CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216340Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: November 9, 2022

To: Opeyemi Udoka DPT, CSM, Regulatory Project Manager, Division of Oncology (DO2)

From: Adesola Adejuwon, PharmD, MBA, Regulatory Review Officer Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, MS, RN, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for KRAZATI™ (adagrasib) tablets, for oral use

NDA: 216340

Background: In response to DO2's consult request dated November 9, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI) and carton and container labeling for the original NDA submission for KRAZATI™ (adagrasib) tablets, for oral use, (Krazati).

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on November 4, 2022, and our comments 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 November 3, 2022.

Carton and Container Labeling:
OPDP has reviewed the proposed carton and container labeling accessed from SharePoint on November 7, 2022, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Adesola Adejuwon at 240 402 5773 or Adesola.Adejuwon@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:	November 3, 2022
To:	Opeyemi Udoka, DPT, CSM Regulatory Health 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)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adesola Adejuwon, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	KRAZATI (adagrasib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 216340
Applicant:	Mirati Therapeutics, Inc.

1 INTRODUCTION

On December 14, 2021, Mirati Therapeutics, Inc. submitted for the Agency's review an original New Drug Application (NDA) 216340 for KRAZATI (adagrasib) tablets. The proposed indication for KRAZATI (adagrasib) tablets is for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with *KRAS G12C* mutation as determined by an FDA approved test, and who have received at least one prior systemic therapy.

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 January 19, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for KRAZATI (adagrasib) tablets. We note that the proposed proprietary name was found to be conditionally acceptable by the Division of Medication Error Prevention and Analysis 2 (DMEPA 2) on February 16, 2022.

2 MATERIAL REVIEWED

- Draft KRAZATI (adagrasib) tablets PPI received on December 14, 2021 and revised on May 3, 2022, and received by DMPP and OPDP on October 11, 2022.
- Draft KRAZATI (adagrasib) tablets Prescribing Information (PI) received on December 14, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 11, 2022.
- Approved LUMAKRAS (sotorasib) NDA 214665 comparator labeling dated May 28, 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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11/03/2022 03:31:02 PM

LASHAWN M GRIFFITHS
11/03/2022 03:32:08 PM

LABEL AND LABELING REVIEW
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)

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

Date of This Review:	May 19, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 216340
Product Name, Dosage Form, and Strength:	Krazati (Adagrasib) tablets, 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Mirati Therapeutics Inc.
FDA Received Date:	December 14, 2021
OSE RCM #:	2021-2133
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Acting Team Leader:	Janine Stewart, PharmD

1 REASON FOR REVIEW

As part of the approval process for Krazati (Adagrasib) tablets, the Division of Oncology 2 (DO2) requested that we review the proposed Krazati prescribing information (PI), container labels, and carton labeling 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 – 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 reviewed the proposed Krazati PI, container labels, and carton labeling and determined that they may be improved to ensure safe product use.

Additionally, we sent an Information Request to the Applicant to clarify what information is [redacted] (b) (4) on the side panel of the container label and carton labeling. The Applicant responded that [redacted] (b) (4) "[a]

[a] Response to Request for Information. MRTX849 – NDA 216340. San Diego (CA): Mirati Therapeutics Inc. 2022 Feb 16. Available from: \\CDSESUB1\evsprod\nda216340\0011\m1\us\response-to-rfi-labeling-[redacted] (b) (4).pdf.

4 CONCLUSION & RECOMMENDATIONS

The proposed Krazati PI, container labels, and carton labeling may be improved to ensure safe product use. We provide specific recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage and Administration Section
   a. The "How should I take MRTX849" section of the Patient Package Insert states "Swallow MRTX849 tablets whole." However, Section 2.2 Recommended Dosage does not provide any information to swallow tablets whole. Clarify whether the tablets can or cannot be crushed.
   b. The reduced dosage information in Table 1 should be presented as the total dose followed by the number of tablets in parentheses to be consistent with the recommended dosage. Thus, revise the dosage information in Table 1 to "400 mg (two 200 mg tablets) twice daily" and "600 mg (three 200 mg tablets) once daily".

4.2 RECOMMENDATIONS FOR MIRATI THERAPEUTICS INC.

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

A. General Comments (Container labels & Carton Labeling)

1. (b) (4) is presented twice on the principal display panel (PDP). Delete (b) (4) to reduce clutter.
2. The established name appears to lack prominence commensurate with the proprietary name. Ensure the font size of the established name is at least half the font size of the proprietary name in accordance with 21 CFR 201.10(g)(2).
3. As currently presented on the PDP, the net quantity statement (120 tablets and 180 tablets) is located right below the strength (200 mg) (b) (4) which may result in the net quantity statement being mistaken as the strength. Relocate the net quantity statement away from the strength to the bottom third of the PDP to minimize confusion.
4. The proposed container labels (b) (4) is uncustomary and suggests a difference in strength, which may lead to confusion. The "120 tablets" and "180 tablets" net quantity statements serve to

differentiate the packaging configurations within the product line. Revise the container labels [redacted] (b) (4) for both of the packaging configurations.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Krazati received on December 14, 2021 from Mirati Therapeutics Inc..

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Krazati</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>Adagrasib</td></tr>
<tr><td>Indication</td><td>treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with KRAS G12C mutation as determined by an FDA approved test, and who have received at least one prior systemic therapy.</td></tr>
<tr><td>Route of Administration</td><td>oral</td></tr>
<tr><td>Dosage Form</td><td>tablets</td></tr>
<tr><td>Strength</td><td>200 mg</td></tr>
<tr><td>Dose and Frequency</td><td>600 mg twice daily

Dosage Reduction for Adverse Reaction
<table>
<tr><th>Dosage Reduction Level</th><th>Reduced Dosage</th></tr>
<tr><td>First dose reduction</td><td>(b) (4) (400 mg) twice daily</td></tr>
<tr><td>Second dose reduction</td><td>(b) (4) (600 mg) once daily</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td>Bottle of 120 tablets
Bottle of 180 tablets</td></tr>
<tr><td>Storage</td><td>Store tablets at room temperature, 20°C to 25°C (68°F to 77°F).</td></tr>
<tr><td>Container Closure</td><td>high density polyethylene (HDPE), white, opaque bottles with induction seal, child-resistant polypropylene (PP) caps, and two 1 g desiccant canisters. Bottle sizes are 215 cc (for 180 count 200 mg tablets) and 150 cc (for 120 count 200 mg tablets).</td></tr>
</table>

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,[b] along with postmarket medication error data, we reviewed the following Krazati labels and labeling submitted by Mirati Therapeutics Inc..

- Container label received on December 14, 2021
- Carton labeling received on December 14, 2021
- Prescribing Information and Patient Package Insert (Image not shown) received on December 14, 2021, available from \\CDSESUB1\evsprod\nda216340\0003\m1\us\adagrasib-uspi.docx

G.2 Label and Labeling Images

Container labels

(b) (4)

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

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Clinical Inspection Summary

Date	May 10, 2022
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	Katie Chon, Clinical Reviewer Paz Vellanki, MD, Team Lead Harpreet Singh, MD, Division Director Division of Oncology 2 Office of Oncologic Products
NDA #	NDA 216340
Applicant	Mirati Therapeutics, Inc.
Drug	Adagrasib
NME (Yes/No)	Yes
Therapeutic Classification	Monoclonal Antibody
Proposed Indication(s)	Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with KRAS G12C mutation who have received at least one prior systemic therapy
Consultation Request Date	January 26, 2022
Summary Goal Date	May 14, 2022
Action Goal Date	TBD
PDUFA Date	June 14, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study 849-001 were submitted to the Agency in support of a New Drug Application (NDA 216340) for adagrasib for the above proposed indication. Four clinical investigators (Drs. Pasi Janne, Gregory Riely, Igor Rybkin/Shirish Gadgeel, and Alexander Spira) were selected for clinical inspection, as well as the contract research organization (CRO), (b) (4).

Although there were some inspectional findings related to under reporting of adverse events and concomitant medication at Dr. Igor Rybkin/Shirish Gadgeel site, the inspections revealed no significant findings at the remining clinical investigator sites or the CRO. Based on the results of these inspections, the Study 849-001 overall appears to have been conducted adequately and the data generated by the inspected clinical investigators and the CRO appear acceptable in support of the respective indication in the NDA.

II. BACKGROUND

Mirati Therapeutics, Inc seeks approval for adagrasib for the treatment of adult patients with locally advanced or metastatic NSCLC with KRAS G12C mutation as determined by an FDA approved test and who have received at least one prior systemic therapy. Adagrasib is a new molecular entity and was granted Breakthrough Therapy Designation for the proposed indication.

Clinical data from Cohort A of an ongoing, phase I/II, dose-finding, multi-cohort study of adagrasib in patients with previously treated metastatic KRAS G12C mutation positive NSCLC was submitted to support this NDA.

The application includes efficacy and safety data from 116 subjects enrolled in Cohort A of the study who received at least one dose of adagrasib. The primary efficacy endpoint is overall response rate (ORR), as assessed by an Independent Review Committee (IRC) according to RECIST v 1.1. Secondary efficacy endpoints are duration of response, progression-free survival (PFS) and one-year survival rate.

Eligible patients were to sign an informed consent prior to any study specific assessment. Baseline tumor assessment was to be performed within 28 days prior to Cycle 1, Day 1 (C1D1) and every 6 weeks from C1D1 (+/- 10-day window), until week 49 and then every 12 weeks.

The first subject was enrolled on January 17, 2020, and the data cutoff date for the NDA is June 15, 2021. At the time of the data cutoff, the study was being conducted at 29 investigational sites in U.S.

Four clinical investigators were identified for inspection by the review division (DO2) and OSI: Dr. Pasi Janne, Site # 808 (Boston MA), Dr. Gregory Riely, Site # 806 (New York, NY), Dr. Igor Rybkin/ Shirish Gadgeel, Site # 811 (Detroit, MI), and Dr. Alexander Spira, Site # 814 (Fairfax, VA). 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.

(b) (4), the CRO was chosen for evaluation of the conduct of study 849-001 in lieu of the Sponsor inspection to examine its conduct and oversight of the study, given that the Master File and related documents are located at (b) (4).

III. RESULTS (by site)

1. **Dr. Pasi Janne** (Site # 808)
   Dana-Farber Cancer Institute
   1450 Brookline Ave
   Boston, MA 2215
   Inspection dates: 02/09 – 02/16/2022

Dr. Pasi Janne was inspected as a surveillance inspection for Study 849-001. This investigator has been previously inspected on 05/05/16, 08/07/15, and 06/21/21, all classified as NAI.

A total of 22 subjects were enrolled into cohort A of the Study 849-001. Of the 22 subjects, 14 subjects were seen at the Dana-Farber Cancer Institute and 8 subjects at the sub-site located at Massachusetts General Hospital.

Source records of 14 subjects with records available at the Dana-Farber Cancer Institute site were reviewed and compared to the line listings included in the NDA submission. Records reviewed include informed consent form, serious adverse events, concomitant medications, inclusion/exclusion criteria, and dates of imaging scans used for efficacy endpoint assessment. In addition, IRB correspondence and approvals, monitoring and sponsor correspondence, study protocols and amendments, clinical site staff training documentation, financial disclosure documents, and drug accountability records were reviewed.

All subjects met inclusion/exclusion criteria, had documentation of KRAS G12c mutation status and had received previous cancer treatment as required per protocol. Computer tomography scans were performed according to protocol specified time points and were verifiable at the site. There were no scans at the site that were not submitted to the Sponsor for central review.

Protocol Violation

Protocol violations not reported to the NDA were observed in 2 subjects who received prohibited medication ondansetron while on adagrasib.

Ondansetron is listed as medication to be avoided (protocol version 1.0 to 6.0) due to the known risk of QT prolongation and Torsade de Pointes The protocol was amended (version 7.0, 12/23/2020) to allow for oral ondansetron at doses up to 4 mg every 6 hours, with a maximum total daily dose of 16 mg for patients without underlying bradycardia, CHF, or congenital long QT syndrome. Use of intravenous ondansetron is to be avoided during the study.

Subject # 849-001-(b) (6): Subject # (b) (6) received adagrasib from (b) (6) thru (b) (6) (Day 1-10). She was hospitalized on Day 10 with grade 3 nausea, vomiting, and renal failure. Nausea and vomiting were reported as serious and intractable, and she was given ondansetron (IV 4mg q8hrs) in addition to metoclopramide, dexamethasone, lorazepam, olanzapine, and famotidine. Ondansetron was administered from (b) (6) thru (b) (6). On day 15 she was diagnosed with CHF with increased cardiac troponin, decreased EF, pericardial effusion, and intermittent tachycardia. She died on day 19 due to progressive CHF attributed to adagrasib.

Reviewer's comment: The administration of ondansetron was reported in the NDA but not reported as a protocol violation. The contribution of ondansetron to the cardiac toxicity observed in this subject is unclear. OSI notes that although IV ondansetron is listed as a medication to be avoided, its use appears justified given the severity of the nausea and vomiting in this subject and concomitant administration of several other anti-emetic drugs in the ICU setting.

Subject # 849-001-(b) (6): Review of the concomitant medication datasets following the on-site inspection revealed one additional protocol violation related to prohibited medications.

Subject #(b) (6) received adagrasib from (b) (6) thru (b) (6). She was reported as having prolonged QTc interval on ECG from (b) (6) thru (b) (6) and persistent hyponatremia. These events were reported as AEs in the study. The subject was given ondansetron (unknown dosage) on (b) (6) purportedly for bronchoscopy. No adverse events related to cardiac arrhythmias were reported.

Reviewer's comment: Administration of ondansetron was reported in the NDA but not reported as a protocol violation. Although there was no apparent harm to this subject, administration of a drug known to have risk of QT prolongation and Torsade de Pointes to a subject with prolonged QT interval placed the subject at risk for a potentially serious event. DO2 should consider an IR to request the Sponsor to update this and other potential protocol violations and proposed a Corrective and Prevention Action plan to monitor investigators for similar violations.

In addition, review of the medical records indicate that two additional subjects were prescribed ondansetron: subject # 849-001-(b) (6) was prescribed ondansetron as needed for nausea (dosage unknown) and subject # 849-001-(b) (6) was restarted ondansetron (dosage unknown) 5 days prior to starting study treatment. Based on the review of the medical history and adverse event logs, this protocol violation did not suggest that the safety of these subjects was placed at undue risk.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Janne at the conclusion of the inspection. Notwithstanding the protocol violations listed above, data generated by Dr. Janne appear to be acceptable in support of the NDA.

2. **Dr. Gregory Riely** (Site # 806)
   Memorial Sloan-Kettering Cancer Center
   1275 York Ave
   New York, NY 10065

   Inspection dates: 02/22 – 02/25 and 02/28/2022

   Dr. Riely was inspected as a surveillance inspection for Study 849-001. This was the first FDA inspection for this investigator.

   At the time of the inspection, the investigator had screened 21 subjects and enrolled 15 subjects into Cohort A of the study. Of the 15 subjects, 13 had discontinued treatment: 6 had died due to disease progression, 1 discontinued due to an AE, 2 in survival follow-up phase, 4 withdrew consent, and 2 subjects were actively on study treatment.

   Source records from all 21 subjects were reviewed and found the site followed protocol procedures. Records from all 15 enrolled subjects were compared to the line listings included in the NDA. Records reviewed include informed consent forms, subject eligibility, adverse events, concomitant medications, protocol deviations, and laboratory values.

   Additional documents reviewed include visit notes, pharmacokinetic worksheets, patient diaries, financial disclosures forms, IRB communications, monitoring logs, investigational product, electronic medical records (EMR), and electronic regulatory binders (PIMS) were also reviewed.

   No discrepancies were observed between the data listings and the source documentations. All subjects met inclusion/exclusion criteria. No under-reporting of AEs or SAEs were observed. All diagnostic imaging performed at the site were appropriately uploaded to (b) (4) database (imaging CRO).

   The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Riely at the conclusion of the inspection.

3. **Dr. Igor Rybkin/ Dr. Shirish Gadgeel** (Site # 811)
   Henry Ford Hospital
   2799 West Grand Blvd.
   Detroit, MI 10016

   Inspection dates: 03/02 – 03/14/2022

   At the inspection preannouncement, FDA was informed that Dr. Igor Rybkin, the investigator who initiated the study at the site, had left the institution in November. Dr. Shirish Gadgeel was the responsible individual for Study 849-001 effective 11/02/2021.

Dr. Gadgeel was previous inspected in 2015 and the inspection classification was NAI.

At the time of the inspection, the site had screened 12 subjects and enrolled 9 subjects in study 849-001. The first subject was enrolled on 03/05/2020 and the last subject on 04/01/2021. Of the 9 subjects enrolled, 5 subjects had died, 1 completed study treatment, 2 are actively receive treatment and 1 subject was lost to follow up.

Source documents were reviewed for all 9 enrolled subjects and compared with the submitted line listings. Records reviewed included informed consent, verification for eligibility, medical assessments notes, laboratory results, follow up visits, drug administration and usage, and safety event records.

Other documents reviewed during the inspection include IRB documents and approvals, delegation log, training records, drug accountability records, monitoring reports, and electronic records.

Two significant issues were observed during the inspection:

A. Three unreported adverse events and one unreported concomitant medication were identified during the inspection:

1. **Subject # 849-001-** (b) (6)**:** According to the source records at the site, the subject was hospitalized on (b) (6), approximately 8 months after initiation of adagrasib, with radiation induced cholecystitis and sepsis. The subject had received intrahepatic radiation beads (Thera Sphere) implantation on (b) (6), apparently for treatment of hepatic metastasis. She received IV piperacillin and vancomycin for sepsis and conservative management for the radiation induced cholecystitis. Blood cultures were negative, and she was discharged 7 days later to continue with adagrasib treatment.

   Reviewer's comment: The adverse event of sepsis and the use of intrahepatic radiation beads to treat the above patient's condition were documented in the physician's discharge summary but not reported to the Sponsor. The clinical investigator failed to report the concomitant treatment with Thera Sphere and sepsis as an adverse event to the Sponsor. This should have been reported in accordance with the investigational plan. We recommend that the review division determines if the above unreported sepsis adverse event would need to be included in its analysis and the impact of intrahepatic radiation bead administration on the efficacy outcome.

2. **Subject # 849-001-** (b) (6): According to the source records, the subject had a Venous Duplex Examination of the lower extremities performed on (b) (6) showing *"total occluding acute and chronic deep vein thrombosis of the left femoral vein"* not reported to the NDA. The subject had prior history of pulmonary emboli and had been on enoxaparin since (b) (6). The subject was hospitalized on study Day 71 with worsening shortness of breath, confusion

and swelling of the leg. He was diagnosed with pneumonia based on the findings of a chest CT and prescribed antibiotics, O2, and alteplase, the later, purportedly for shortness of breath. He developed progressive respiratory failure and mild hemoptysis. A decision was made to make the subject DNR and placed on hospice care. The subject died 4 days after admission. The cause of death was pneumonia.

Reviewer's comment: The clinical investigator failed to report DVT as adverse event to the Sponsor. This should have been reported in accordance with the investigational plan. The adverse event DVT is not currently included in the proposed labeling text for the product. We recommend that the review division determines if the above unreported adverse event would need to be included in its analysis.

3. **Subject # 849-001-(b) (6)**: Based on the source records, the subject had an EEG performed on 1(b) (6) to evaluate seizure but seizure was not reported as an AE to the NDA. The subject was hospitalized on (b) (6) (study day 120) with sudden onset of lower extremity weakness and mental status changes. CT scan did not reveal acute changes. The altered mental status progressively worsened, and the subject was transferred to the ICU and transitioned to hospice care. The subject had been on levetiracetam for seizure. The subject died 24 days after admission. The event of mental status change was reported as fatal (Grade 5), and the cause of death was reported as due to malignancy.

   Reviewer's comment: The clinical investigator failed to report the adverse event of seizure to the Sponsor. This should have been reported in accordance with the investigational plan.
   The adverse event seizure is not currently included in the proposed labeling text for the product. We recommend that the review division determines if the above unreported adverse event would need to be included in its analysis.

B. Three patients were not re-consented using revised informed consent form: in January 2021, the clinical investigator submitted a Request for Planned Change to the Henry Ford Health System IRB to implement amendment to protocol 849-001 (v. 7.0, 12/23/2020) and revised consent forms associated with the protocol. Study protocol v 7.0 contained numerous revisions, including updates on clinical safety experience, AE management guidelines and guidance on use of concomitant medications. The associated ICF contained updates on clinical safety experience and revisions to inform subjects on the risks of adagrasib. In addition to updating the incidence of the previous listed AEs, new AEs were added to list, including new risks of nausea, anemia, vertigo, peripheral edema, and cardiac failure.

Three subjects (ID # 849-001-(b) (6), # 849-001-(b) (6), and # 849-001-(b) (6)) were not properly re-consented using the revised version of the informed consent (Version 7).

Following a Full Board Meeting, on 02/09/2021 the IRB approved the implementation of the protocol but did not consider the risk of subjects increased and recommended against re-consenting currently active subjects.

Reviewer's comment: It is the responsibility of the CI and the research staff to ensure that participants are informed of any changes or new information that may influence their decision to continue to participate in a research protocol. Three subjects (ID # 849-001-(b) (6), # 849-001-(b) (6), and # 849-001-(b) (6)) were receiving adagrasib at the time of the consent form amendment (version 7.0) and should have been re-consented for the study

4. **Dr. Alexander Spira** (Site # 814)
Virginia Cancer Specialists
8613 Lee Highway
Fairfax, VA 22031

Inspection dates: 02/28 – 03/04/2022

Dr. Alexander Spira was inspected as a surveillance inspection for Study 849-001. Dr. Spira was previously inspected in 01/2017 while he was at Virginia Cancer Specialists located in Fairfax, VA and classified as no action indicated (NAI).

At the time of the inspection, the site had screened 14 subjects and enrolled 11 subjects into cohort A of the study: 8 subjects had died due to progressive disease, and 3 were on active treatment.

Source records of all 11 enrolled subjects were reviewed and compared to the line listings included in the NDA submission. Records reviewed include subject selection criteria, informed consent forms, clinical source data, adverse event reports, serious adverse event reports, case report forms (CRFs), RECIST1.1 tumor assessment worksheets, laboratory results, and subject questionnaires. The subject source records were compared to the line listings and were found to be the same. No unreported serious adverse events observed.

In addition, FDA 1572s, the protocol and amendments, Institutional Review Board (IRB) submissions and approvals, sponsor/monitor correspondence, test article accountability, staff training, and financial disclosures were reviewed.

The RECIST tumor assessment worksheets at the site were compared with the line listings submitted to the NDA with the data cut off 06/15/2021 and no discrepancies were observed. There were no scans at the site that were not submitted to the Sponsor for central review.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Spira at the conclusion of the inspection. The data generated by Dr. Spira appear to be

acceptable in support of the NDA.

5. (b) (4)

Inspection dates: (b) (4)

(b) (4) was inspected as data audit and surveillance inspection for Study 849-001. This CRO has been previously inspected in (b) (4) and received a final classification of NAI.

Records reviewed at the inspection included review of the study master file, standard operating procedures (SOPs) related to the study, site monitoring, handling of adverse events, data collection, determining if the CRO discovered any non-compliant sites, and how the CRO tried to bring these sites into compliance. Information was also obtained concerning procedures for selection of clinical investigators, selection of monitors, monitoring procedures and frequency, contract services used, and other sponsor/CRO monitor related activities.

There were no issues with the investigators or monitoring staff qualifications, training, experience, or compliance with the investigational plan. No objectionable conditions or practices were observed.

The inspection reviewed site records of 4 sites selected for inspection (Site # 001-806 Gregory Riely, Site # 001-808 Pasi Janne, Site #001-811, Shirish Gadgeel, and Site 001-814 Alexander Spira), records from Site 001-808A Rebecca Heist was also reviewed. Records reviewed include monitoring visit logs, monitoring visit reports in additional to Form 1572, financial disclosure forms, and IRB correspondence.

There were no issues or discrepancies observed related to the frequency of monitoring visits, communication, procedure for review of source documents, implementation of corrective actions to delay AE reporting or protocol deviations nor review of drug accountability records by the monitors with the inspected sites.

Reviewer's Comment: inspection of (b) (4) *occurred prior to Dr. Rybkin/ Dr. Gadgeel (Site # 811), thus the monitoring reports reviewed during the* (b) (4) *inspection did not capture the concerns raised during the site # 811 inspection. The inspection found no regulatory violations at the site. No Form FDA 483 was issued to* (b) (4) *at the conclusion of the inspection.*

{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}

Lee Pai-Scherf on behalf of Karen Bleich, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

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

CC:

Central Doc. Rm.
Review Division /Project Manager/Opeyemi Udoka
OSI/ GCP Program Analysts/Yolanda Patague
OSI/Database PM/Dana Walters

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

/s/

LEE HONG PAI SCHERF
05/10/2022 04:46:00 PM

KASSA AYALEW
05/11/2022 05:51:57 AM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 216340
Submission Number	003
Submission Date	12/14/2021
Date Consult Received	1/14/2022
Drug Name	Adagrasib
Indication	Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with KRAS G12C mutation as determined by an FDA approved test and who have received at least one prior systemic therapy.
Therapeutic Dose	600 mg BID
Clinical Division	DO2
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the Applicant's document.

This review responds to your consult dated 1/14/2022 regarding the Applicant's QT evaluation. We reviewed the following materials:

- Previous IRT review dated 09/22/2020 (link) and 01/04/2022 (link) in DARRTS
- Proposed label (NDA216340 / SDN0003; link)
- Concentration-QT modeling report (NDA216340 / SDN0001, link)
- QT evaluation report submission checklist (NDA216340 / SDN0008, link)
- Study 849-001 Cohort A clinical study report (NDA216340 / SDN0001, link)
- Study 849-001 Cohort B-D clinical study report (NDA216340 / SDN0001, link)
- Study 849-001 integrated summary of safety report (NDA216340 / SDN0002, link) and narratives (NDA216340 / SDN0002, link)

1 SUMMARY

Adagrasib (or MRTX849) causes concentration dependent QTcF prolongation. At the recommended therapeutic dose, 600 mg BID, mean increases in QTc from baseline >20 ms cannot be excluded according to both the by-time and concentration-QTc analyses. 6.6% patients had QTc >500 ms. One patient (ID (b) (6)) experienced a fatal cardiac arrest, which was probably related to adagrasib based on review of the patient narrative. The QTcF was prolonged (around 500 ms) at the time of the cardiac arrest.

The QT effect of adagrasib was evaluated in subjects with advanced solid tumors with KRASG12C mutation (Study 849-001) at the recommended therapeutic dose, 600 mg

BID. The by-time which showed that adagrasib is associated with mean increases in the QTcF interval >20 msec from baseline – see Table 1 for summary of results.

C-QTc analysis also showed mean increases >20 msec at therapeutic exposures. Adagrasib exposure may be impacted by high fat diet. Based on the Applicant's findings, high calorie and high fat diets increase Cmax and AUC∞ of adagrasib tablet formulation by 20% and 38%, respectively. No other extrinsic or intrinsic factors have clinically meaningful influence on adagrasib PK.

Table 1: Point Estimates and the 90% CIs by Visit and Time (FDA Analysis)

Treatment	Study	VISIT	N	Time (Hours)	ΔQTCF (msec)	90% CI (msec)
Adagrasib 600 mg BID	849-001	C1D1	234	4.0	1.1	(-0.7 to 2.9)
Adagrasib 600 mg BID	849-001	C1D8	229	0.0	23.8	(21.3 to 26.4)
Adagrasib 600 mg BID	849-001	C1D8	213	4.0	21.9	(19.2 to 24.7)
Adagrasib 600 mg BID	849-001	C2D1	215	0.0	18.1	(15.6 to 20.6)
Adagrasib 600 mg BID	849-001	C2D1	194	4.0	17.9	(15.4 to 20.5)
Adagrasib 600 mg BID	849-001	C3D1	198	0.0	15.3	(12.3 to 18.2)
Adagrasib 600 mg BID	849-001	C5D1	164	0.0	17.7	(14.9 to 20.5)

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

Our outlier analysis including both triplicated and single ECGs in subjects with post-baseline and valid baseline measurements showed QTcF > 500 msec were observed in 6.6% (17/257) patients and increases from baseline in QTcF > 60 msec were observed in 13.2% (34/257) patients in patients receiving adagrasib 600 mg BID in study 849-001, which is consistent with the values in the product labeling.

Of 260 patients who received adagrasib 600 mg BID in study 849-001, 7 (2.7%) patients experienced 8 SAEs of QT prolongation/TdP. The 8 SAEs are electrocardiogram QT prolonged (2 events), syncope (1 event), ventricular fibrillation (1 event), ventricular tachycardia (1 event), cardiac arrest (1 event), and seizure (2 events). The SAEs of seizure and prolonged QT showed no evidence of ventricular arrhythmias. Please see section 4.6.

Dr. Fred Senatore, the lead cardiologist in DCN, was consulted on the SAEs of syncope, ventricular fibrillation/ventricular tachycardia, and fatal cardiac arrest (Subject ID (b) (6)). Based on the narrative, the cause of the fatal cardiac arrest was probably related to MRTX849, which is different from the Applicant's assessment. The QTcF was prolonged (500 ms, where prolongation is defined as > 460 msec in women) at the time of the cardiac arrest. There were no reported concomitant medications or concomitant conditions that might have been a confounder to QTc prolongation. The other SAEs reviewed by Dr. Senatore were not related to MRTX849 (see Appendix 5).

1.1 RESPONSES TO QUESTIONS POSED BY APPLICANT

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

1. For Subject ID [redacted] (b) (6) who had SAEs of ventricular fibrillation/ventricular tachycardia, Dr. Senatore suggests asking the Applicant to re-evaluate the resuscitated post-arrest ECG to ascertain whether the polymorphic ventricular tachycardia (PMVT) was a torsade de points (TdP) form of PMVT, and to confirm the two separate ECGs as suggested by the narrative text: pre-arrest monomorphic ventricular tachycardia and resuscitated post-arrest PMVT. If they are the same ECG consequent to lack of clarity in text content, the Applicant should explain the reason for two distinct diagnoses from the same ECG (see Appendix 5 for his full assessment).
2. QTcF interval prolongation was also detected in Study 849-006 in healthy subjects taking lower doses of adagrasib.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are our proposed edits to the label submitted to SDN0001 (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.

[redacted] (b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

3 APPLICANT'S SUBMISSION

3.1 OVERVIEW

3.1.1 QTc Assessment

The Applicant's QTc assessment strategy was reviewed previously (see Protocol review and TQTwaiver request reviews).

In the current submission, the Applicant has conducted concentration-QTc analysis, as a primary analysis, using all but 12 subjects from study 849-001 while cohort 4 of study 849-006 was used for exploration of QT hysteresis and heart-rate time profiles (See section 3.2.3). The Applicant reports that, the 12 subjects were excluded from the analysis because of non-BLQ concentration at baseline possibly due to protocol violation during sample collection. The IRT's analysis differs from the Applicant's analysis in that, the by-time point analysis was used as a primary analysis of study 849-001 and 849-006, separately. Study 849-006 was used mainly to inform drug effect on PR intervals since study 849-001 did not collect that information. Details of the reviewer's analysis are provided in section 4.3. Table 2 summarizes the study design of the 5 cohorts of study 849-001. The safety analysis is focused on the safety population who received adagrasib (MRTX849) 600 mg BID dosing (n = 260).

Table 2. Summary of Study 849-001

Study part	Patient population	Dose and number of subjects received any dose	Matching PK/ECG schedule
Phase 1/1b (dose finding)	Solid tumor with KRAS G12C mutation in tumor tissue	600 mg BID (n = 20) 150 mg QD (n = 1) 300 mg QD (n = 1) 600 mg QD (n = 2) 1200 mg QD (n = 1)	Cycle 1 (4 weeks per cycle): Day 1: predose and peak (4 h post-dose) Day 8: predose and peak Cycle 2: Day 1: predose and peak Cycle 3 and 5: Day 1: predose
Phase 2, Cohort A	Non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation in tumor tissue	600 mg BID (n = 116)	
Phase 2, Cohort B	NSCLC with *KRAS* G12C mutation detected in blood	600 mg BID (n = 56)	
Phase 2, Cohort C	Colorectal cancer (CRC) with *KRAS*	600 mg BID (n = 44)	

	G12C mutation detected in tumor tissue and/or blood		
Phase 2, Cohort D	Other solid tumors with *KRAS* G12C mutation detected in tumor tissue and/or blood	600 mg BID (n = 24)	

Source: Reviewer's independent analysis. Note: The table lists number of subjects in ISS population.

3.1.2 Nonclinical Safety Pharmacology Assessments

MRTX849 was evaluated for its effect on the hERG potassium channel, stably expressed in Chinese hamster ovary (CHO) cells. The screening hERG study for MRTX849 resulted in an IC50 of 4.8 μM which is approximately 54-fold higher than the mean free Cmax at steady state (0.089 μM) in patients after administration of 600 mg BID.

In the isolated Guinea pig Langendorff study, MRTX849 increased QTc by 15 ms, decreased PR interval by 15 ms, and decreased ventricular development pressure by 20 mmHg at 5 μM.

In a single-dose cardiovascular study in telemetry implanted dogs, there were no adverse findings in blood pressure, heart rate, or ECG parameters, included no changes in QT interval, at doses of MRTX849 at doses up to 25 mg/kg. During the conduct of the 28-day repeat dose toxicity study in dogs, blood pressure and ECG parameters were measured in the pre-dose phase, at the end of the 28-day treatment period, and near the end of the recovery period. There were no MRTX849 treatment-related effects in any ECG parameters or blood pressure up to 25 mg/kg/day, the highest dose tested.

3.2 APPLICANT'S RESULTS

3.2.1 By-Time Analysis

There were positive findings (median of ΔQTcP ≥20 msec) at several timepoints.

Reviewer's comment: *For Study 849-001, the Applicant used QTcP for the analysis. The positive findings were also obtained in the reviewer's analysis for ΔQTcF. 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 Applicant's analysis for QTcP in Study 849-001. The applicant did not provide the categorical analysis for Study 849-006.

Reviewer's comment: *We cannot directly compare the categorical analysis in Study 849-001 because we used QTcF instead of QTcP. However, there were outliers in the*

reviewer's analysis for QTcF and ΔQTcF in Study 849-001. In addition, the outlier number cited in the Applicant's proposed label was generated from the ISS adeg dataset including both triplicate ECGs and single ECGs. FDA's categorical analysis included triplicate ECGs only. Based on additional review of the ECG data, FDA reviewer was able to confirm the QTcF and ΔQTcF outlier counts in the label. Please see Section 4.4 for more details.

3.2.3 Exposure-Response Analysis

In absence of placebo control, baseline adjusted QTcP (QTcP = population corrected QT) was the dependent variable, while adagrasib concentration and steady state visit were the only independent predictors as presented in Equation 1. ΔQTcij is the observed QTc change from baseline in the i^{th} subject at time j, θ_0 is the population mean intercept in the absence of a treatment effect; $\eta_{0,i}$ is the random effect associated with the intercept term θ_0; θ_1 is the population mean slope of the assumed linear association between concentration and ΔQTc; $\eta_{1,i}$ is the random effect associated with the slope term θ_1; C_{ij} is the concentration for the i^{th} subject at time j; θ_2 is increase in QTcP at steady state; SSV_1 is either 1 for steady state visit or 0 for baseline visit. ε_{ij} is the residual within subject variability, assumed to be normally distributed with mean zero and variance σ^2

Equation 1: Linear mixed effect model for ΔQTcF

$$\Delta QTcF_{ij} = (\theta_0 + \eta_{0i}) + (\theta_1 + \eta_{1i}) \times C_{ij} + \theta_2 \times SSV_1 + \epsilon_{ij}$$

The results of the Applicant's analysis show a statistically significant linear relationship between adagrasib concentration and QTcP interval prolongation (See Table 3).

Table 3. Concentration-ΔQTcP Model Parameters of adagrasib

Parameter	Estimate	SE	RSE (%)	95% CI
Intercept (θ_0, ms)	-2.07	1.34	64.7	(-4.7, 0.563)
If Visit steady state (ms)	7.93	1.62	20.4	(4.77, 11.1)
Slope (θ_1, ms/(ng/mL))	0.00753	0.000806	10.7	(0.00595, 0.00911)
BSV Intercept (η_0, ms)	6.84	1.2	17.5	(4.89, 9.56)
BSV Slope (η_0, ms/(ng/mL))	0.0054	0.000545	10.1	(0.00444, 0.00657)
Residual error (σ, ms)	15.9	0.41	2.58	(15.1, 16.7)

BSV = between subject variability; CI = confidence interval; ΔQTcP = QTcP change from baseline; QT = ECG QT interval; QTcP = population corrected QT; RSE = relative standard error; SE = standard error

Source: Applicant's concentration-QT modeling report, page 24/64

Based on the concentration-QTc model, the predicted mean (90% CI) QTcP change from baseline (ΔQTcP) was 18.8 (16.4, 21.1) ms at the population geometric mean Cmax,ss in patients after administration of MRTX849 600 mg BID (2240 ng/mL).

Reviewer's comment: *In contrast to the Applicant's analysis, the reviewer used ΔQTcF as the dependent variable instead of ΔQTcP. Furthermore, reviewer's model evaluated adagrasib concentration and baseline QTcF as the only predictors of ΔQTcF. Despite the differences, the findings from the reviewer's analysis are consistent with the Applicant's findings (see section 4.5 for details).*

3.2.4 Safety Analysis

In Study 849-001, electrocardiograms were collected in triplicate predose at baseline (on Cycle 1 Day 1, or where applicable, on PK Lead-In Period Day 1), 4 hours after the first

dose; then predose and 4 hours postdose on Cycle 1 Day 8 and Cycle 2 Day 1; then predose on Day 1 of Cycles 3 and 5.

ICH thresholds included QTcF > 500 msec in 6.6% (17/257) patients in the 600 mg Twice Daily Total group and 8.8% (10/114) patients in Cohort A (ISS Table 14.3.6.2). (Patient 001-(b) (6), who initiated treatment at a dose of 150 mg once daily, experienced a QTcF of 505.3 msec at Cycle 14, Day 1, by which time the patient had dose escalated to 600 mg twice daily; Phase 1/1b CSR Listing 16.2.10.3, Phase 1/1b CSR Listing 16.2.5.1.) Increases from baseline in QTcF > 60 msec were observed in 13.0% (34/262) patients who received any MRTX849, 13.2% (34/257) in the 600 mg Twice Daily group, and 14.9% (17/114) of patients in Cohort A (ISS Table 14.3.6.2).

A medical search using the Torsade de pointes/QT prolongation SMQ (broad search) was performed, excluding preferred term of multiple organ dysfunction syndrome (this term was removed from the Torsade de pointes/QT prolongation SMQ in MedDRA version 23, but this study used version 21.0). Among the 600 mg Twice Daily Total group, 17.7% developed ≥ 1 TEAE in this search, which included electrocardiogram QT prolonged 16.9%, and syncope, cardiac arrest, ventricular fibrillation, and ventricular tachycardia in < 1% each. Severity of the AEs was assessed as Grade 3 for electrocardiogram QT prolonged in 4.6% patients, Grade 3 for syncope in < 1% patients, Grade 4 for ventricular tachycardia and ventricular fibrillation in < 1% patients (reported in same patient), and Grade 5 for cardiac arrest (ISS Table 14.3.3.1.5a.).

ISS Table 14.3.5.1.1a is a summary of time to the first TEAE of Grade 3 electrocardiogram prolonged and the duration Grade 3 electrocardiogram prolonged. The median time to Grade 3 electrocardiogram prolonged was 8.0 days, and the maximum was 22 days (approximately Cycle 2 Day 1) for both Cohort A and the 600 mg Twice Daily Total group. Median durations of Grade 3 electrocardiogram prolonged events were 4 days (range: 2 to 23 days) for Cohort A and 5 days (range: 2 to 23 days) for the 600 mg Twice Daily Total group.

Reviewer's comment: *The Reviewer's analysis is in general consistent with the Applicant's results. Dr. Fred Senatore was consulted on cardiac SAEs that could be related to QTc prolongation and/or TdP. His review is presented in the Appendix.*

4 REVIEWERS' ASSESSMENT

Per the Applicant's study report, a total of 229 patients with 1038 paired plasma concentrations and ECG measurements post first MRTX849 dose at the designated times from Study 849-001 were used for the concentration-QTc analysis. A total of 12 patients from Study 849-001 were excluded because of non-BLQ concentration at baseline. These 12 subjects did not participate in PK run-in and therefore, based on the Applicant's assessment, the non-BLQ samples at baseline in these subjects might be due to protocol violation in PK sampling (e.g., collection of samples in wrong tubes)

In our analyses, for Study 849-001, the dataset used for by-time analysis and categorical analysis was derived from the Applicant's ISS analysis ADaM dataset: adeg.xpt (\\cdsesub1\evsprod\NDA216340\0002\m5\datasets\iss\analysis\adam\datasets\adeg.xpt), and C-QTc analysis was derived from the Applicant's analysis C-QTc dataset: acqt.xpt (\\cdsesub1\evsprod\NDA216340\0008\m5\datasets\mira-pmx-mrtx849-

213\analysis\legacy\datasets\acqt.xpt). For Study 849-006, the dataset used for by-time analysis and categorical analysis was derived from the Applicant's ADaM dataset: adeg.xpt (\\cdsesub1\evsprod\NDA216340\0001\m5\datasets\849-006\analysis\adam\datasets\adeg.xpt). Only triplicate ECG data were included. Table 4 shows the analysis population used in this review.

Table 4. Analysis Population

Analysis Population	Used for	Number of subjects 600 mg BID dose
Safety population (ISS dataset)	AE evaluation	260
ECG population 1 (ISS dataset): subject with valid baseline data and post-dose data, including single ECGs	Categorical analysis to match the Applicant's label	257 (including single ECGs data from subjects 849-001-(b) (6), 849-001-(b) (6), and 849-001-(b) (6))
ECG population 2 (ISS dataset): subject with valid baseline data and post-dose data, excluding single ECGs	Reviewer's categorical analysis	256
ECG population 3 (ISS dataset): subject with valid baseline data and post-dose data from Cycle 1 Day 1 to Cycle 5 Day 1	By-time analysis	255
PK-QT population (CSR dataset) *	CQT	223

*Excluding 12 subjects with non-BLQ concentrations and dataset has a different data cut-off date from ISS.

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The IRT review is based on QTcF. This is acceptable, because there are no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) as shown in section 4.3.2.

4.2 ECG ASSESSMENTS

4.2.1 Overall

For study 849-001, ECGs were read using an automatic algorithm with manual overreads in the case of prolongation of QTc. The PR and QRS intervals as well as ECG waveforms were not collected in study 849-001. Based on general site and monitor practices for source verification and query resolution, it is anticipated that all or nearly all of the reported ECG parameters were fully automated (Applicant's response to IR). For study 849-006, ECG reading was fully automated.

4.2.2 QT Bias Assessment

Not applicable

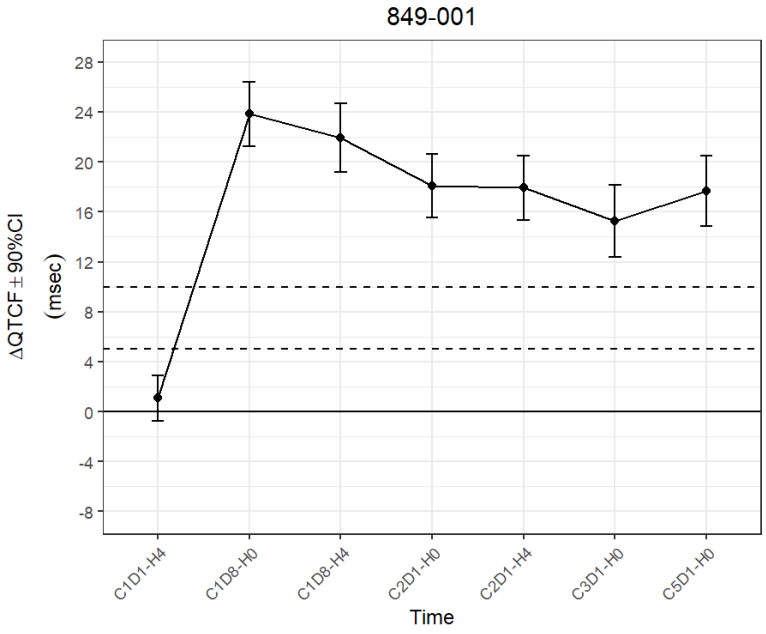
4.3 By-Time Analysis

The analysis population used for the by-time analysis included all subjects with a baseline and at least one post-dose triplicate ECG from Cycle 1 Day 1 to Cycle 5 Day 1 (ECG population 3). In addition, our post-baseline records had paired plasma concentrations and ECG measurements post first adagrasib dose at the designated times from Study 849-001. The statistical reviewer evaluated the ΔQTcF effect using descriptive (parametric) statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for the treatment of adagrasib 600 mg BID in Study 849-001 and the treatment of adagrasib 400 mg BID in Study 849-006. The ΔQTcF values by treatment, visit, and time in two studies are shown in Table 6.

Figure 1: Mean and 90% CI of ΔQTcF Time-course (unadjusted CIs)



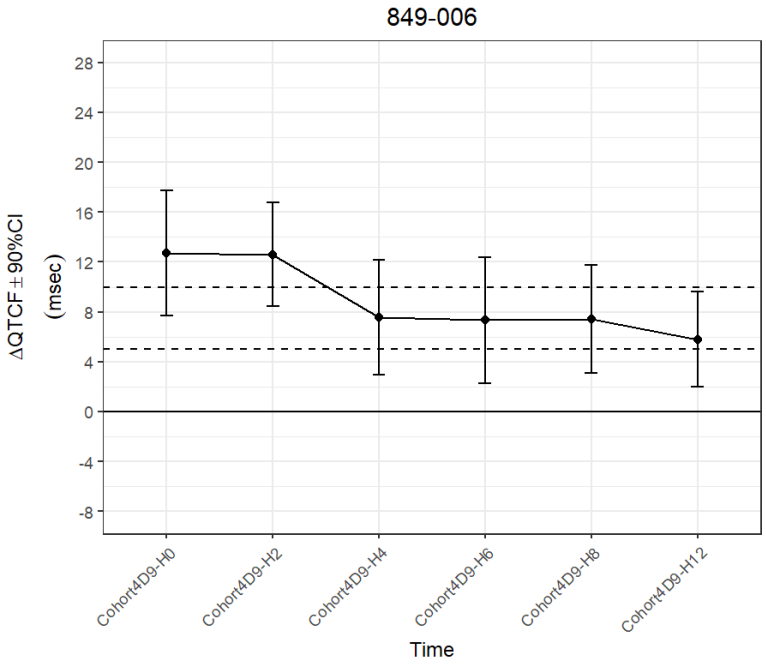


Table 5: Point Estimates and the 90% CIs Corresponding to the Upper Bounds for ΔQTcF by Visit and Time

Treatment	Study	VISIT	Analysis Nominal Period Day (C)	N	Time (Hours)	ΔQTCF (msec)	90% CI (msec)
Adagrasib 600 mg BID	849-001	C1D1	1	234	4.0	1.1	(-0.7 to 2.9)
Adagrasib 600 mg BID	849-001	C1D8	8	229	0.0	23.8	(21.3 to 26.4)
Adagrasib 600 mg BID	849-001	C1D8	8	213	4.0	21.9	(19.2 to 24.7)
Adagrasib 600 mg BID	849-001	C2D1	1	215	0.0	18.1	(15.6 to 20.6)
Adagrasib 600 mg BID	849-001	C2D1	1	194	4.0	17.9	(15.4 to 20.5)
Adagrasib 600 mg BID	849-001	C3D1	1	198	0.0	15.3	(12.3 to 18.2)
Adagrasib 600 mg BID	849-001	C5D1	1	164	0.0	17.7	(14.9 to 20.5)
Adagrasib 400 mg BID	849-006	Cohort4D9	1	19	0.0	12.7	(7.7 to 17.7)

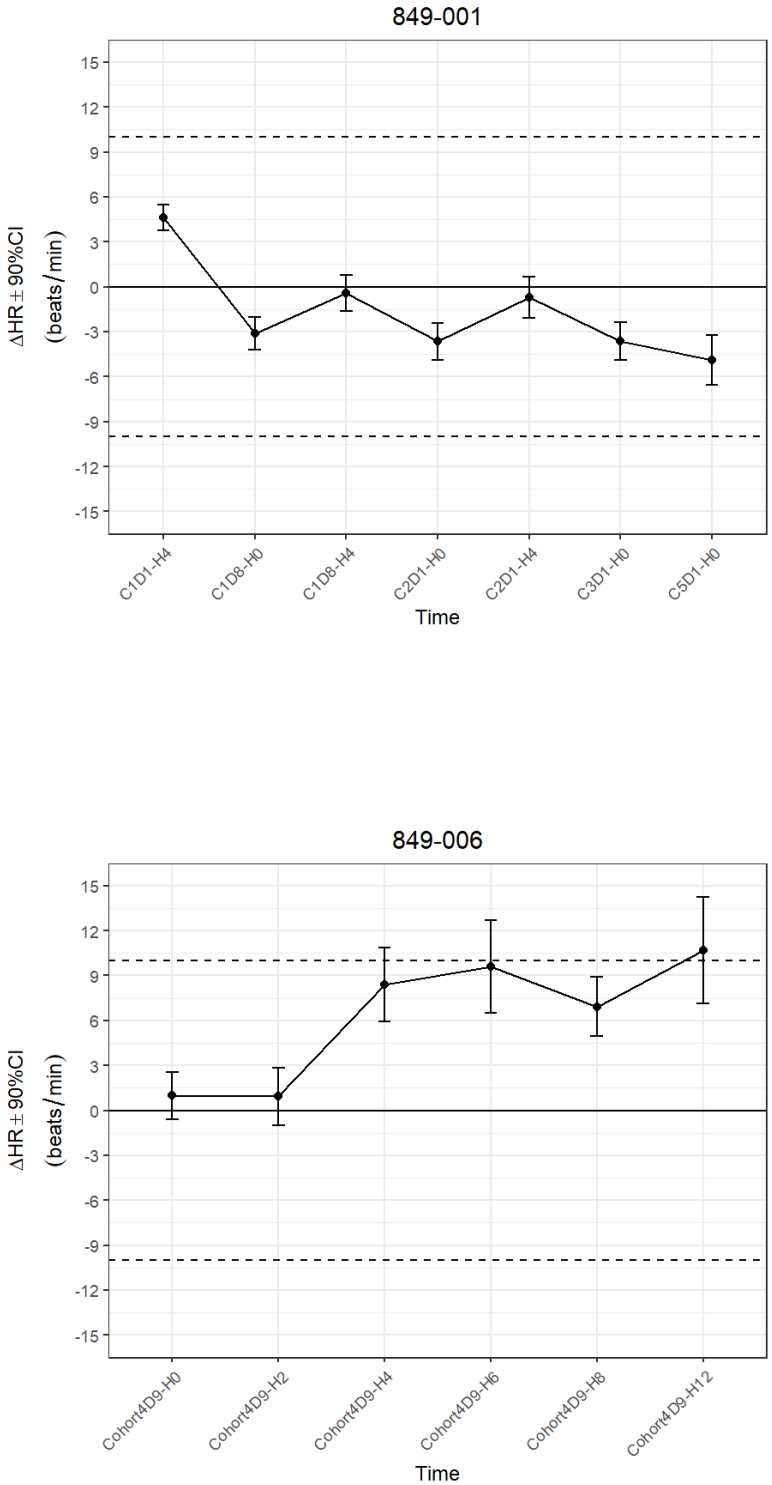
4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for the treatment of adagrasib 600 mg BID in Study 849-001 and the treatment of adagrasib 400 mg BID in Study 849-006.

Figure 2: Mean and 90% CI of ΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔPR for the treatment of adagrasib 400 mg BID in Study 849-006. The maximum mean ΔPR values by treatment are shown in Table 6. PR interval was not collected in Study 849-001.

Figure 3: Mean and 90% CI of ΔPR Time-course

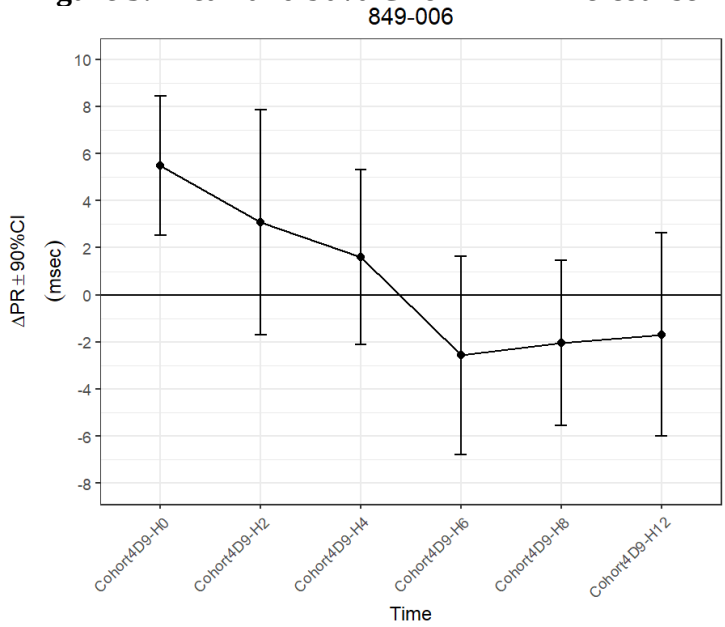


Table 6. Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔPR

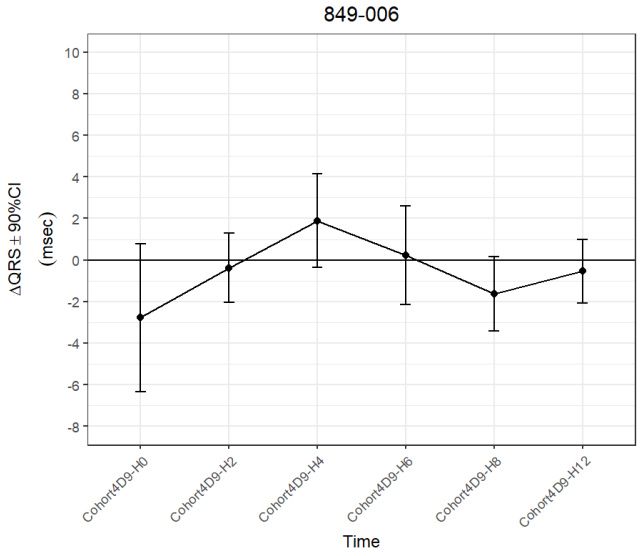
Treatment	N	Time (Hours)	ΔPR (msec)	90% CI (msec)
Adagrasib 400 mg BID	19	0.0	5.5	(2.5 to 8.4)

Reviewer's Comment: The reviewer's assessment determined that the PR changes were not concentration dependent and therefore not clinically meaningful.

4.3.4 QRS

Figure 4 displays the time profile of ΔQRS for the treatment of adagrasib 400 mg BID in Study 849-006. QRS interval was not collected in Study 849-001.

Figure 4: Mean and 90% CI of ΔQRS 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 ECG population 2. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

Table 7 lists the number of subjects, as well as the number of observations with QTcF values of ≤450 msec, >450 and ≤480 msec, >480 and ≤500 msec, and >500 msec with or without a change from baseline >60 msec.

For the treatment of adagrasib 600 mg BID in Study 894-001, there were 3 and 11 subjects who experienced QTcF values >500 msec without a change from baseline >60 msec and values >500 msec with a change from baseline >60 msec, respectively.

There were no subjects who experienced QTcF >450 msec in Study 849-006.

Table 7. Categorical Analysis for QTcF (maximum)

Study	Treatment	Total (N)		Value <=450 msec		450 msec < Value <=480 msec		480 msec < Value <=500 msec		Value >500 msec & <=60 msec		Value >500 msec & >60 msec	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
849-001	Adagrasib 600 mg BID	256	1498	126 (49.2%)	1130 (75.4%)	92 (35.9%)	302 (20.2%)	24 (9.4%)	48 (3.2%)	3 (1.2%)	7 (0.5%)	11 (4.3%)	11 (0.7%)

Note: Only triplicate ECGs were included in the table. Subjects 849-001-(b) (6) and 849-001-(b) (6) had both triplicate and single ECGs. Subject 849-001-(b) (6) had only single ECGs. All three subjects had

QTcF > 500 msec and ΔQTcF values >60 msec in their single ECGs, which were not included in the table. When including single ECGs, the numbers match the Applicant's label.

Table 8 lists the categorical analysis results for ΔQTcF (<=30 msec, >30 and <=60, and >60 msec). For the treatment of Adagrasib 600 mg BID, there were 31 subjects who experienced ΔQTcF values >60 msec in Study 894-001. There were no subjects who experienced ΔQTcF values >60 msec in Study 849-006.

Table 8. Categorical Analysis for ΔQTcF (maximum)

Study	Treatment	Total (N)		Value <=30 msec		30 msec < Value <=60 msec		Value >60 msec	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
849-001	Adagras b 600 mg BID	256	1498	107 (41.8%)	1143 (76.3%)	118 (46.1%)	316 (21.1%)	31 (12.1%)	39 (2.6%)

Note: Only triplicate ECGs were included in the table. Subjects 849-001-(b) (6), 849-001-(b) (6), and 849-001-(b) (6) with ΔQTcF values >60 msec by single ECG were not included in the table.

4.4.2 HR

Table 9 lists the categorical analysis results for maximum HR (<=100 beats/min and >100 beats/min). There were no subjects who experienced HR values >100 beats/min in Study 894-006.

Table 9. Categorical Analysis for HR (maximum)

Study	Treatment	Total (N)		Value <=100 beats/min		Value >100 beats/min	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
849-001	Adagras b 600 mg BID	256	1498	199 (77.7%)	1382 (92.3%)	57 (22.3%)	116 (7.7%)

4.4.3 PR

There were no subjects who experienced PR values >220 msec with 25% increase over baseline in Study 849-006.

4.4.4 QRS

There were no subjects who experienced QRS values >120 msec in Study 849-006.

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects in study 849-001 with baseline and at a least one post-baseline ECG, with time-matched PK (PK-QT population). Study 849-006 was excluded from the concentration-QTc analysis to limit data heterogeneity that could result from pooling trials with different designs, population, and dosages.

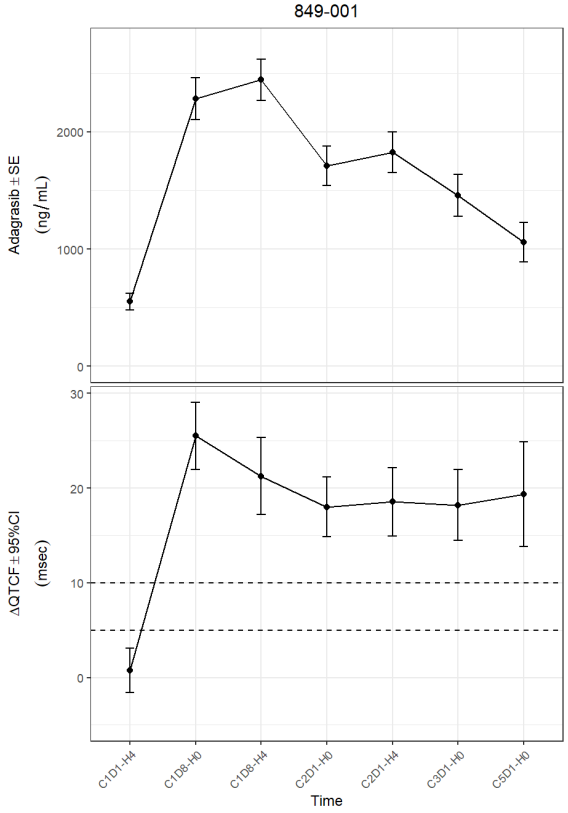
4.5.1 QTc

Prior to evaluating the relationship between drug concentration and ΔQTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis. These assumptions include:

1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR);
2) absence of delay between plasma concentration and ΔQTcF; and
3) absence of a nonlinear relationship.

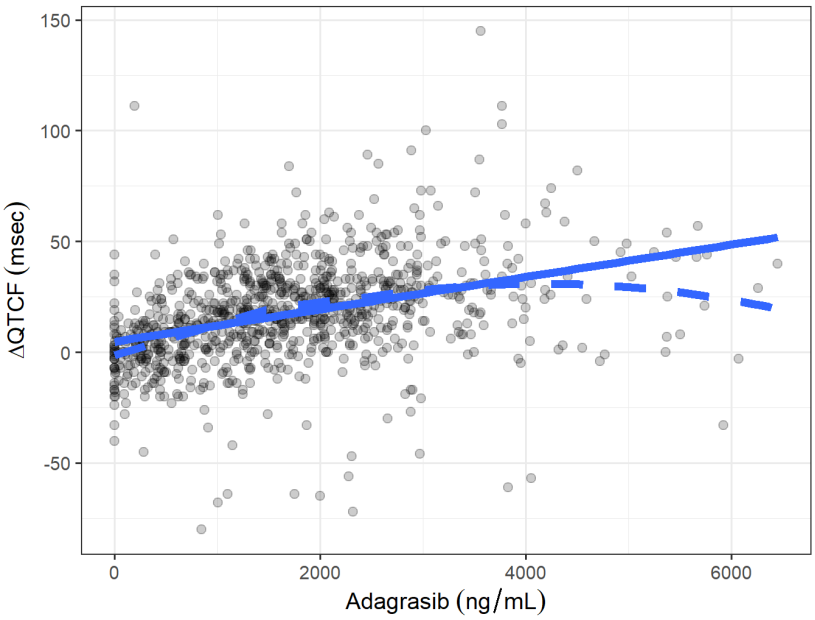
Figure 2 shows the time-course of ΔHR in both study 849-001 and 849-006, with an absence of significant ΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔQTcF, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)[1]



[1] ΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 10.

Figure 7: Goodness-of-fit Plot for QTcF

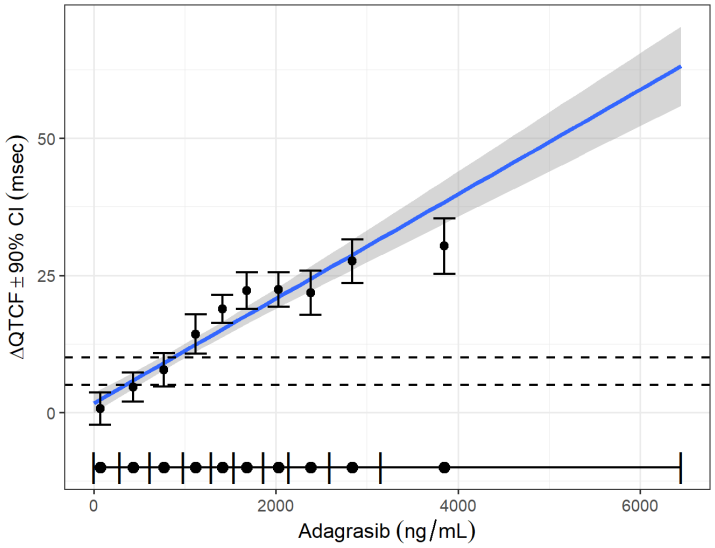


Table 10. Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Adagrasib (ng/mL)	ΔQTCF (msec)	90.0% CI (msec)
Adagrasib 600 mg BID	1	1344.1	14.5	(13.1 to 15.9)
Adagrasib 600 mg BID	8	2241.4	23.1	(21.0 to 25.2)

4.5.1.1 Assay Sensitivity

Not applicable

4.6 SAFETY ASSESSMENTS

The reviewer's safety analysis was performed on the ISS dataset, which included study 849-001, a phase 1/2 open-label, single arm, multiple expansion cohort trial of MRTX849 in patients with advanced solid tumors with KRS G12C mutation. In total 265 patients received treatment. The safety analysis is focused on the safety population who received MRTX849 600 mg BID dosing (n = 260).

Outlier analysis including both triplicated and single ECGs in subjects with post-baseline and valid baseline measurements showed that QTcF > 500 msec were observed in 6.6% (17/257) patients and increases from baseline in QTcF > 60 msec were observed in 13.2% (34/257) patients in the 600 mg BID group, consistent with the Applicant's results (section 3.2.4).

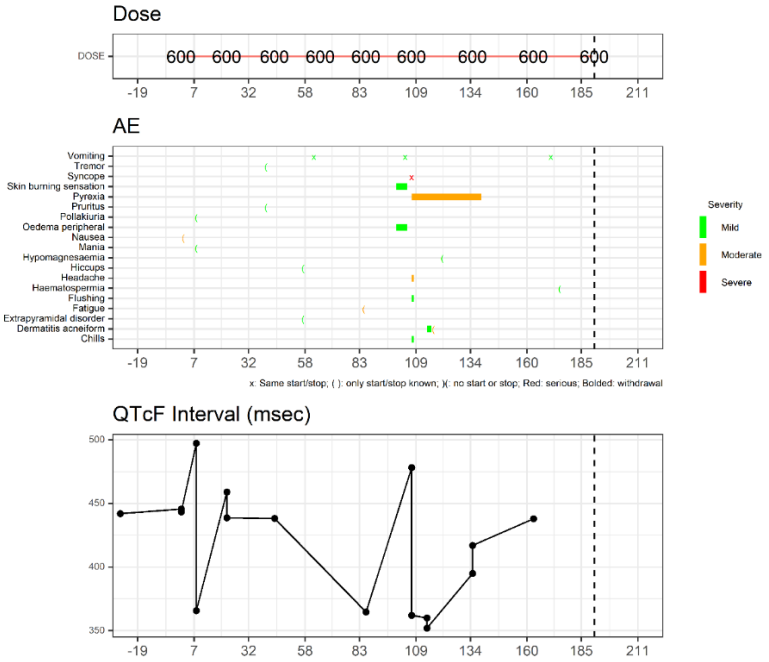
Table 11 showed the broad SMQ (version 21.0) of 'Torsade de pointes/QT prolongation' plus preferred term (PT) of 'seizure' in patients receiving 600 mg BID dosing. Of 260 patients who received MRTX849 600 mg BID, 7 patients experienced 8 SAEs of electrocardiogram QT prolonged (2 events), syncope (1 event), ventricular fibrillation (1 event), ventricular tachycardia (1 event), cardiac arrest (1 event), and seizure (2 events).

Table 11. Broad SMQ of 'Torsade de pointes/QT prolongation' Plus Preferred Term of 'Seizure', ISS Dataset.

PT	AEs n (%)	SAEs n (%)	Grade ≥ 3 n (%)	Not recovered n (%)
Total	51 (19.6%)	7 (2.7%)	19 (7.3%)	19 (7.3%)
Electrocardiogram QT prolonged	44 (16.9%)	2 (0.8%)	12 (4.6%)	15 (5.8%)
Seizure	5 (1.9%)	2 (0.8%)	3 (1.2%)	2 (0.8%)
Syncope	3 (1.2%)	1 (0.4%)	2 (0.8%)	0 (0%)
Ventricular fibrillation	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
Ventricular tachycardia	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
Cardiac arrest	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)

The reviewer's analysis showed similar results to the Applicant's ISS report except for an additional AE of a Grade 3 non-SAE syncope of subject (b) (6) on study day 107 (Figure 8). The subject received the first crossover treatment of Cetuximab + MRTX849 on day 107 and QTcF was 478 msec (pre-dose).

Figure 8. AE Progression for Subject (b) (6).



A review of the narratives of the 4 patients with SAEs of seizure or prolonged QT showed no evidence of ventricular arrhythmias:

- **Subject (b) (6): Electrocardiogram QT prolonged, blood creatinine increased, dehydration, diarrhoea, nausea**

  The subject was a 78-year-old White, non-Hispanic or Latino female with a diagnosis of non-small cell lung cancer who enrolled in Cohort A. On Day 7, the subject called the Investigator to report ongoing nausea and diarrhea. On Study Day 8, the subject was hospitalized with Grade 3 nausea, Grade 2 diarrhea, Grade 2 creatinine increase, Grade 2 dehydration, and Grade 3 QT prolongation. She presented with ongoing nausea and diarrhea. Laboratory results included creatinine 1.83 mg/dL (0.6-1.5). Electrocardiogram revealed **QTcF 566 msec**. On Day 9, electrocardiogram revealed normalized QT interval. On Day 22, nausea, and diarrhea downgraded to Grade 1. The events of blood creatinine increased and electrocardiogram QT prolonged resolved on Day 9. The events of dehydration, diarrhoea, and nausea resolved on Day 21. MRTX849 was interrupted and reduced due to the events of electrocardiogram QT prolonged and nausea. MRTX849 was restarted at 400 mg BID on Study Day 11. The Investigator/Applicant assessed all the events as **related/possibly related to MRTX849. No ventricular arrhythmias were reported.**
- **Subject (b) (6): Seizure**

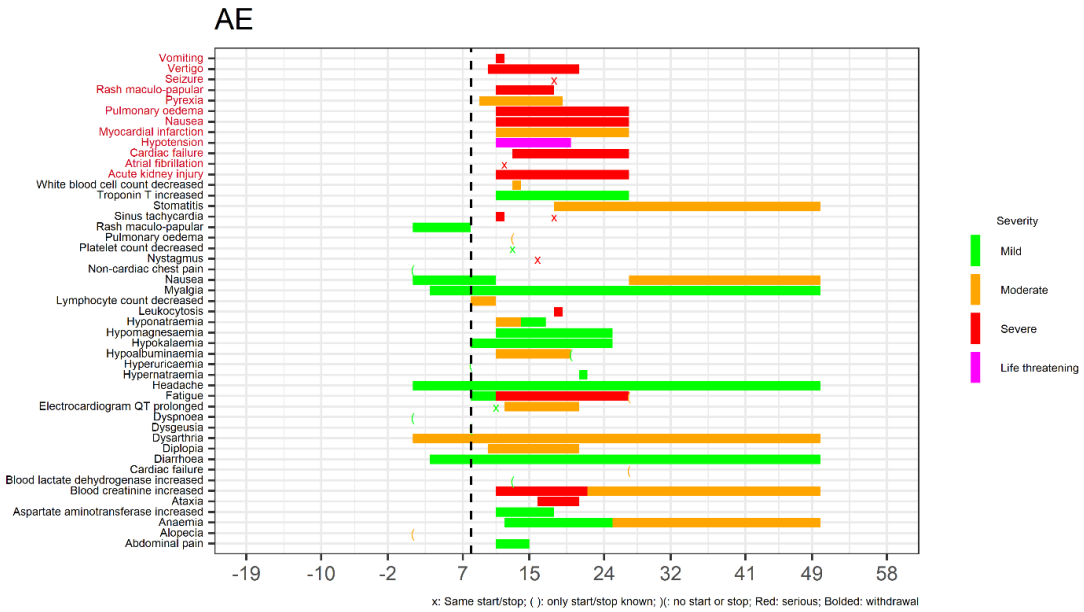
  The subject was a 69-year-old Black or African American, non-Hispanic or Latino male with a diagnosis of non-small cell lung cancer who enrolled in Cohort A. On Study Day 175, the subject presented to the emergency department after experiencing 2 seizures that morning at home. The first seizure lasted 5 minutes, minimal bleeding and frothing noted at the mouth, and no bladder incontinence. The second seizure was similar to the previous seizure and lasted 5 minutes. The last MRTX849 was taken on Day 174 prior to the two seizure events. **The subject had experienced his first seizure approximately 7 months before, after which intracranial metastasis were diagnosed. At that time, the subject**

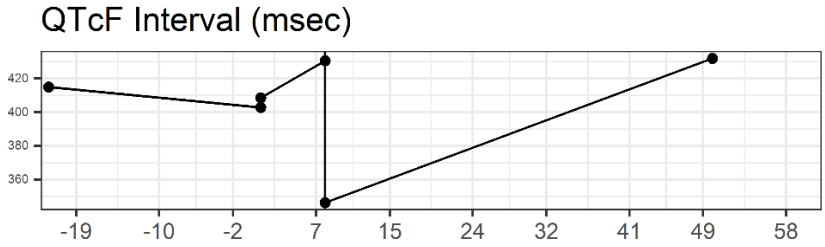
was started on levetiracetam 500 BID but reported he had not been taking for 4 days prior to current seizure due to inability to refill the prescription. The Investigator assessed the event of seizure as **not related to MRTX849**. The Investigator cited alternate etiology as malignancy for which the subject was being treated, and concurrent, or underlying illness of metastasis.

- **Subject (b) (6): Seizure, vomiting, vertigo, rash maculo-papular, pyrexia, pulmonary oedema, nausea, myocardial infarction, hypotension, cardiac failure, atrial fibrillation, acute kidney injury**

  The subject was a 64-year-old White, non-Hispanic or Latino female with a diagnosis of non-small cell lung cancer who enrolled in Phase Cohort B. Figure 9 shows AE progression through time (study day). On Day 9, the subject experienced SAE of pyrexia (102° F). On Day 10, the subject developed SAE of vertigo. **On Day 11**, the subject experienced SAEs of vomiting, rash maculo-papular, hypotension, acute kidney injury, myocardial infarction, nausea, and pulmonary oedema, and was admitted for acute hypoxic respiratory failure due to pneumonia, initially complicated by septic shock. Electrocardiogram (ECG) revealed sinus rhythm, borderline right axis deviation, left posterior fascicular block, low voltage; precordial leads, nonspecific ST/T wave abnormalities; inferolateral leads**. The QT interval was prolonged when corrected for heart rate and compared to previous ECG (date not provided),** left posterior fascicular block, ST/T wave findings noted, and the axis had changed. On Day 12, the subject experienced SAE of atrial fibrillation. On Day 13, the subject experienced SAE of cardiac failure. **On Day 18, the subject experienced SAE of seizure. The final dose of study treatment was taken on Study Day 8, 10 days prior to the seizure event. No ventricular arrhythmia events were reported.** The Investigator/Applicant assessed the events of pyrexia, vertigo, vomiting, rash maculo-papular, hypotension, acute kidney injury, myocardial infarction, nausea, and pulmonary oedema, atrial fibrillation, cardiac failure, and seizure as **related/possibly related to MRTX849**.

Figure 9. AE Progression for Subject (b) (6).





- **Subject (b) (6): Electrocardiogram QT prolonged**

  The subject was a 55-year-old White, non-Hispanic or Latino female with a diagnosis of non-small cell lung cancer who enrolled in Cohort B. On Study Day 6, the subject presented to clinic for study visit and pre-dose ECG revealed QTcF average at 443 msec. The subject denied any cardiac symptoms like chest pain/chest tightness, palpitations, lightheadedness/dizziness, or syncope. Physical examination was notable for pedal edema of the ankle and 8 cm jugular vein distension. **Four-hour post-dose ECG revealed QTcF average at 587 msec.** Repeat echocardiogram revealed LVEF at 55%. On the same day, a 12-lead ECG revealed sinus rhythm, short PR interval, recent probable posterior infarct, nonspecific T abnormalities, and prolonged QT interval. New or worsening ischemia or infarct and significant repolarization change was observed when compared to electrocardiogram which was done 8 days prior to study treatment administration. Laboratory results indicated blood urea nitrogen (BUN) 29, and creatinine 1.5 (reference range and units not provided). The subject was subsequently hospitalized for observation which included trending of troponin q6h, telemetry monitoring, and serial ECGs q6hs. On Study Day 7, troponin was trended overnight (q6h) and remained <0.03 ng/mL (<0.10). An echocardiogram revealed LVEF 65%. The subject was discharged from the hospital on the same day. **No ventricular arrythmias were reported.** MRTX849 was interrupted and the dose was reduced due to the event. MRTX849 was restarted on Study Day 17. The Investigator/Applicant assessed the event of electrocardiogram QT prolonged as **related to MRTX849**.

Dr. Fortunato Senatore, the lead cardiologist in DCN, was consulted on the 3 patients with 4 SAEs of **syncope, ventricular fibrillation/ventricular tachycardia, and cardiac arrest**. His complete review is included as an Appendix. Below summarize his conclusions:

- **Subject (b) (6): Syncope, sepsis, haemothrax, pleural effusion, malignant neoplasm progression (fatal)**
  In the case of subject (b) (6), there is agreement with the Applicant's assessment that events of sepsis, hemothorax, pleural effusion, and syncope are **not related to MRTX849** but rather to the underlying lung cancer.

- **Subject (b) (6): Ventricular fibrillation, ventricular tachycardia, and acute respiratory failure (fatal)**
  In the case of subject (b) (6), the events of ventricular tachycardia / ventricular fibrillation and acute respiratory failure are **probably not related to MRTX849** but rather to the underlying lung disease (lung cancer and severe COPD).

Consideration should be given to asking the Applicant for a re-evaluation of the resuscitated post-arrest ECG to ascertain whether the PMVT is not TdP, and to confirm two separate ECGs as suggested by the narrative text: pre-arrest monomorphic ventricular tachycardia and resuscitated post-arrest PMVT. If they are the same ECG consequent to lack of clarity in text content, the Applicant should explain the reason for two distinct diagnoses from the same ECG.

- **Subject (b) (6): Cardiac arrest (fatal)**
  In the case of subject (b) (6), the cause of the fatal cardiac arrest was **probably related to MRTX849**. The QTcF was prolonged (500 ms, where prolongation is defined as > 460 msec in women) at the time of the cardiac arrest. There were no reported concomitant medications or concomitant conditions that might have been a confounder to QTc prolongation.

In conclusion, 3 subjects (1.2%) experienced QT prolongation-related SAEs (2 electrocardiogram QT prolongations and 1 cardiac arrest).

In product labeling, QTc prolongation risk is managed by (1) avoiding use in patients with congenital long QT syndrome and in patients with concurrent QTc prolongation, (2) monitoring ECGs and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, and in patients who are taking medications that are known to prolong the QT interval, and (3) withholding dose until severe QTc prolongation reducing to (b) (4) or returning to baseline and reducing dose at the next lower level. The reviewers find this risk management plan acceptable.

5 APPENDIX: CLINICAL CARDIOLOGY CONSULTATION (REVIEW FROM DR. SENATORE)

Executive Summary

- In the case of subject (b) (6), there is agreement with the Applicant's assessment that events of sepsis, hemothorax, pleural effusion, and syncope are not related to MRTX849 but rather to the underlying lung cancer.

- In the case of subject (b) (6), the events of ventricular tachycardia / ventricular fibrillation and acute respiratory failure are probably not related to MRTX849 but rather to the underlying lung disease (lung cancer and severe COPD). Consideration should be given to asking the Applicant for a re-evaluation of the resuscitated post-arrest ECG to ascertain whether the PMVT is not TdP, and to confirm two separate ECGs as suggested by the narrative text: pre-arrest monomorphic ventricular tachycardia and resuscitated post-arrest PMVT. If they are the same ECG consequent to lack of clarity in text content, the Applicant should explain the reason for two distinct diagnoses from the same ECG.

- In the case of subject (b) (6), the cause of the fatal cardiac arrest was probably related to MRTX849. The QTcF was prolonged (500 ms, where prolongation is defined as > 460 msec in women) at the time of the cardiac arrest. There were no

reported concomitant medications or concomitant conditions that might have been a confounder to QTc prolongation.

Background

MRTX849 is an inhibitor of the RAS GTPase family approved for the treatment of locally advanced or metastatic non-small cell lung cancer with KRAS G12C mutation as determined by an FDA approved test, and who have received at least one prior systemic therapy. The approval was based on an accelerated approval pathway with *objective response* rate and *duration of response* as the intermediate endpoints reasonably likely to predict outcome. Continued approval is contingent upon verification of a clinical benefit in a confirmatory trial.

The label contains a warning about QT prolongation, whereby ECG and electrolyte monitoring are required in patients at risk, and in patients taking concomitant medications known to prolong the QT interval. The label instructs the provider to withhold or permanently discontinue dosing as necessary.

The Division's QT-IRT performed a safety assessment of the Integrated Summary of Safety dataset to evaluate QT prolongation. The dataset was comprised of 256 subjects receiving treatment and 260 patients receiving the therapeutic dose of 600 mg BID. Broad SMQ (version 21.0) of Torsade de pointes (TdP)/QT prolongation showed that 47 (18%) patients experienced TEAEs and 5 (2%) patients experienced SAEs of TdP/QT prolongation.

Three TdP/QT prolongation-related SAEs were identified: 1) syncope; 2) ventricular fibrillation; and 3) cardiac arrest. The Applicant considered these events to be not related to study drug.

This consultation will review these three events and assess whether they are attributable to study drug. The review strategy will include ascertaining: 1) the temporal relationship between the last dose of study drug and onset of the SAE; 2) the presence of concomitant medications that may have also induced QT prolongation; 3) the subject's medical history including cardiac history of antecedent conduction defects; and 4) QT and other ECG data from the SAE narrative.

Subject (b) (6): Syncope, sepsis, hemothorax, pleural effusion, malignant neoplasm progression (fatal)

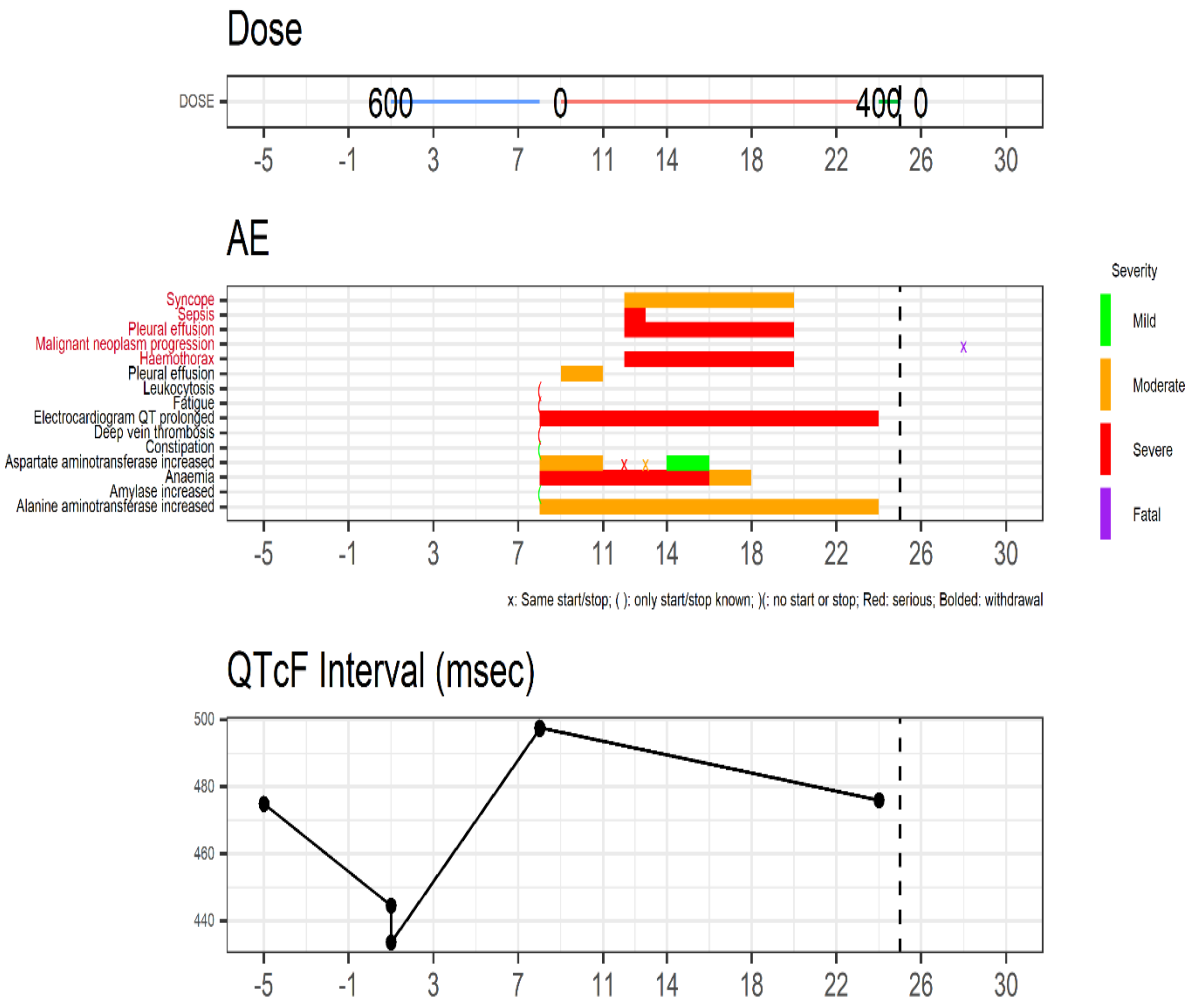
The CSR was available (page 475) for complete description of narratives, medical history, concomitant medication, etc. Below is a brief description of the events. **Grade 3 QT prolongation was accompanied by syncope SAE.**

The subject was a 75-year-old White, non-Hispanic or Latino male with a diagnosis of non-small cell lung cancer who enrolled in Phase 2 NSCLC with KRAS G12C mutation detected in tumor tissue (Cohort A). Figure 10 shows the AE progression, dose levels, and QTcF through time (unit: day; if two QTcFs were shown on the same day, one was pre-dose and the other was at 4 h post-dose, i.e. at Tmax). The treatment was held due to Grade 3 QT prolongation and the subject experienced Grade 2 pleural effusion (from Day 9 to 11) and underwent thoracentesis on Day 10.

On Study Day 12, the subject presented to the emergency department with complaint of a syncopal episode. During transport to hospital, electrocardiogram revealed atrial fibrillation. The Investigator noted the subject had no prior history of seizures or atrial fibrillation. Additional symptoms included generalized fatigue, increased abdominal distention, and shortness of breath. Shortness of breath was unchanged from baseline. The Investigator noted the subject was taking unspecified blood thinners secondary to detected deep vein thrombosis. Unspecified diagnostic testing revealed pleural effusion and left hemothorax. The event of sepsis resolved on the following day after onset (Day 13). The events of hemothorax, pleural effusion, and syncope resolved on Day 20. On Day 22, the subject was discharged. Dosing was adjusted to 400 mg BID from Day 24 to 25. The Investigator/Applicant assessed the events of sepsis, hemothorax, pleural effusion, and syncope as **not related** to MRTX849, citing alternate etiology as malignancy for which the subject was being treated.

On Study Day 28, Grade 5 malignant neoplasm progression was reported. The event was considered a fatal event and an SAE. The Investigator/Applicant assessed the event of malignant neoplasm progression as **not related** to MRTX849.

Figure 10. AE Progression for Subject (b) (6).



Cardiology Assessment

The subject's medical history included non-small cell lung cancer, prostate cancer, diarrhea, anemia, chronic obstructive pulmonary disease (COPD), dehydration, hypothyroidism (*another cause of QT prolongation*), hypocalcemia (*another cause of QT prolongation*), and non-Hodgkin's lymphoma. The subject was also on an extensive list of medications (page 478 CSR) but none were on the list of medications known to cause QT prolongation (https://www.uspharmacist.com/article/drug-induced-qt-prolongation).

The SAE of syncope occurred in conjunction with sepsis, left hemothorax, pleural effusion, and fatal disease progression. The syncopal episode occurred at home earlier on the day of presentation to the emergency room. The episode lasted for 30 seconds and the patient did not fall. There was no history of seizure disorder. On route to the hospital for syncope, the subject was noted to be in atrial fibrillation (no prior history of Afib). Three days prior to this event, the subject's dose of 600 mg BID was withheld due to grade-3 QTcF prolongation. This resulted in slowly resolving QTcF prolongation. Although MRTX849 very likely caused the QTcF prolongation as expected, the syncopal episode may have been caused by concomitant events (sepsis, pleural effusion, disease progression, atrial fibrillation). The ECG at the time of the syncopal episode revealing atrial fibrillation made no mention of QTcF prolongation or a ventricular arrhythmia. Furthermore, the syncopal episode occurred during resolution of QTcF interval consequent to MRTX849 discontinuation 3 days earlier. Hence, the syncopal episode, as well as the cause of death attributable to disease progression, were not likely related to MRTX849-mediated QT prolongation / TdP.

Impression: There is agreement with the Applicant's assessment that events of sepsis, hemothorax, pleural effusion, and syncope are not related to MRTX849 but rather to the underlying lung cancer.

Subject (b) (6): Ventricular fibrillation, ventricular tachycardia, and acute respiratory failure (fatal)

Please see iss narratives page 177 for complete description of narratives, medical history, concomitant medication, etc. Below is a brief description of the events. **The investigator and Applicant had different conclusions regarding these events.**

The subject was a 63-year-old White, non-Hispanic or Latino female with a diagnosis of non-small cell lung cancer who enrolled in Phase 2 NSCLC with KRAS G12C mutation detected in blood Cohort (Cohort B). The final dose of study treatment was taken on Study Day 5. The subject discontinued MRTX849 following study treatment interruption due to subject non-compliance on Study Day 6.
On Study Day 9, the subject presented to the emergency department with complaints of continued nausea, vomiting, and abdominal pain. At that time, electrocardiogram was within normal limits. Vital signs included pulse 80, temperature 97.8° F, and blood pressure 95/75 mmHg. She had acidosis, with arterial pH 7.09, arterial partial pressure of carbon dioxide 98 mmHg, and partial pressure of oxygen 139 mmHg (on 100% oxygen by bag valve mask). She was admitted, and during her hospital course she became restless and was gasping for air, for which she underwent emergency intubation followed by hypotension treated with norepinephrine; she subsequently experienced Grade 4, treatment-related ventricular tachycardia and Grade 4, treatment-related ventricular fibrillation with electrocardiograms showing **QTc ranging between 388 and 472**

msec (baseline 427 msec), underwent cardioversion, and developed Grade 5 acute respiratory failure.
The Investigator assessed events as related to study treatment as the subject developed what seemed like cardiogenic shock and ventricular fibrillation. Although no formal echocardiogram was performed due to hemodynamic instability, post arrest bedside echo showed global LV dysfunction. Investigator reported that the subject did not have a prior history of coronary artery disease and previous echocardiogram showed normal LV ejection fraction, therefore a side effect of the study treatment could not be ruled out with any degree of certainty. **The Investigator also cited alternate etiology as malignancy for which the subject was being treated.**
The Applicant assessed the events as unlikely related to MRTX849. A cardiologist also consulted and performed an independent assessment. The subject had oxygen-requiring COPD, non-small cell lung cancer, chronic pleural effusions and atelectasis was admitted with severe respiratory acidosis and without evidence of congestive heart failure. The subject's electrocardiogram at admission did show possible cardiac ischemia (new minor ST segment elevation in leads V5 and V6), though her troponin level was normal. She then had a respiratory decompensation followed by monomorphic ventricular tachycardia degenerating to ventricular fibrillation, without evidence of Torsade de pointes. Her QTcF intervals were not prolonged. The post-CPR electrocardiogram is consistent with an anterior-lateral wall acute ischemia or a MI (additional cardiovascular injury markers were not measured). The most likely diagnosis is an acute respiratory decompensation in a subject with long standing tenuous pulmonary status, followed by ventricular arrhythmias and a possible acute myocardial infarction. A relationship to MRTX849 was unlikely.

Cardiology Assessment
The subject's medical history included non-small cell lung cancer, oxygen-requiring chronic obstructive pulmonary disease (COPD), chronic pleural effusions, atelectasis of the right lower lobe, peripheral edema (subject may have had intermittent heart failure in the past based on peripheral edema in the absence of deep vein thrombosis or portal hypertension), anemia, proteinuria, and hypoalbuminemia. The subject's medication history included diuretics, pain meds, meds to treat COPD including steroids, and prochlorperazine (presumably for nausea and vomiting).

Three days prior to the index SAE (ventricular tachycardia / ventricular fibrillation, and acute respiratory failure leading to death), the subject discontinued MRTX849 with the last dose taken four days prior to the index SAE. The reason for discontinuation was reported to be non-compliance. Three days before the events, an echocardiogram showed normal left ventricular ejection fraction (64%) with no regional wall motion abnormalities but with grade 1 left ventricular diastolic dysfunction. Upon presentation to the emergency room for nausea / vomiting / abdominal pain / diaphoresis / dyspnea, the ECG was normal (i.e., no report of QTc prolongation or dysrhythmia). Troponin levels were normal and Covid testing was negative. The subject's anemia did not raise a concern about exacerbating oxygen transfer in the setting of atelectasis and COPD (Hb 10.5 g/dL with normal range 11.5—15.5 g/dL). The subject did not have a history of coronary artery disease. Lower extremity scanning was negative for deep venous thrombosis. Chest x-ray revealed worsening right lower lobe atelectasis and small bilateral pleural effusions unchanged from previous imaging. The subject was hemodynamically stable and afebrile. Arterial blood gasses demonstrated a combined severe respiratory and metabolic acidosis (lactic acidosis). On the same day of presentation, the subject experienced cardiogenic shock and cardiac arrest followed by

multifocal ventricular tachycardia (QTc 448 ms) upon resuscitation. The narrative did not specify whether the multifocal ventricular tachycardia, also known as polymorphic ventricular tachycardia (PMVT), was a torsades de pointes (TdP) form of PMVT. An independent cardiologist contracted by the Applicant specified that an ECG around the time of respiratory decompensation leading to cardiac arrest was monomorphic ventricular tachycardia (thus ruling out TdP). Based on integrating the narrative from the Applicant with input from the independent cardiologist, it appeared that the monomorphic ventricular tachycardia occurred before the cardiac arrest, and the PMVT occurred following resuscitation.

Of note, ECG presentation of PMVT shows various QRS amplitude and may be caused by several etiologies (e.g., congenital QT prolongation, acquired QT prolongation, ischemia, Takotsubo's cardiomyopathy). TdP, however, is defined as the combination of PMVT *plus* a prolonged QT interval. Thus, TdP is a specific form of PMVT but the two terms are not identical (see links).

(https://emcrit.org/ibcc/tdp/#:~:text=Polymorphic%20ventricular%20tachycardia,actually%20not%20the%20same%20thing)

(https://litfl.com/polymorphic-vt-and-torsades-de-pointes-tdp/)

(b) (4)

Ongoing laboratory analysis continued to show respiratory and metabolic acidosis along with signs of heart failure (NTproBNP > 5600 pg/mL with normal < 125 pg/mL). The QTc intervals hovered over the upper range of normal and were consistent with baseline readings. Post-arrest echocardiogram showed global left ventricular dysfunction. The subject died due to respiratory decompensation, whereby all the SAE events were considered by the Applicant and the independent cardiologist to be unrelated to study drug. However, the investigator cited the events to be related to study drug because of a lack cardiac history prior to these cardiac events, normal cardiac function upon admission, and no other explanation for these events (i.e., DVT→pulmonary embolism). The independent cardiologist's retrospective review of the admission ECG showed new minor ST-segment elevation in the antero-lateral leads (V5, V6) suggestive of myocardial infarction; however, lab findings did not support cardiac ischemia.

The ventricular arrhythmia (monomorphic ventricular tachycardia pre-arrest and PMVT post resuscitation) were likely due to the subject's respiratory compromise and metabolic acidosis rather than a QTc prolonging effect. However, the post-arrest ECG finding of PMVT should have been further evaluated to rule out TdP. Based on the content of the narrative, it is surprising that the independent cardiologist made no mention of the PMVT but only mentioned monomorphic ventricular tachycardia on the ECG prior to degeneration into ventricular fibrillation. Suboptimal text clarity made it difficult to interpret whether or not the same ECG was referenced to describe both monomorphic ventricular tachycardia and PMVT. This aspect of the narrative should be clarified.

In general, the data does not support attribution of these SAEs to MRTX849: the normal ECG on admission, the prolonged (4-day time span) between the last dose of MRTX849 and index event (T_{max} 6 hours, $T_{1/2}$ 23 hours as per label), the normal QTc interval (hovering over the upper limit of normal), the presence of precardiac-arrest monomorphic

ventricular tachycardia, the severe respiratory and metabolic acidosis, lung cancer and severe COPD that very likely caused the heart failure and ultimate demise.

***Impression*: The events of ventricular tachycardia / ventricular fibrillation and acute respiratory failure are probably not related to MRTX849 but rather to the underlying lung disease (lung cancer and severe COPD). Consideration should be given to asking the Applicant for a re-evaluation of the resuscitated post-arrest ECG to ascertain whether the PMVT is not TdP, and to confirm two separate ECGs as suggested by the narrative text: pre-arrest monomorphic ventricular tachycardia and resuscitated post-arrest PMVT. If they are the same ECG consequent to lack of clarity in text content, the Applicant should explain the reason for two distinct diagnoses from the same ECG.**

Subject (b) (6): Cardiac arrest (fatal)

Please see iss narratives page 220 for complete description of narratives, medical history, concomitant medication, etc. Below is a brief description of the events. Some concomitant medication such as granisetron hydrochloride and prochlorperazine have potential to prolong QT as well.

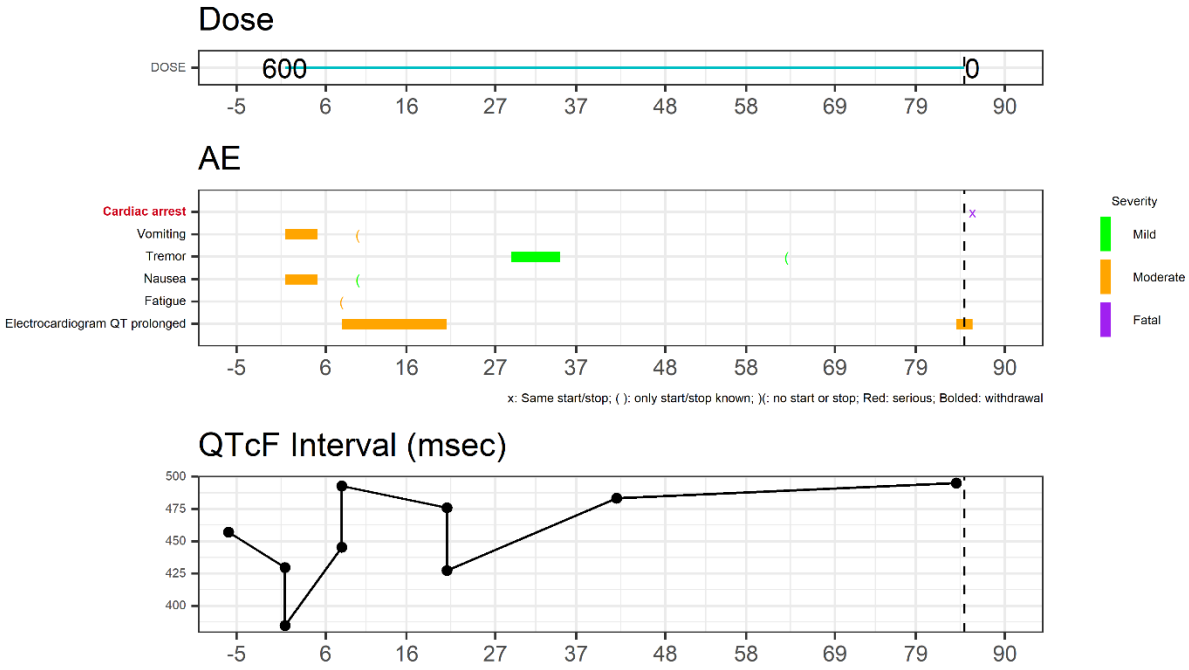
The subject was a 62-year-old White, non-Hispanic or Latino female with a diagnosis of colorectal cancer who enrolled in Phase 2 Colorectal cancer with KRAS G12C mutation detected in tumor tissue and/or blood Cohort (Cohort C). Figure 11 shows the AE progression, dose levels, and QTcF through time (unit: day).

On Study Day 86, Grade 5 cardiac arrest (verbatim term: cardiac arrest) was reported. The event was considered a fatal event, an SAE, and a discontinuation of treatment due to adverse event. The last dose of study treatment prior to the event was MRTX849 600 mg BID on Study Day 85. Prior to this event, the subject reported nonserious Grade 2 electrocardiogram QT prolonged following the first and fourth dosing periods of MRTX849 600 mg BID.

On Study Day 86, the subject's husband noticed the subject was not breathing in her sleep. She was transported to the emergency department via emergency medical services. On arrival, the subject was in asystole with cardiopulmonary resuscitation in progress. Treatment included epinephrine, intubation, and intraosseous line insertion. The subject died due to Grade 5 cardiac arrest. Cause of death was reported as unknown.

The Investigator/Applicant assessed the event of cardiac arrest as **not related** to MRTX849.

Figure 11. AE Progression for Subject (b) (6).



Cardiology Assessment

The subject's medical history included active metastatic colorectal adenocarcinoma and a past history of iron-deficiency anemia, cholecystectomy, gastro-esophageal reflux disease, hypercholesterolemia, splenectomy, polypectomy, hypothyroidism, arthritis, breast cancer with peritoneal carcinomatosis and possible other metastases, and central venous catheterization (possibly due to past cancer treatment). The subject's medication history included levothyroxine, medications for nausea and vomiting (granisetron, lorazepam, prochlorperazine), pramipexole for tremor, and epinephrine for cardiac arrest.

Granisetron blocks both sodium and potassium channels, thus potentially affecting both depolarization and repolarization through prolongation of PR, QRS, and QT intervals. The other concomitant medications are not reported to prolong the QT interval; levothyroxine tends to shorten the QTc interval from a baseline prolonged QTc interval that is observed in hypothyroidism.

The subject has been on MRTX849 600 mg BID for 85 days when, on Day 86, the subject experienced a fatal out-of-hospital cardiac arrest. The subject's husband noted that the subject was not breathing in her sleep. She was in asystole on arrival to the emergency room with CPR in progress. She was intubated and treated with epinephrine. The cause of death was reported as unknown. Both the investigator and the Applicant assessed the event of cardiac arrest as not related to MRTX849.

Serial ECGs showed the expected QTcF prolongation. Baseline QTcF intervals varied from 325 msec to ~450 msec. Over the course of the 85 days of treatment with MRTX849, the QTcF varied from ~ 425 msec to 500 msec. On approximately Day 85, the QTcF was 500 msec.

<u>Impression</u>: Based on the narrative, the cause of the fatal cardiac arrest was probably related to MRTX849. The QTcF was prolonged (500 ms, where prolongation is defined as > 460 msec in women) at the time of the cardiac arrest. There were no reported concomitant medications or concomitant conditions that might have been a confounder to QTc prolongation.

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