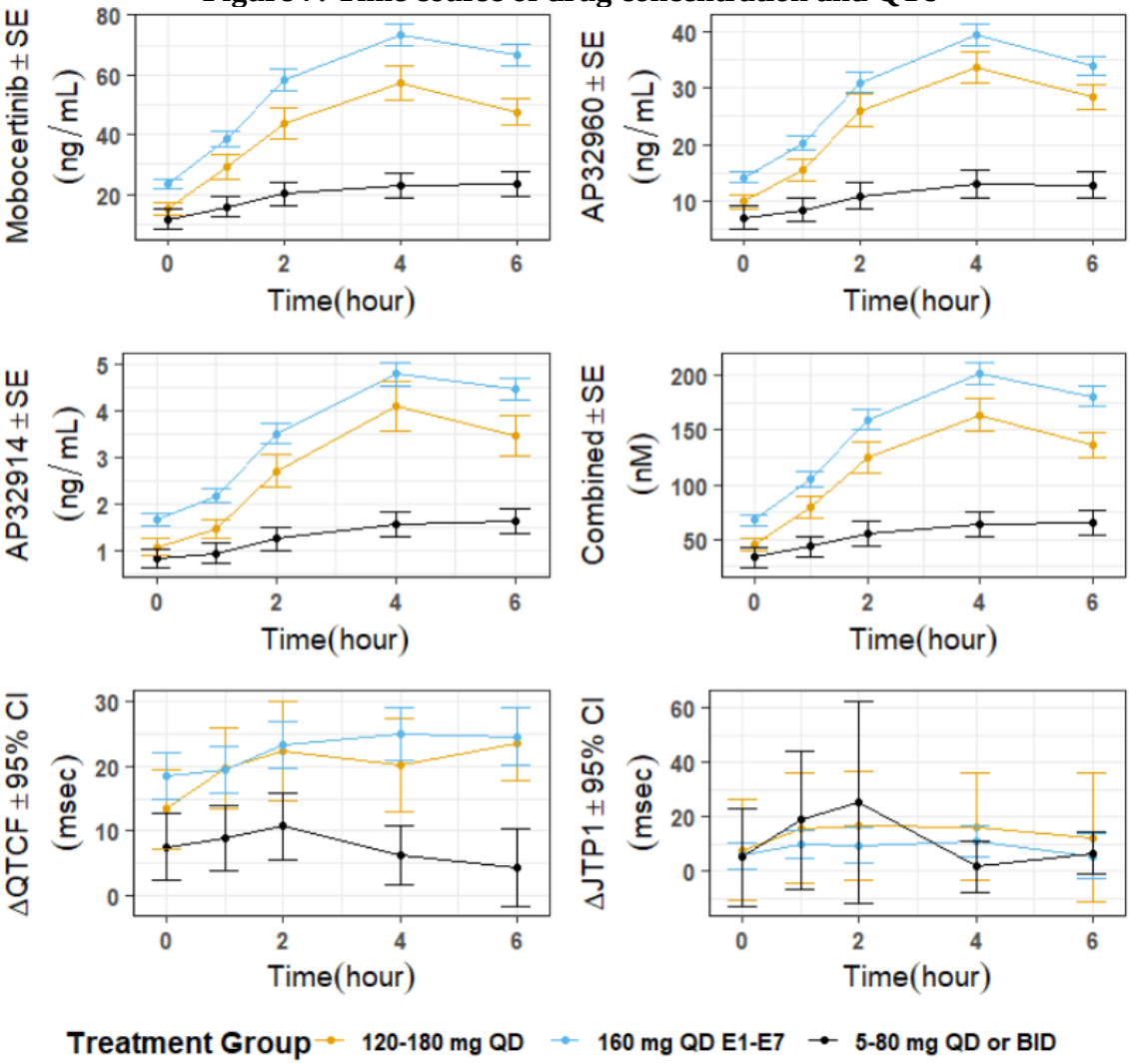
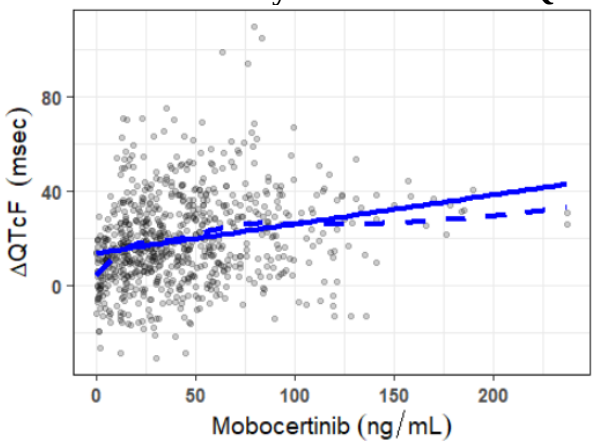


Figure 8: Assessment of linearity of concentration-QTc relationship



The linear model was applied to the data with mobocertinib concentration or log transformed mobocertinib concentration as the exposure covariate (ΔQTcF ~ 1 + exposure + baseline QTcF, random effect on the slope and intercept). The goodness-of-

fit plots are shown in Figure 9 and predictions of QTc increases at the geometric mean Cmax in expansion cohorts 1-7 are provide in Table 8. The linear model with log transformed concentration data showed a lower AIC (5827.7) compared with the model with normal concentration (5836.1).

Figure 9: Goodness-of-fit plot for QTc. Left: normal concentration; Right: log-transformed concentration

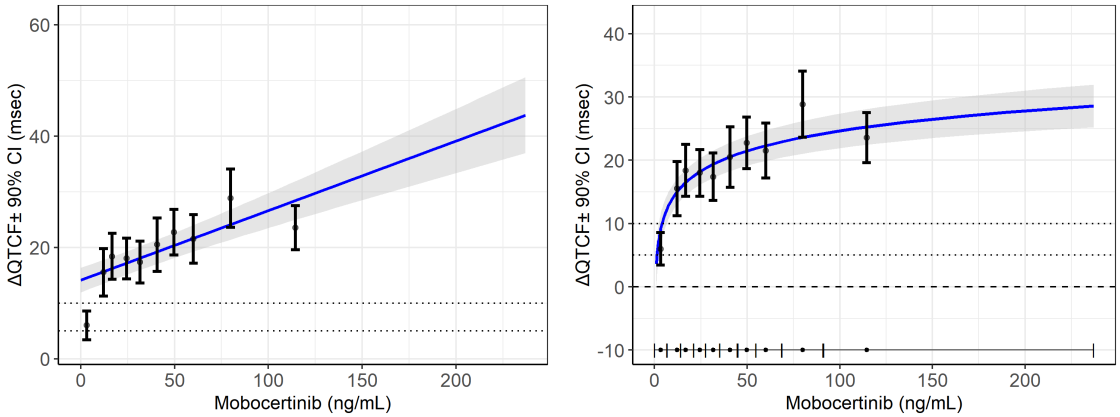


Table 8: Predictions from concentration-QTc models

Actual Treatment	Exposure Covariate	Mobocertinib (ng/mL)	ΔQTCF (msec)	90.0% CI (msec)
Mobocertin b 160 mg QD	Concentration	69.6	22.8	(20.3, 25.4)
Mobocertin b 160 mg QD	Log(concentration)	69.6	23.0	(20.5, 25.5)

The reviewer's supportive analyses using combined concentration as the exposure covariate also suggested positive exposure-response relationships and similar predictions (non-transformed data: 23.1 msec [90% CI: 20.6-25.6 msec]; log-transformed data: 23.0 msec [90% CI: 20.5-25.5 msec]).

4.5.1.1 Assay sensitivity

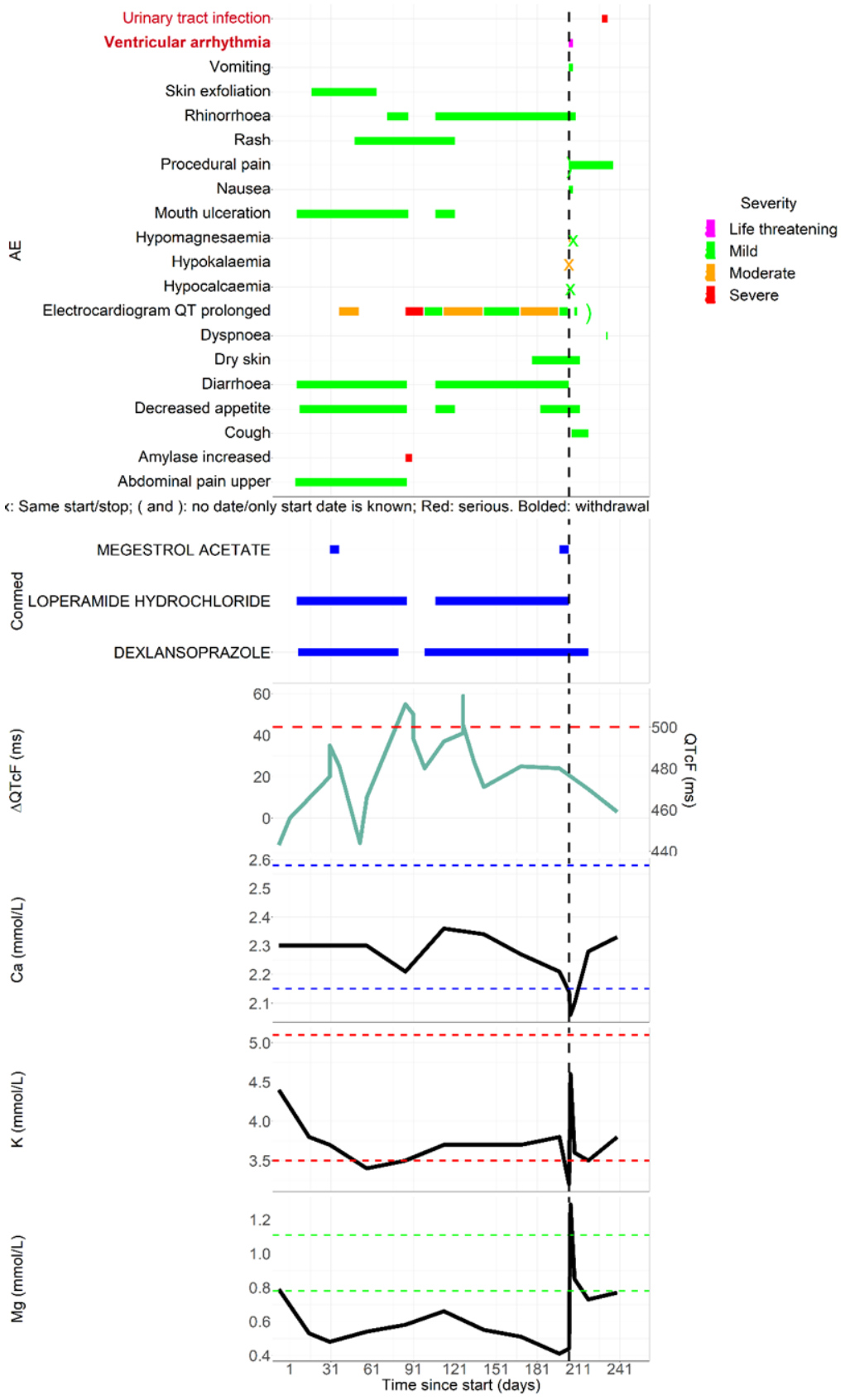
Not applicable.

4.5.2 Other ECG intervals

The reviewer's exploratory analysis suggested a positive exposure-response relationship between mobocertinib concentration and JTPc intervals. QTc prolongation with JTPc prolongation has been associated with predominant hERG block and torsade risk. The wide confidence intervals in ΔJTPc (Figure 5 and Figure 6) are likely because challenges associated with accurately determining the peak of the T wave in flat T waves, which were observed in some patients. In addition, interpretation of JTPc findings should be done together with best practice multi-ion channel in vitro pharmacology data (draft ICH S7B Q&As 08/2020). Thus, while the JTPc findings should be interpreted with caution, they are unlikely to change the overall interpretation of the QTc findings.

4.6 SAFETY ANALYSIS

Below is a graphic representation of the narrative for the patient with the torsade event. The patient had several AEs of QT interval prolongation and hypomagnesemia prior to the arrhythmia.



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/s/

NAN ZHENG
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Hezhen Wang is the primary clinical pharmacology reviewer.

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YU YI HSU
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