

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219839Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: June 11, 2025

To: Maritsa Stephenson, Regulatory Project Manager
Division of Oncology 2 (DO2)

Barbara Scepura, Associate Director for Labeling, DO2

From: Kelle Caruso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments ZEGFROVY™ (sunvozertinib) tablets, for oral use

NDA: 219839

Background:

In response to DO2's consult request dated January 8, 2025, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for ZEGFROVY™ (sunvozertinib) tablets, for oral use.

PI:

OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on June 5, 2025, and our comments are provided below.

PPI:

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

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on June 5, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Kelle Caruso at Kelle.Caruso@fda.hhs.gov or (301) 796-5044.

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/s/

KELLE E CARUSO
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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: June 11, 2025

To: Maritsa Stephenson, PharmD, BCPS
Regulatory Health Project Manager
Division of Oncology II (DO2)

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

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

From: Jessica Chung, PharmD, MS
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kelle Caruso, PharmD, BCPS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): TRADENAME (sunvozertinib)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 219839

Applicant: Dizal (Jiangsu) Pharmaceutical Co., Ltd. c/o Aleon Pharma International, Inc.

1 INTRODUCTION

On November 7, 2024, Dival (Jiangsu) Pharmaceutical Co., Ltd. c/o Aleon Pharma International, Inc. submitted for the Agency's review an original New Drug Application (NDA) 219839 for TRADENAME (sunvozertinib) tablets. The proposed indication is for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology II (DO2) on January 8, 2025, for DMPP and OPDP to review the Applicant's proposed Patient Package Inset (PPI) for TRADENAME (sunvozertinib) tablets.

2 MATERIAL REVIEWED

- Draft TRADENAME (sunvozertinib) tablets PPI received on November 7, 2024, and received by DMPP and OPDP on June 5, 2025.
- Draft TRADENAME (sunvozertinib) tablets Prescribing Information (PI) received on November 7, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 5, 2025.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the 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 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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06/11/2025 11:04:01 AM

RUTH I MAYROSH
06/11/2025 11:12:56 AM

BARBARA A FULLER
06/11/2025 11:23:44 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	June 9, 2025
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 219839
Product Name, Dosage Form, and Strength:	Zegfrovoy (sunvozertinib) Tablets, 150 mg and 200 mg
Applicant Name:	Dizal (Jiangsu) Pharmaceutical Company
FDA Received Date:	June 5, 2025
TTT ID #:	2024-11601-2
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 PURPOSE OF MEMORANDUM

Dizal (Jiangsu) Pharmaceutical Company submitted revised container labels and carton labeling received on June 5, 2025 for Zegfrovy. The Division of Oncology 2 (DO2) requested that we review the revised container labels and carton labeling for Zegfrovy (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Dizal (Jiangsu) Pharmaceutical Company implemented all of our recommendations and we have no additional recommendations at this time.

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

^a Stewart, J. Label and Labeling Review Memo for Zegfrovy (NDA 219839). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 MAY 16. TTT ID: 2024-11601-1.

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JANINE A STEWART
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Clinical Inspection Summary

Date	May 20, 2025
From	Lee Pai-Scherf, MD Michele Fedowitz, MD, Team Leader Kassa Ayalew, MD, MPH, Division Director, for Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE, OSI
To	Katie Chon, Clinical Analyst Timil Patel, Medical Officer, Team Leader Paz Vellanki, Supervisory Associated Director Division of Oncology 2 (DO2), Office of Oncology Products
NDA #	NDA 219839
Applicant	Dizal (Jiangsu) Pharmaceutical Co Ltd.
Drug	Sunvozertinib
NME (Yes/No)	Yes
Therapeutic Classification	EGFR Tyrosine Kinase Inhibitor
Proposed Indication(s)	For the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy
Consultation Request Date	January 8, 2025
Summary Goal Date	March 15, 2025 (extension to May 25, 2025)
Action Goal Date	June 25, 2025
PDUFA Date	July 7, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study DZ2019E0001 were submitted to the Agency in support of New Drug Application (NDA) 219839 for sunvozertinib for patients with previously treated locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations. Two clinical investigators, Drs. Dongqing Lv (Site # 328), James Yang (Site # 501), the Contract Research Organization, (b) (4) and the imaging CRO, (b) (4) were inspected.

Inspections of Drs. Yang and Lv, and the imaging CRO, (b) (4) did not find significant concerns regarding the study conduct, data discrepancies or integrity, Good Clinical Practice (GCP), or regulatory compliance. Inspection of CRO (b) (4) observed delays in data query resolution and issues with investigational drug accountability record keeping. These deficiencies are unlikely to affect overall reliability

of the data generated from the sites. (b) (4) provided a corrective and preventive action plan (CAPA) that was reviewed and found to be adequate.

Based on these inspections, Study DZ2019E0001 appears to have been conducted adequately and the data generated by the inspected clinical investigators and the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indication.

Of note, the inspection results of Dr. Lv, and the imaging CRO, (b) (4) are based on a summary provided by the FDA field investigator and are therefore preliminary. If significantly new or different information is contained in the final FDA Establishment Inspection Report, an addendum to this clinical inspection summary will be filed.

II. BACKGROUND

Dizal Pharmaceutical Co., Ltd submitted NDA 219839 seeking approval for sunvozertinib for the treatment of patients with locally advanced or metastatic EGFR exon 20 insertion mutation NSCL whose disease has progressed on or after platinum-based chemotherapy. The primary evidence of efficacy and safety supporting this indication is based on data from Study DZ2019E0001.

DZ2019E0001 is an ongoing, phase 1/2, multi-cohort, open-label, multicenter study of sunvozertinib administered orally in patients with advanced stage NSCL with EGFR or HER2 mutations. The study included Part A (phase 1) and Part B (phase 2, pivotal study). The primary analysis population to support the proposed indication consists of 107 patients randomized to Cohort 2 in Part 2 of the study who received sunvozertinib at a dosage of 300 mg once daily. Sunvozertinib was to be continued until disease progression, intolerable adverse events, treatment discontinuation criteria were met or withdrawal of consent by the patients.

The primary efficacy endpoint to support approval is objective response rate (ORR) assessed by BICR according to RECIST, version 1.1. The secondary efficacy endpoints are duration of response (DoR) per BICR, ORR and DoR by investigator assessment, progression-free survival (PFS) per BICR and overall survival (OS).

Written informed consent was to be obtained from all subjects prior to any study-specific procedures. Baseline screening procedures, including physical exam, laboratory tests, ophthalmological exam, echocardiogram/MUGA scan, lung function test (LFT), electrocardiogram (ECG), and MRI of the brain, were to be performed within 29 days prior to initiation of treatment.

Tumor imaging with CT or MRI scan (chest/abdomen/pelvis) are to be performed at screening/baseline within 28 days prior to initiation of treatment, on Cycle 3, Day 1, then every 6 weeks until objective disease progression or withdraw from study.

(b) (4) was responsible for the central review of radiographic images from Study DZ2019E0001.

At the time of the data cut-off date (July 29, 2024), a total of 202 subjects had been enrolled in Cohort 2, Part B of the study: 91 subjects were randomized to the 200 mg Arm and 111 to the 300 mg Am. Subjects were enrolled across 80 study sites across 11 countries, globally, with 60% of the subjects enrolled in China. Eleven subjects were enrolled across 5 sites in the U.S.

III. RESULTS (by site)

1. Dr. Dongqing Lv (Site # 328)

No. 150 Ximen Road,
Linhai District, Zhejiang 317099
CHINA

Inspection dates: May 6 – 9, 2025

Dr. Lv was inspected as BIMO review-based inspection for Study DZ2019E0001. This was the first inspection for this investigator.

At the time of the data cutoff date, the site had screened 14 subjects, 7 of whom were enrolled in the DZ2019E0001. At the time of the inspection two subjects are on study treatment, four had died and one is in survival follow-up.

Source records for all 7 subjects enrolled at the site were reviewed. Records reviewed included, but were not limited to informed consent form, eligibility criteria and adverse event reporting. No significant discrepancies were found when source data were compared with the data submitted to the NDA.

The inspection also verified that radiology studies to assess the primary efficacy endpoint were performed according to protocol specified time points and all scans were submitted for central review.

Based on the preliminary results provided by the FDA field investigator, data generated by Dr. Lv appear to be acceptable in support of the NDA.

2. Dr. Chih-Hsin (James) Yang (Site # 501)

C 7 Chung-Shan S. Road
Taipei, NA 10002
Taiwan

Inspection dates: April 28, 2025

Dr. Yang was inspected as BIMO review-based inspection for Study DZ2019E0001. Dr. Yang was previously inspected in 2013.

At the time of the inspection, the site had screened 15 subjects and enrolled 10 subjects: 5 subjects received sunvozertinib 200mg and 5 subjects received 300mg daily. All subjects had discontinued study treatment due to disease progression.

Source records for the 5 subjects who received sunvozertinib 300mg were reviewed in full and compared with the data listings submitted to the NDA. Records reviewed included, but were not limited to, informed consent forms, inclusion and exclusion criteria, adverse event reporting, concomitant medications, investigational product dosing, assessment of subjects, both clinically and laboratory wise. The inspection did not observe significant issues related to the study conduct.

The inspection verified that imaging scans to evaluate the primary efficacy endpoint were performed as specified in the protocol and all scans were submitted for central review, consistent with the data submitted to the NDA. No discrepancies were found.

Additional records reviewed during the inspection included, but were not limited to, financial disclosure forms, staff training information, CR/sponsor monitoring activities documents, and Ethics Committee approvals and communications. No issues were observed.

Based on the inspection, the data generated at Dr. Yang's site appear acceptable in support of the proposed indication in the NDA.

3.

(b) (4)

Inspection dates: (b) (4)

This inspection assessed (b) (4) oversight responsibilities for Study DZ2019E0001. This was the first inspection for this CRO. (b) (4) was contracted by the Sponsor, Dizal to conduct oversight of investigators, conduct medical monitoring, review of safety data and data management queries and coding review of sites outside of mainland China, while Dizal is responsible for those of sites of mainland China.

Documents reviewed included investigational site monitoring process and reports, informed consent documents, written procedures, safety and adverse event management plan and reporting. Selected records and procedure for 12 clinical sites (Sites # 0201, 0501, 0609, 0610, 0702, 0705, 0503, 0505, 0101, 0105, 0212, and 0404) and nine randomly selected subjects (b) (6)

(b) (6) were reviewed for compliance.

The inspection did not observe issues related to safety/adverse event handling or reporting for DZ2019E0001.

The following deficiencies were observed, specifically:

- Failure to ensure timely resolution of data queries according to established procedures.
- Failure to accurately and timely record investigational drug accountability.

Reviewer's Comment: Based on the nature of the deficiencies, they are unlikely to affect overall reliability of the safety and efficacy data generated from the sites. Although not timely, all data queries were addressed and resolved prior to the data cut-off of July 29, 2024, and there is no evidence of subject harm due to investigational product record keeping deficiencies. The above inspection findings were acknowledged by (b) (4) during the inspection. (b) (4) acknowledged the above deficiencies and provided a CAPA on May 13, 2025, which was reviewed and found to be adequate.

Notwithstanding the deficiencies described above, there is no evidence of impact on data integrity or subject safety.

4. (b) (4)

Inspection dates: (b) (4)

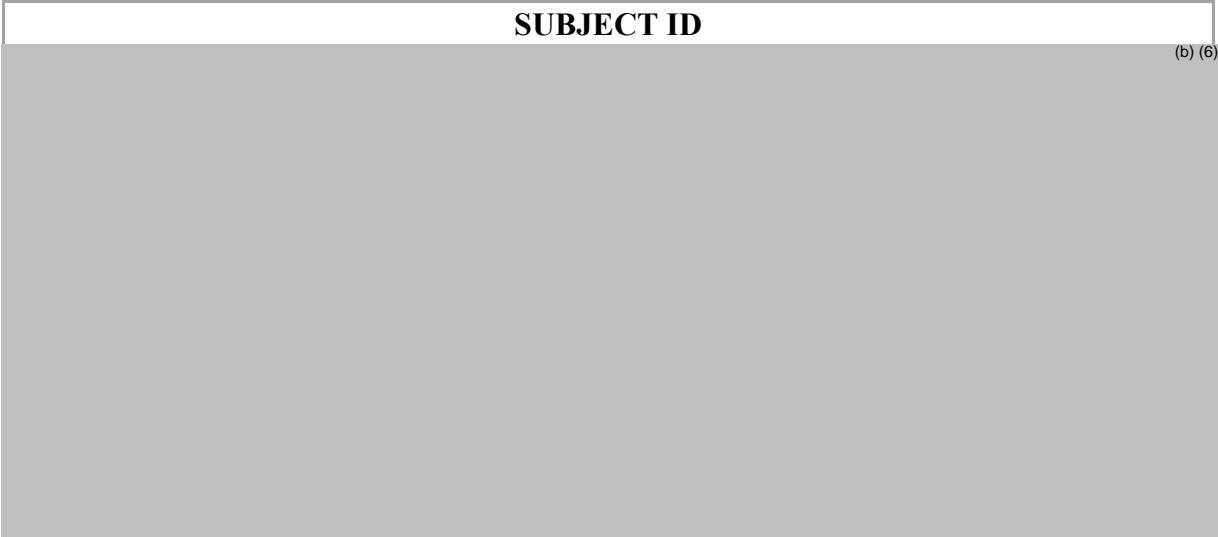
This inspection reviewed (b) (4) responsibilities to perform an independent central imaging review for Study DZ2019E0001. The firm was last inspected in (b) (4).

Records reviewed included, but were not limited to, (b) (4) adherence to the Imaging Review Charter, readers training and assessment, and reader blinding and adjudication procedures. The review found the processes adequate.

The inspection verified tumor response data for all 49 subjects who received sunvozertinib at a dosage of 300 mg once daily reported by the Sponsor as have achieved an objective response. Tumor measurements at all time points were verified in 11 out of 49 subjects. For all remaining subjects, tumor measurements for the two visits which confirmed the best overall response and disease progression, if applicable, were reviewed and compared to the efficacy line listings submitted to the NDA. No discrepancies were observed. The ID of these subjects are as follow:

SUBJECT ID

(b) (6)



***Bold font** – subjects for whom all tumor time points were verified.

Based on the preliminary results provided by the FDA field investigator, the imaging review data generated by (b) (4) appear acceptable in support of the proposed indication in the NDA.

{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}*

Michele Fedowitz, M.D.
Team Leader
Good Clinical Practice Assessment Branch
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Kassa Ayalew, M.D.,
Division Director, Division of Clinical Compliance Evaluation
Office of Scientific Investigation, for
Jenn Sellers, M.D., Ph.D.
Branch Chief
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CC:

Review Division /Project Manager/Maritsa Stephenson
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	May 16, 2025
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 219839
Product Name, Dosage Form, and Strength:	Zegfrovoy (sunvozertinib) Tablets, 150 mg and 200 mg
Applicant Name:	Dizal (Jiangsu) Pharmaceutical Company
FDA Received Date:	April 30, 2025
TTT ID #:	2024-11601-1
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 PURPOSE OF MEMORANDUM

Dizal (Jiangsu) Pharmaceutical Company submitted revised container labels and carton labeling received on April 30, 2025 for Zegfrovy. The Division of Oncology 2 (DO2) requested that we review the revised container labels and carton labeling for Zegfrovy (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The container labels and carton labeling are unacceptable from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Dizal (Jiangsu) Pharmaceutical Company in Section 3.

3 RECOMMENDATIONS FOR DIZAL (JIANGSU) PHARMACEUTICAL COMPANY

A. General Comments (Container Label(s) and Carton Labeling)

1. The net quantity statement “30 tablets” is presented in small font. To improve readability, we recommend increasing the font size of this important product information.

B. Container Label(s)

1. We recommend relocating the net quantity statement “30 tablets” above the manufacturer’s name “Dizal” to minimize the risk of the net quantity statement being overlooked.
2. You indicated that the “FPO” that appears in the lower right quadrant of the principal display panel “represents a linear barcode to control labeling versions”. As currently presented, there are two barcodes on the container label located in close proximity to each other. The drug barcode is often used as an additional verification during the medication use process. The presence of barcodes in close proximity to one another could lead to scan errors. We recommend presenting the version control information in a format or a smaller size that does not compete with or distract from the presentation of the linear barcode containing the NDC number.

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

^a Stewart, J. Label and Labeling Review for Zegfrovy (NDA 219839). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 MAR 17. TTT ID: 2024-11601.

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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)

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Date of This Review:	March 17, 2025
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 219839
Product Name, Dosage Form, and Strength:	Zegfrovy (sunvozertinib) Tablets, 150 mg and 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Dizal (Jiangsu) Pharmaceutical Company
FDA Received Date:	November 7, 2024
TTT ID #:	2024-11601
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 INTRODUCTION

As part of the approval process for Zegfrovy (sunvozertinib) Tablets, the Division of Oncology 2 (DO2) requested that we review the proposed Zegfrovy Prescribing Information (PI), Patient Package Insert (PPI), container label(s), and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B

3 CONCLUSION

The proposed Zegfrovy Prescribing Information (PI), Patient Package Insert (PPI), container label(s), and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Oncology 2 (DO2) in Section 4 and for Dizal (Jiangsu) Pharmaceutical Company in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Section 2 Dosage and Administration

- a. In Section 2.2 *Recommended Dosage*, revise the information regarding swallowing Zegfrovy tablets whole to read "Swallow ZEGFROVY tablet(s) whole. Do not split, crush, chew, or dissolve the tablets."

2. Section 16 How Supplied/Storage and Handling

- a. For improved readability, revise Section 16 as follows to present the packaging configurations in a tabular format and using sub headers for the information provided.

How Supplied:

ZEGFROVY (sunvozertinib) tablets are supplied in bottles with a child-resistant cap as follows:

Tablet Strength	Description	Quantity	NDC Code
150 mg	yellow, biconvex film-coated tablets, debossed with "150" on one side and Dizal company logo on the other side.	30	XXXXXX-XXX-XX
200 mg	yellow, biconvex film-coated tablets, debossed with "200" on one side and Dizal company logo on the other side.	30	XXXXXX-XXX-XX

Storage and Handling:

Store ZEGFROVY at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

B. Patient Package Insert (PPI)

1. In the "How Should I take ZEGFROVY?" section, revise the sentence of the bulleted statements regarding swallowing Zegfrovy tablets whole to read "Swallow ZEGFROVY tablets whole. Do not split, crush, chew, or dissolve the tablet(s)."

5 RECOMMENDATIONS FOR DIZAL (JIANGSU) PHARMACEUTICAL COMPANY

A. General Comments (Container Label(s) and Carton Labeling)

1. The product identifier is missing. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.

We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier

requirements apply to your product's labeling, we request you add a placeholder to the carton labeling.

2. Remove the statement (b) (4) as this is not required information and adds clutter to the labels. (b) (4)
3. The net quantity statement competes for prominence with the strength statement. Move the strength upward to appear closer to the established name and away from the net quantity statement. In addition, revise the net quantity statement to appear with less prominence. We recommend this to minimize the risk of the net quantity being confused as the strength or vice versa.
 - a. Further, we recommend changing the color of the numerical net quantity statement to appear in the same gray font color as "tablets" and reduce the font size of the numerical number (i.e., 30). Then move the net quantity statement to appear in the bottom third of the container label and carton labeling.
4. Revise the order of the product information that appears on the back panel to present the information in the customary order and to present important product information with prominence as follows:

Each tablet contains ### mg of sunvozertinib.

Recommended Dosage: See prescribing information.

Storage: Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Keep out of reach of children.

Manufactured for:

Dizal (Jiangsu) Pharmaceutical Co., Ltd.
Shanghai, 201203, China

To improve readability, increase the font size of this important product information.

B. Container labels

1. Clarify the purpose and information that will be part of the box labeled 'FPO' that appears in the lower right quadrant of the principal display panel.
2. As currently presented, the manufacturer logo and name "Dizal" competes in prominence with critical product information (e.g., proprietary name, established name, etc.). Critical product information such as the proprietary name, established name should appear as the most prominent information on the principal display panel in accordance with 21 CFR 201.15. Reduce the size of

the manufacturer logo and name so it does not compete with the prominence of important product information on the principal display panel.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Zegfrovy received on November 7, 2024 from Dikal (Jiangsu) Pharmaceutical Company.

Table 2. Relevant Product Information for Zegfrovy	
Initial Approval Date	N/A
Active Ingredient	sunvozertinib
Indication	For the treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.
Dosage Form	Tablets
Strength	150 mg and 200 mg
Route of Administration	Oral
Dose and Frequency	(b) (4) mg once daily with food until disease progression or intolerable toxicity. <i>Dosage Modifications for CYP3A Inhibitors</i> If concomitant use of (b) (4) strong CYP3A inhibitor is unavoidable, reduce ZEGFROVY dosage to (b) (4) mg once daily.
How Supplied	150 mg: 30-count HDPE bottles 200 mg: 30-count HDPE bottles
Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].
Container Closure	75 mL bottle made of white, high-density polyethylene (HDPE) with a foil seal and a (b) (4) child-resistant (CR) screw closure (b) (4)

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Zegfrovy labels and labeling submitted by Dizal (Jiangsu) Pharmaceutical Company.

- Prescribing Information with Patient Package Insert received on November 7, 2024, available from <\\CDSESUB1\EVSPROD\nda219839\0001\m1\us\114-labeling\draft\annotated\1-14-1-3-zegfrovy-uspi-word.docx>.
- Container label(s) received on November 7, 2024.
- Carton labeling received on November 7, 2024.

B.2 Container Label(s) and Carton Labeling Images

(b) (4)

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

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

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

/s/

JANINE A STEWART
03/17/2025 03:04:09 PM

TINGTING GAO
03/17/2025 03:07:55 PM

Interdisciplinary Review Team for Cardiac Safety Studies
QT Study Review

Submission	NDA 219839
Submission Number	0001
Submission Date	11/7/2024
Date Consult Received	12/16/2024
Drug Name	ZEGFROVY (sunvozertinib)
Indication	For the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR Exon20ins, whose disease has progressed on or after platinum-based chemotherapy.
Therapeutic Dose	(b) (4) mg QD
Clinical Division	DO2
Protocol Review	DZ2019E0001 Part B (01/13/2021) DZ2020E0001 (06/14/2022)

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 12/16/2024 regarding the Applicant’s QT evaluation. We reviewed the following materials:

- Previous IRT review dated [01/13/2021](#), [06/14/2022](#) and [07/07/2023](#) in DARRTS;
- Investigator’s brochure (NDA 219839/ SN0001; [link](#));
- Proposed label (NDA 219839/ SN0001; [link](#));
- Summary of clinical safety (NDA 219839/ SN0001; [link](#));
- ISS patient narratives (NDA 219839/ SN0001; [link](#));
- Cardiac safety report on study DZ2020E0001 (WU-KONG6) (NDA 219839/ SN0001; [link](#));
- Cardiac safety report on study DZ2019E0001 (WU-KONG1B) (NDA 219839/ SN0001; [link](#)); and
- Summary of clinical pharmacology studies, including QT evaluation submission checklist (page 124) and highlights of clinical pharmacology and cardiac safety (page 129) (NDA 219839/ SN0001; [link](#)).

1 SUMMARY

Sunvozertinib treatment does not cause mean QTc interval prolongation ≥ 20 msec based on data from studies DZ2019E0001 Part B (WU-KONG1B) and DZ2020E0001 (WU-KONG6) – see Table 1 for overall results. Without a positive control or an exposure margin of at least twice the high clinical exposure scenario, we are reluctant to conclude that sunvozertinib has no effect on the QTc interval (ICH E14 Q&A 6.1).

Study DZ2019E0001B (WU-KONG1B) was a Phase I/II, single arm, multicenter study to evaluate antitumor activity, safety, tolerability, and PK of sunvozertinib in locally advanced or metastatic non-small cell lung cancer (NSCLC) patients with EGFR exon20 insertion mutation (b) (4) Only the dose expansion (Part B) was used for QTc assessment.

The DZ2020E0001 (WU-KONG6) study was an open-label, single-arm, multicenter phase 2 clinical study to evaluate the efficacy, safety/tolerability, and pharmacokinetics of sunvozertinib (300 mg QD) in NSCLC patients carrying EGFR exon 20 insertion mutations who have progression or intolerance after receiving at least 1 line but no more than 3 lines of prior systemic therapy.

The highest dose in the QTc assessment was the therapeutic dose and which is considered to be sufficient to characterize QTc effects in alternative QT assessments (ICH E14 Q&A 6.1). Data were analyzed using concentration-QTc analysis as the primary analysis, which did not suggest that sunvozertinib is associated with large mean increases in the QTcF interval (section 4.5). The findings of the primary analysis are further supported by the by-time analysis (section 4.3) and categorical analysis (section 4.4).

Table 1: Summary of findings

QT assessment pathway	☐ Thorough QT study ☐ Substitute for thorough QT study (5.1) ☒ Alternative QT study when a thorough QT study is not feasible (6.1)				
Clinical QT study findings	- The high clinical exposure is when the drug is administered in moderate hepatic impaired participants (NCI-ODWG) which increases $C_{max,ss}$ by 1.4-fold. (section 3.1). The metabolite, DZ0753, had similar exposure in normal and hepatic impairment. - The highest dose of 300 mg QD in the QTc assessment covers the maximum anticipated high exposure (C_{max}) by 0.6 and 1.0-fold for Sunvozertinib (DZD9008) and its metabolite (DZ0753) respectively.				
	ECG parameter	Treatment	Concentration (ng/mL)	ΔQTcF (msec)	90% CI (msec)
	Δ QTcF	Sunvozertinib 300 mg QD (Pop PK predicted Steady state Cmax in NSCLC)	619.0	0.7	(-0.8 to 2.3)
	Δ QTcF	Sunvozertinib 300 mg QD (Highest exposure in QTc assessment – WU-KONG1B)	523.5	0.9	(-0.5 to 2.2)
	Δ QTcF	Sunvozertinib 300 mg QD in patient with moderate hepatic impairment (High clinical exposure scenario)	842.0	0.4	(-1.7 to 2.5)

In vitro and in vivo findings	Integrated nonclinical risk assessment was not performed.

2 RECOMMENDATIONS

Below are proposed edits to the label submitted to SDN 0001 ([link](#)).

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

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

Reviewer’s comment: We propose to use labeling language for this product consistent with the “QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry” draft guidance ([link](#)).

3 APPLICANT’S SUBMISSION

3.1 OVERVIEW

ZEGFROVY (sunvozertinib, DZD9008, MW: 584.09 g/mol) is a tyrosine kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. The application was submitted under accelerated approval. The recommended dose is (b) (4) mg (tablets) orally once daily (QD), taken with food.

The CS-IRT previously reviewed the QT assessment proposal based on study DZ2020E0001 (WU-KONG6) ([06/14/2022](#) and [07/07/2023](#)) and found the analysis can be used to support excluding large mean increases (20 msec) in QTc interval, pending on review of the data. We also reviewed the Applicant’s safety analysis related to torsade de pointe and recommended the Division to request the narratives of one treatment-related ventricular arrhythmia and one treatment-related syncope.

In this submission, the Applicant submitted two cardiac safety reports, one based on study DZ2020E0001 (WU-KONG6), and one based on study DZ2019E0001 Part B (WU-KONG1B). The Applicant used concentration-QTc (C-QTc) analysis as primary analysis, for the two studies separately. See Appendix for more information about the two studies.

Study WU-KONG1B was a phase 2, open-label, randomized study to evaluate the anti-tumor efficacy of sunvozertinib. Patients with NSCLC with EBFR or HER2 mutation were randomized into Cohort 1 (200 mg QD) and Cohort 2 (300 mg QD) at a 1:1 ratio before the optimal recommended phase 2 dose was selected. Dosing occurs under fed conditions.

Study WU-KONG6 was an open-label, single-arm, multicenter phase 2 clinical study to evaluate the efficacy, safety/tolerability, and PK of sunvozertinib (300 mg, QD) in NSCLC patients carrying EGFR exon 20 insertion mutations who have progression or intolerance after receiving at least 1 line but no more than 3 lines of prior systemic therapy. Dosing is suggested to be taken with food.

3.1.1 Clinical Pharmacology

Pharmacokinetics (PK) data from the clinical studies demonstrated an approximately dose-proportional increase in exposure at the dosages ranging from 50-400 mg QD PO with multiple-dose administration.

After multiple dosing, sunvozertinib was absorbed with a median T_{max} of 4 to 6 hours under modified fasted condition across all doses. The median T_{max} of primary metabolite DZ0753 was about 4 hours after single or multiple dosing.

The mass-balance study demonstrated primary route of elimination via feces (~78.6%) and minor elimination via urine (10.3%) based on radioactive dose recovery. The primary metabolite DZ0753 is a pharmacologically active metabolite of sunvozertinib with similar potency against EGFR exon20ins and wild-type EGFR in cellular assays as sunvozertinib.

Sunvozertinib and DZ0753 have similar plasma protein binding (~90%).

DZ0753 is present at approximately ~3.2% of the parent drug (sunvozertinib or DZD9008) in plasma after a single dose, whereas the steady-state exposure ($C_{max, ss}$ and AUC_{24ss}) of metabolite DZ0753 was approximately 13% - 18% of that of sunvozertinib in NSCLC patients.

Based on the in vitro and in vivo ADME studies, sunvozertinib is primarily metabolized by CYP3A4. In addition, sunvozertinib also showed reversible and time-dependent inhibition of CYP2D6 and CYP3A4.

Food (with either low-fat or high-fat meal) has minimal impact on the exposure of sunvozertinib and after multiple QD dose.

Sunvozertinib exhibits low to moderate apparent clearance and high volume of distribution, resulting in slow elimination $t_{1/2}$ of approximately 48 hours, resulting in steady state exposure achieved within 15 days of once daily dosing. After multiple dose the accumulation ratio was about 2 to 3 folds for C_{max} or AUC respectively.

Clinical drug-drug interaction (DDI) study showed that AUC and C_{max} of sunvozertinib increase by 52% and 32% when co-administered with the strong CYP3A inhibitor itraconazole. The proposed label instructs to reduce dosage (b) (4) when using concomitantly with (b) (4) strong CYP3A4 inhibitors.

Age, sex, race, mild and moderate renal impairment were found to be not significant covariates using PopPK model.

The hepatic impairment study showed that the AUC and C_{max} of sunvozertinib increased by up to 12% and 36% in moderate hepatic impaired subjects (total bilirubin >1.5 to 3 times ULN and any value for AST) as compared with normal function subjects. No dose adjustment is recommended for patients with mild or moderate hepatic impairment. Sunvozertinib has not been studied in patients with severe hepatic impairment. There is no

dose recommendation and no contraindication for this population. The 36% increase in C_{max} at steady state in patients with moderate hepatic impairment is considered to be the high clinical exposure scenario.

Table 2. Summary of Dose and Exposure Assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	300 mg QD, oral tablets	sunvozertinib = 619 ng/mL DZ0753 = 89.8 ng/mL
Applicant's High clinical exposure scenario	1.36-fold increase in moderate hepatic impaired participants (NCI-ODWG)	sunvozertinib = 842 ng/mL DZ0753 = 89.8 ng/mL*
Highest dose in QT assessment	300 mg QD oral tablets	sunvozertinib = 523 ng/mL** DZ0753 = 89.8 ng/mL
C_{max} Ratio	Sunvozertinib clinical exposure = 523/619 = 0.84 Sunvozertinib high clinical exposure = 523/842 = 0.62 DZ0753 = 1.0 over clinical and high clinical exposure	

* C_{max} for DZ0753 is reported to be similar between subjects with normal hepatic function when compared to moderate HI.

** C_{max} at Cycle 3 Day 1 (WU-KONG1B)

3.1.2 Nonclinical Safety Pharmacology Assessments

See previous review ([07/07/2023](#)).

The hERG safety margin of sunvozertinib is 7.6-fold, indicating it could potentially prolong QTc through direct hERG inhibition at clinical exposures.

The in vivo study assessed the potential effects of sunvozertinib on ECG parameters following single dose oral administration in the conscious telemetry dogs. The PK data showed that the mean concentration of sunvozertinib in plasma was ~414 ng/mL. No QTc prolongations were observed at exposure ~0.5-fold the high clinical exposure based on total concentration.

3.2 APPLICANT'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for sunvozertinib is exposure-response analysis, please see section 3.2.3 for additional details.

The Applicant performed by-time analyses separately using MMRM for two studies: WU-KONG1B and WU-KONGG6. The Applicant performed analysis using two separate models, one for data before Cycle 3 Day 1 and the other for data after Cycle 3 Day 1. The 90% upper confidence bound (UCL) was <10 msec at all time-points which included data from 5 or more patients, except for one time point. The time point with a UCL >10 msec (10.8 msec) in WU-KONG6 for Cycle 14. Notably, at this time point there was only data from 6 patients.

Reviewer's comment: Reviewer also conducted by-time analysis using MMRM model for both studies, separately. Only the results of study WU-KONG1B with semi-automatic measurement data are shown in the report, as results for study WU-KONG6 and results with automatic measurement data from the ECG warehouse algorithm were consistent. Reviewer only used data with recorded time points, including those with six or more

patients available. Therefore, reviewer used the same data with the Applicant before Cycle 3 Day 1, but different after Cycle 3 Day 1. The reviewer's analysis results are similar to the Applicant's analysis results before Cycle 3 Day 1. Per the reviewer's analysis, the 90% upper bound CI for $\Delta QTcF$ was <10 msec at all time points except at time 0 on Cycle 11 Day 1. However, the ECG collection time was not standardized starting at cycle 4. Please see section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Not applicable as neither study included a positive control.

3.2.1.2 QT Bias Assessment

No QT bias assessment was conducted by the Applicant.

3.2.2 Categorical Analysis

The Applicant performed outlier analysis by study:

- QTc (i.e., >500 msec or >60 msec over baseline): WU-KONG1B (n=1) and WU-KONG6 (n=2).
- HR (>100 beats/min and 25% over baseline): WU-KONG1B (n=19) and WU-KONG6 (n=7).
- PR (>200 msec and 25% over baseline): WU-KONG1B (n=3) and WU-KONG6 (n=1).
- QRS (>120 msec and 25% over baseline): WU-KONG1B (n=1) and WU-KONG6 (n=0).

Reviewer's comment: The reviewer's analysis results are similar to the Applicant's analysis results. The reviewer's analysis results are shown below. Please see section 4.4 for additional details.

- QTc (i.e., >500 msec or >60 msec over baseline): WU-KONG1B (n=2) and WU-KONG6 (n=2).
- HR (>100 beats/min and 25% over baseline): WU-KONG1B (n=23) and WU-KONG6 (n=10).
- PR (>220 msec and 25% over baseline): WU-KONG1B (n=2) and WU-KONG6 (n=0).
- QRS (>120 msec and 25% over baseline): WU-KONG1B (n=1) and WU-KONG6 (n=0).

3.2.3 Exposure-Response Analysis

In this current submission, the Applicant submitted two separate cardiac safety reports, one based on study DZ2020E0001 (WU-KONG6), and one based on study DZ2019E0001 Part B (WU-KONG1B), and the QTc analysis in both studies was performed according to ICH E14 guidance and following the C-QT white paper (Garnett et al, 2017), using the data collected from each study separately.

The analysis for each of the studies used the prespecified linear mixed effect (LME) model with Fridericia heart-rate corrected QT interval (Δ QTcF) as a dependent variable along with plasma concentrations of sunvozertinib and DZ0753 as the explanatory variables, centered baseline QTcF as an additional covariate, a fixed intercept, and slope for the concentration per patient. In both the analysis, the following 3 models were explored: the full model with both analytes (sunvozertinib and DZ0753), the individual model with sunvozertinib alone, and the individual model with DZ0753 alone. The Applicant used the model recommended in the white paper except for the model with 2 analytes which did not include the interaction term.

In WU-KONG1B, all the C-QTc models had a significant intercept and the model with the lowest AIC was the model with both sunvozertinib and DZ075. Since the difference in AIC was small, the Applicant chose the model with sunvozertinib only as the primary model for WU-KONG1B. This primary model predicted Δ QTcF at the geometric mean $C_{\max}$ of sunvozertinib was 0.92 msec (90% CI: -0.42 to 2.26 msec) on C3D1 ($C_{\max}$ 522.2 ng/mL after 300 mg QD dose) for WU-KONG1B. Based on this concentration QTc analysis of WU-KONG1B, a QTcF (Δ QTcF) effect exceeding 20 msec can be excluded up to sunvozertinib plasma concentration of 1547 ng/mL. These results from Applicant's analysis support excluding a ≥ 20 msec mean increase in QTcF at therapeutic dose of 300 mg QD. The Applicant's results for WU-KONG6 were similar.

Reviewer's comment: Overall, the findings from our C-QTc analysis are similar to those reported by the Applicant. Please see section 4.5 for additional details.

3.2.4 Safety Analysis

As of July 29, 2024, a total of 467 advanced NSCLC patients with EGFR or HER2 mutations have been enrolled into DZ2019E0001 (WU-KONG1, n = 315), DZ2019E0002 (WU-KONG2, n = 48), and DZ2020E0001 (WU-KONG6, n = 104) studies. All patients who received at least one dose of sunvozertinib and included in the safety analysis set. The median treatment duration was 6.9 months (range: 0.03 – 51.35 months).

Among all the 467 patients dosed with sunvozertinib, 9 patients (2.0%) were reported to have QTcF increase from baseline >60 msec, 7 patients (1.5%) were reported to have QTcF absolute >500 msec, 4 patients (0.9%) experienced QTcF >500 msec and change from baseline >60 msec. None of these cases were reported to have clinical signs or symptoms.

In addition to the QTcF change, below treatment emergent adverse events (TEAEs) were reported at lower frequency by the data cut-off:

- (1) Dizziness: 46 (9.9%) patients received sunvozertinib were reported to have dizziness, among them 19 (4.1%) were considered drug related according to investigator's assessment.
- (2) Syncope: 3 patients (0.6%) reported syncope, and none was drug related per investigator's assessment.
- (3) Seizure: 5 patients (1.1%) were reported to have seizure which was not drug related according to investigator's assessment.
- (4) Ventricular arrhythmia: 1 patient (0.2%) was reported to have ventricular arrhythmia which was drug related upon investigator's assessment.

No treatment emergent Torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, and flutter were reported by data cut-off.

Reviewer's comment: See section 4.6 for the reviewer's assessment based on the same safety database.

4 REVIEWERS' ASSESSMENT

C-QTc and by-time analyses were performed for the two studies separately. This is because the two studies used different ECG measurement methods and QT bias was observed in WU-KONG1B (section 4.2). However, the categorical analysis was performed on the pooled dataset.

Since the two studies showed similar QTc prolongation in by-time analysis for the 300 mg dose cohort and similar prediction of QTc prolongation at clinical exposure in the C-QTc analysis, only WU-KONG1B is presented as below for by-time and C-QTc analysis. Both studies are presented for the categorical analysis.

No significant differences in the results for C-QTc and by-time analysis were observed between different QTc measurement methods (Applicant-submitted vs the ECG warehouse algorithm). Subsequent sections therefore only present the results based on the QTc measurements submitted by the Applicant.

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The Applicant used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., $|\text{mean}| > 10$ beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader blinded to subject and treatment for both studies. Compared to the ECG warehouse algorithm, we observed significant bias in QT measurements for study WU-KONG1B, automatic measurements generated from the ECG warehouse algorithm were used to perform sensitivity analysis. C-QT analysis using automatic measurements showed similar C-QTc relationship and similar prediction of change from baseline QTcF at clinical exposure. The ECG acquisition and interpretation for studies WU-KONG1B and WU-KONG6 is therefore acceptable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline, semi-automated measurement methodology, with documented time points, and at least one post-dose ECG from the WU-KONG1B study. The time points used for by-time analysis at which data from 6 or more patients were available.

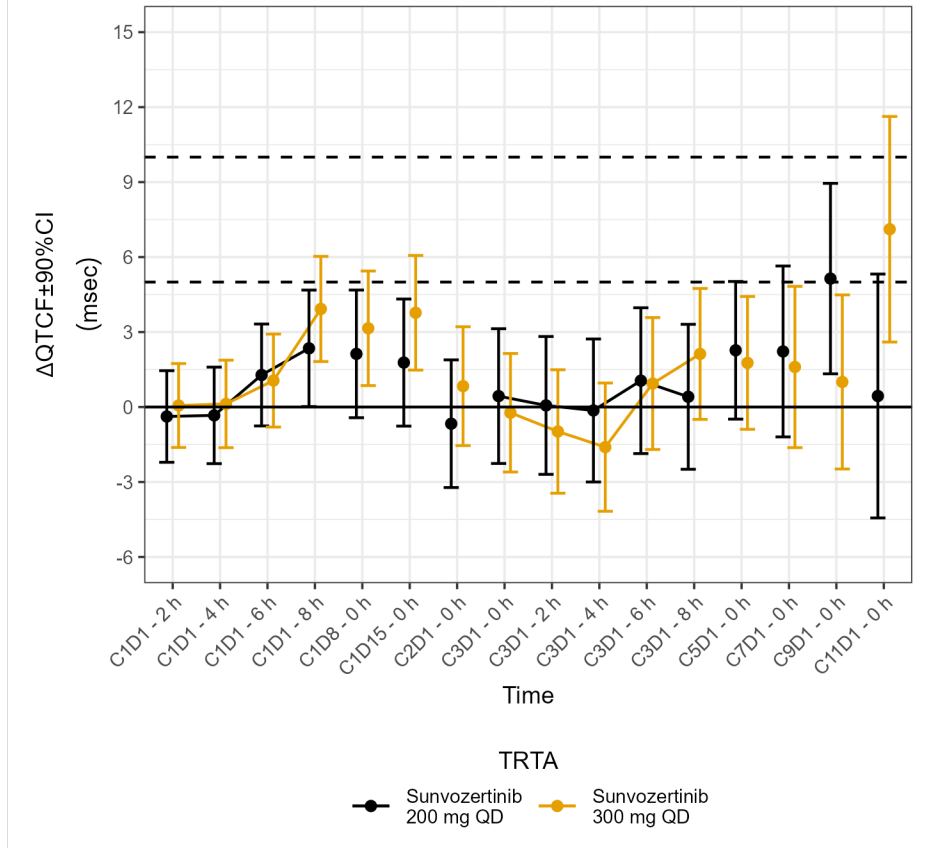
The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF , ΔHR) independently. The model includes treatment, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The model also includes an unstructured covariance matrix to explain the associations among repeated measures within the treatment.

Starting at cycle 4 ECGs could be collected at any time. All by-time analyses include only ECGs that were collected at pre-dose. Consequently, not all participants might have contributed to all time-points starting at cycle 4.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for different treatment groups in the WU-KONG1B study.

Figure 1. Mean and 90% CI of ΔQTcF Time-Course (Unadjusted CIs) for study WU-KONG1B



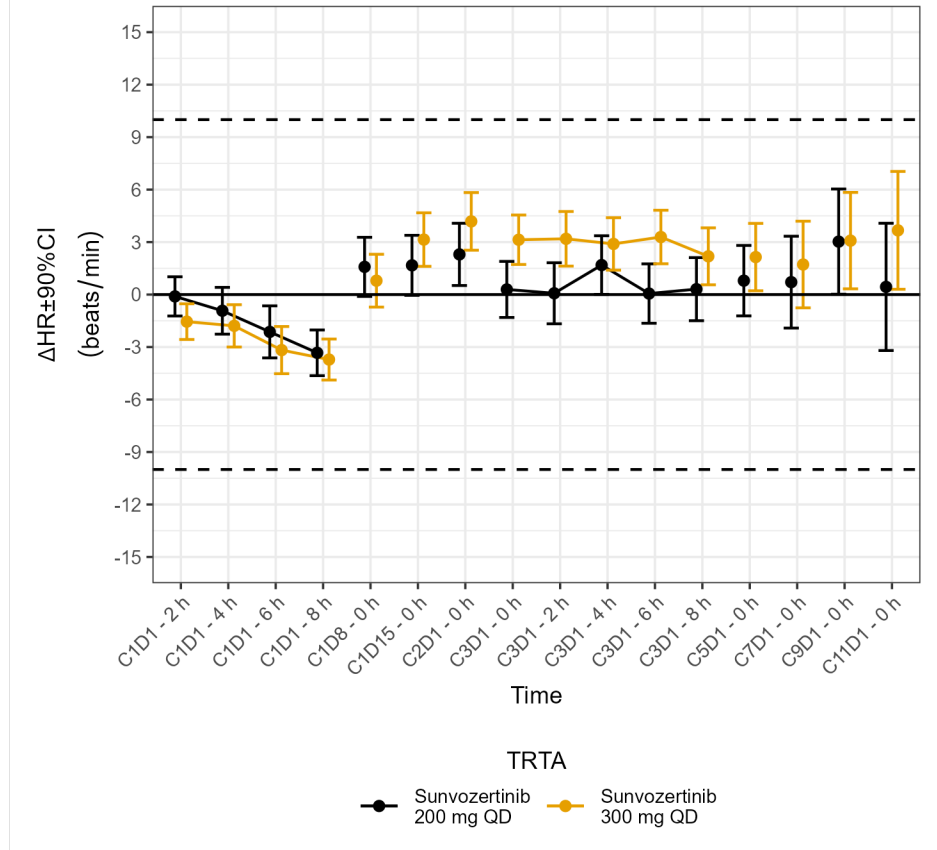
4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for different treatment groups in the WU-KONG1B study.

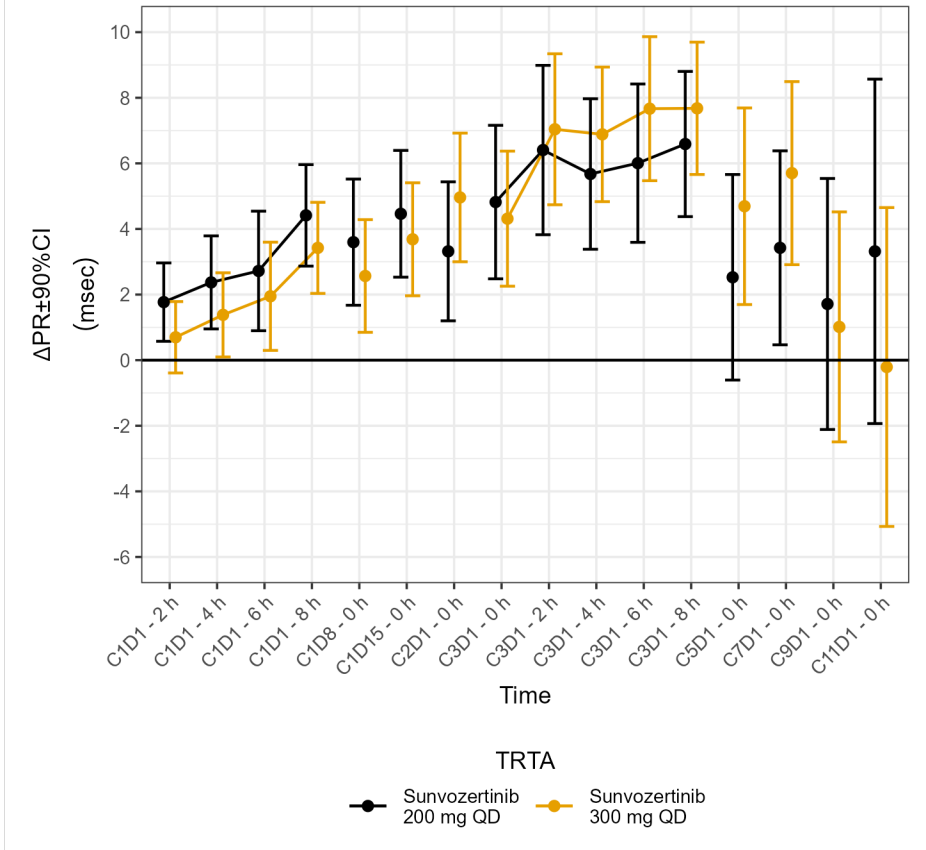
Figure 2. Mean and 90% CI of Δ HR Time-Course for study WU-KONG1B



4.3.3 PR

Figure 3 displays the time profile of Δ PR for different treatment groups in the WU-KONG1B study. An increase in PR was observed on Cycle 3 Day 1 in both WU-KONG1B and WU-KONG6 studies. The magnitude of the mean Δ PR was less than 10 msec in WU-KONG1B study but reach 11.6 msec at 8-hour Cycle 3 Day 1 in WU-KONG6 study.

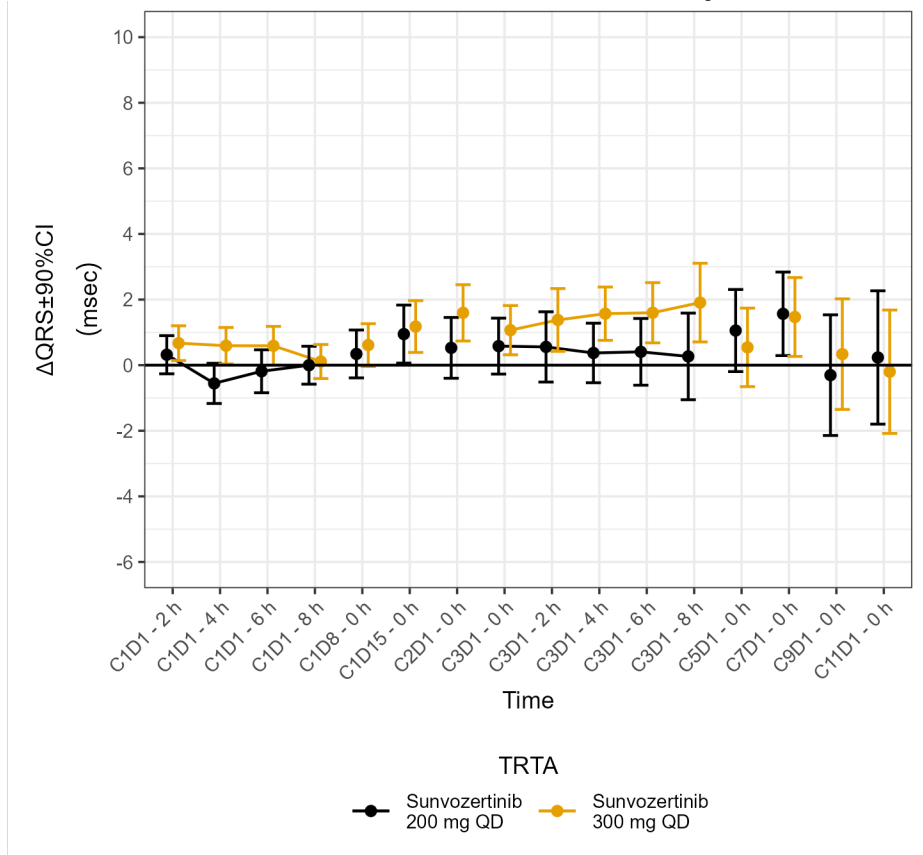
Figure 3. Mean and 90% CI of Δ PR Time-Course for study WU-KONG1B



4.3.4 QRS

Figure 4 displays the time profile of Δ QRS for different treatment groups in the WU-KONG1B study.

Figure 4. Mean and 90% CI of Δ QRS Time-Course for study WU-KONG1B



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different semi-automatic ECG measurements, either using absolute values, change from baseline, or a combination of both with combined data from both studies. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

Table 3 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 without a change from baseline >60 msec. There were 2 subjects who had observed QTcF >500 msec without a change from baseline >60 msec in the sunvozertinib 300 mg QD treatment group from study WU-KONG1B.

Table 3. Categorical Analysis for QTcF (Maximum)

Study Identifier	Actual Treatment	Total (N)		Value <=450 msec		450 msec < Value <=480 msec		480 msec < Value <=500 msec		Value >500 msec & <=60 msec	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
WU-KONG1B	Sunvozeritinib 200 mg QD	83	1523	54 (65.1%)	1376 (90.3%)	27 (32.5%)	145 (9.5%)	2 (2.4%)	2 (0.1%)	0 (0%)	0 (0%)
	Sunvozeritinib 300 mg QD	102	1823	72 (70.6%)	1612 (88.4%)	25 (24.5%)	172 (9.4%)	3 (2.9%)	27 (1.5%)	2 (2.0%)	12 (0.7%)
WU-KONG6	Sunvozeritinib 300 mg QD	101	1644	91 (90.1%)	1607 (97.7%)	9 (8.9%)	35 (2.1%)	1 (1.0%)	2 (0.1%)	0 (0%)	0 (0%)

Table 4 lists the categorical analysis results for Δ QTcF (<30 msec, >30 and <60, and >60 msec). There were 2 subjects who had observed QTcF change from baseline above 60 msec in the sunvozeritinib 300 mg QD treatment group from study WU-KONG6.

Table 4. Categorical Analysis for Δ QTcF (Maximum)

Study Identifier	Actual Treatment	Total (N)		Value <=30 msec		30 msec < Value <=60 msec		Value >60 msec	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
WU-KONG1B	Sunvozeritinib 200 mg QD	83	1523	74 (89.2%)	1510 (99.1%)	9 (10.8%)	13 (0.9%)	0 (0%)	0 (0%)
	Sunvozeritinib 300 mg QD	102	1823	83 (81.4%)	1783 (97.8%)	19 (18.6%)	40 (2.2%)	0 (0%)	0 (0%)
WU-KONG6	Sunvozeritinib 300 mg QD	101	1644	86 (85.1%)	1613 (98.1%)	13 (12.9%)	29 (1.8%)	2 (2.0%)	2 (0.1%)

4.4.2 HR

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

There were 29 subjects in the sunvozeritinib 200 mg QD treatment group and 28 subjects in the sunvozeritinib 300 mg QD treatment group from study WU-KONG1B having observed maximum HR above 100 beats/min. Thirteen of them in the sunvozeritinib 200 mg QD treatment group and six of them in the sunvozeritinib 300 mg QD treatment group were 25% increase over baseline.

There were 36 subjects in the sunvozeritinib 300 mg QD treatment group from study WU-KONG6 having observed maximum HR above 100 beats/min. Ten of them was 25% increase over baseline.

Table 5. Categorical Analysis for HR (Maximum)

Study Identifier	Actual Treatment	Total (N)		Value ≤100 beats/min		Value >100 beats/min	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
WU-KONG1B	Sunvozertinib 200 mg QD	87	1599	58 (66.7%)	1529 (95.6%)	29 (33.3%)	70 (4.4%)
	Sunvozertinib 300 mg QD	108	1898	80 (74.1%)	1797 (94.7%)	28 (25.9%)	101 (5.3%)
WU-KONG6	Sunvozertinib 300 mg QD	104	1677	68 (65.4%)	1552 (92.5%)	36 (34.6%)	125 (7.5%)

4.4.3 PR

Table 6 lists the categorical analysis results for PR (≤ 220 msec, and > 220 msec; with and without 25% increase over baseline). There was one subject in the sunvozertinib 300 mg QD treatment group and one subject in the sunvozertinib 200 mg QD treatment group who had observed PR > 220 msec with 25% increase over baseline from study WU-KONG1B.

Table 6. Categorical Analysis for PR

Study Identifier	Actual Treatment	Total (N)		Value ≤220 msec		Value >220 msec & <25%		Value >220 msec & ≥25%	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
WU-KONG1B	Sunvozertinib 200 mg QD	83	1529	78 (94.0%)	1510 (98.8%)	4 (4.8%)	18 (1.2%)	1 (1.2%)	1 (0.1%)
	Sunvozertinib 300 mg QD	103	1841	94 (91.3%)	1811 (98.4%)	8 (7.8%)	29 (1.6%)	1 (1.0%)	1 (0.1%)
WU-KONG6	Sunvozertinib 300 mg QD	101	1643	95 (94.1%)	1626 (99.0%)	6 (5.9%)	17 (1.0%)	0 (0%)	0 (0%)

4.4.4 QRS

Table 7 lists the categorical analysis results for QRS (≤ 120 msec, and > 120 msec; with and without 25% increase over baseline). There was one subject who had observed QRS > 120 msec with 25% increase over baseline in the sunvozertinib 300 mg QD treatment group from study WU-KONG1B.

Table 7. Categorical Analysis for QRS

Study Identifier	Actual Treatment	Total (N)		Value <=120 msec		Value >120 msec & <25%		Value >120 msec & >=25%	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
WU-KONG1B	Sunvozertin ib 200 mg QD	83	1529	80 (96.4%)	1472 (96.3%)	3 (3.6%)	57 (3.7%)	0 (0%)	0 (0%)
	Sunvozertin ib 300 mg QD	103	1841	97 (94.2%)	1765 (95.9%)	5 (4.9%)	74 (4.0%)	1 (1.0%)	2 (0.1%)
WU-KONG6		101	1644	95 (94.1%)	1543 (93.9%)	6 (5.9%)	101 (6.1%)	0 (0%)	0 (0%)

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK. For the exposure response, only the data from study DZ2019E0001 is presented, where a total of 83 subjects after 200 mg QD dose and 103 subjects after 300 mg QD dose had adequate PK data which contributed to the PK analysis and constitute the PK analysis population.

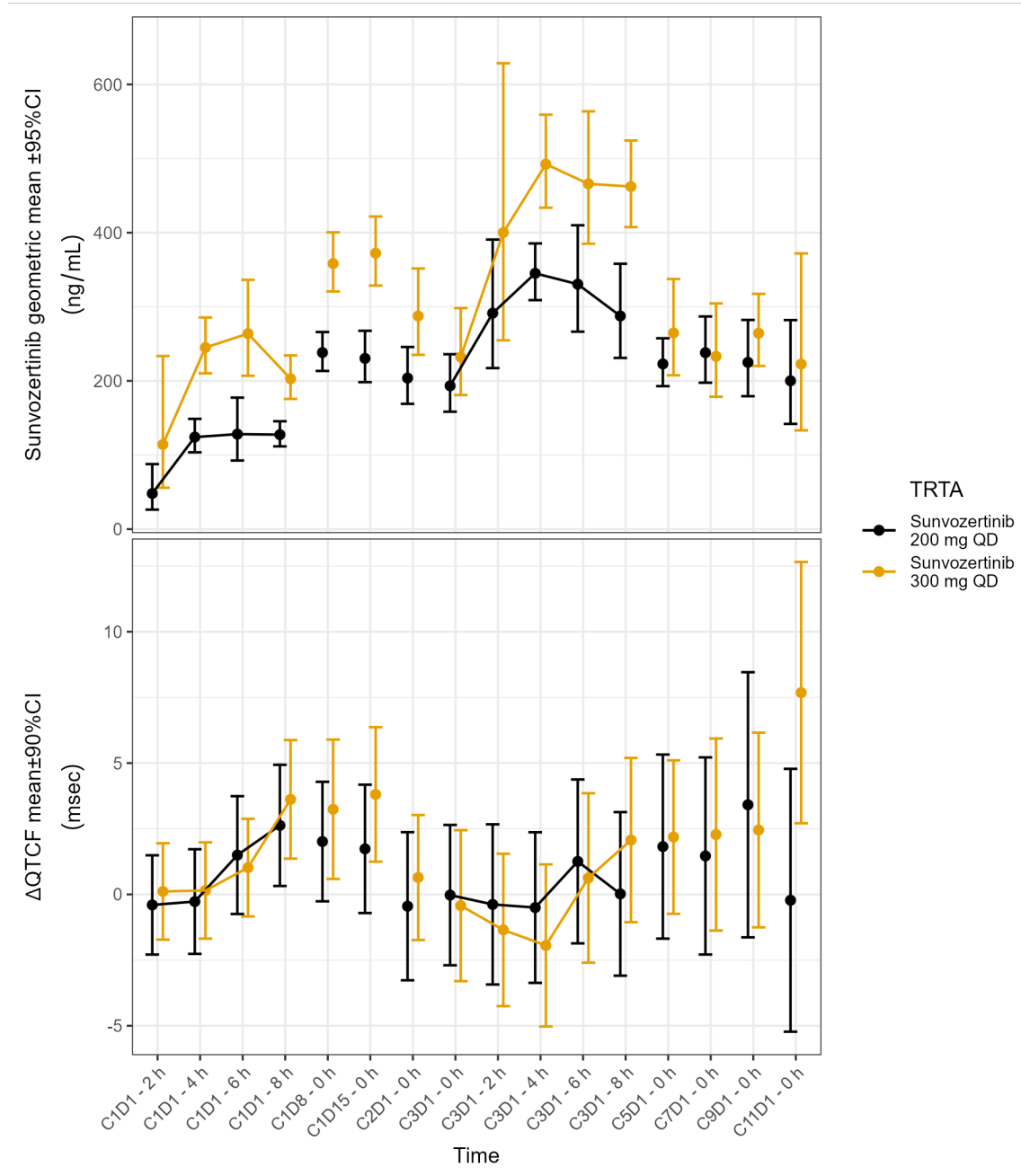
As noted earlier, starting at cycle 4 ECGs could be collected at any time. Therefore, starting at cycle 4 only ECGs with a corresponding time-matched PK was considered in the analysis.

4.5.1 QTc

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

Figure 2 shows the time-course of Δ HR, with an absence of significant Δ HR changes. Figure 5 shows the time-course of sunvozertinib concentration (top) and QTcF (bottom) and offers an evaluation of the relationship between time-course of drug concentration and Δ QTcF. Although there is some indication for delayed QTcF increase in Cycle 1 Day 1, it is unlikely to impact the assessment of linearity of the CQT relationship. This is because: i) no time point has mean Δ QTcF >5 msec; ii) the increase is not dose dependent; and iii) no delay is observed in Cycle 3 Day 1 when the exposure is higher than Cycle 1 Day 1. Figure 6 shows the relationship between drug concentration and Δ QTcF and supports the use of a linear model.

Figure 5. Time-Course of Drug Concentration (Top) and QTcF (Bottom)¹



¹ Δ QTcF shown were obtained via descriptive statistics and might differ from Figure 1

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

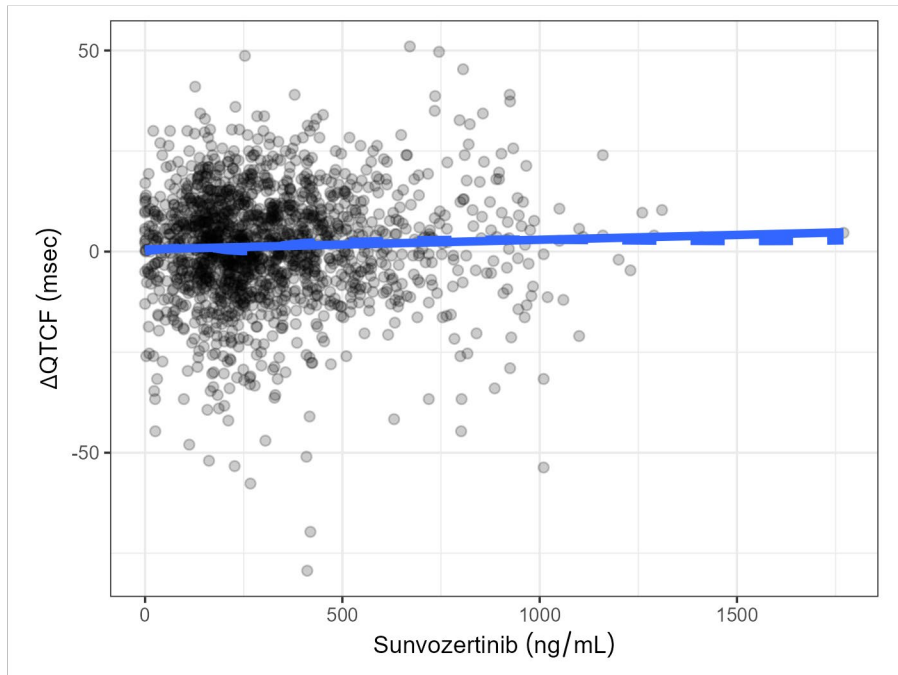
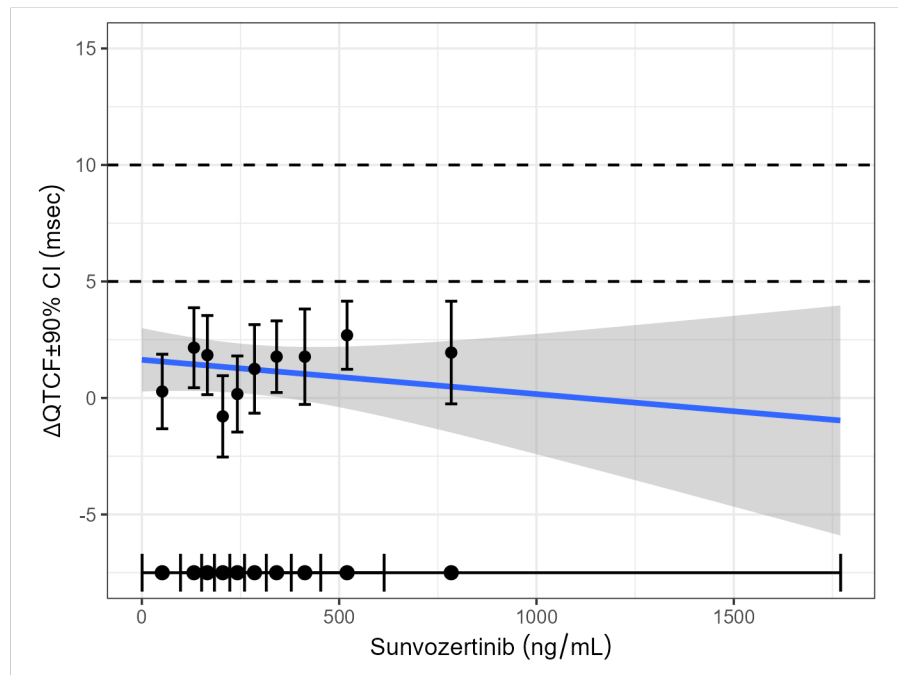


Figure 7. Goodness-of-Fit Plot for Δ QTcF



Finally, the linear model was applied to the data. Predictions from the concentration-QTcF model are provided in Table 8. The overall results of the reviewer analysis were comparable with the Applicant predicted values. Findings from the sensitivity analysis using QTc intervals measured automatically by the ECG warehouse algorithm are

consistent with semi-automatic reading, both indicating that sunvozertinib treatment is not associated with clinically significant QTc prolongation.

Table 8. Predictions From Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Sunvozertinib (ng/mL)	ΔQTcF (msec)	90.0% CI (msec)
Sunvozertinib 200 mg QD	15	230.4	1.3	(0.2 to 2.4)
Sunvozertinib 200 mg QD	8	238.3	1.3	(0.2 to 2.4)
Sunvozertinib 300 mg QD	8	358.3	1.1	(0.0 to 2.2)
Sunvozertinib 300 mg QD	15	372.3	1.1	(-0.0 to 2.2)
Sunvozertinib 200 mg QD	1	376.2	1.1	(-0.0 to 2.2)
Sunvozertinib 300 mg QD	1	523.5	0.9	(-0.5 to 2.2)
Highest therapeutic or clinical trial dosing regimen		619.0	0.7	(-0.8 to 2.3)
Applicant's high clinical exposure scenario		842.0	0.4	(-1.7 to 2.5)

4.5.1.1 Assay Sensitivity

Not Applicable.

4.6 SAFETY ASSESSMENTS

In total, 36 subjects (8%) reported treatment emergent adverse events (TEAEs) of broad SMQ of "Torsade de pointes/QT prolongation".

Electrocardiogram QT prolonged: Twenty-nine subjects (6%) experienced TEAE of electrocardiogram QT prolonged. Five subjects (1%) experienced Grade 3 electrocardiogram QT prolonged: no subjects discontinued treatment due to QT prolongation, one subject had an SAE (subject ID: (b) (6)), and two subjects had QTcF >500 msec (b) (6). See [ISS](#) Section 2.4 (page 56) for the narrative of Grade 3 QT prolongations. Three additional subjects ((b) (6)) had QTcF >500 msec and change from baseline > 60 msec without reporting of a Grade 3 QT prolongation. See section 5.3.1 for graphic patient profile (GPP) for subject (b) (6) (maximum QTcF: 511 msec – not captured in ADEG, see below, baseline: 383 msec), (b) (6) (maximum QTcF: 517 msec, baseline: 413 msec), (b) (6) (maximum QTcF: 516 msec, baseline: 446 msec), (b) (6) (maximum QTcF: 522 msec, baseline: 458 msec), and (b) (6) (maximum QTcF: 516 msec, baseline: 448 msec). Electrolytes were below lower limit of normal (horizontal dash line in GPP) at the time of QT prolongation for subject (b) (6) (calcium), (b) (6) (calcium and potassium), and (b) (6) (calcium). Note that subject (b) (6) was hospitalized on Day 22 for worsening of asthenia. On Day 22 about 2 hours post dose of sunvozertinib, bedside ECG showed QTc interval of 511 msec; sinus rhythm; and ST-T changes in the anterolateral and posterior walls (without central ECG interpretation). The subject had prolonged hospitalization due to the SAE of QTc prolongation, and sunvozertinib was interrupted due to the event. The

investigator considered this event related to sunvozertinib based on timing ([narrative](#), page 1864). This QTc was not captured in the ADEG dataset, therefore, not reflected on the GPP and not reflected in the Applicant's count in section 3.2.4. Subject (b) (6) and (b) (6) had no electrolyte imbalance, were not receiving concomitant medications with known QTc prolonging risks, and did not have a relevant cardiac medical history. Based on the timing of the events (C1D8 6 hours postdose for subject (b) (6) and C3D1 2 hours postdose for subject (b) (6); median T_{max} for sunvozertinib: 4 to 6 hours postdose), they could be related to the study drug. Narratives were not provided by the Applicant for these two subjects.

Seizure: Five subjects (1%) experienced TEAE of seizure (subject ID: (b) (6)). None of them were SAEs or led to treatment discontinuation. Three subjects ((b) (6)) discontinued treatment or had dose interruption due to disease progression before or around the time of the seizure events; these AEs were likely due to disease progression ([narrative](#), page 67). There were no concurrent QTc prolongation at the seizure event for subject (b) (6), and (b) (6). Subject (b) (6) had no ECG data at the time of the seizure event.

Syncope: Three subjects (0.6%) experienced TEAE of syncope (subject ID: (b) (6)). Subject (b) (6) did not have QTcF >480 msec at the time of the syncope events. Subject (b) (6) had not QTc data at the time of the syncope event.

Ventricular arrhythmia: One subject (0.2%) experienced TEAE of ventricular arrhythmia. The event was considered related to treatment by the investigator. It was considered not related to treatment by the Applicant because the subject had a history of arrhythmia and reduced ejection fraction (55%) during the screening phase with left ventricular enlargement, mitral and tricuspid regurgitation. QTc was below 480 msec at the time of the ventricular arrhythmia event (maximum QTcF: 465 msec, baseline: 449 msec). See section 5.3.2 for GPP.

- (b) (6) (WU-KONG6): A 72-year-old Asian male subject (b) (6) was enrolled in WU-KONG6 study and received sunvozertinib (300 mg, oral QD) for NSCLC. From Day 91 to Day 96, sunvozertinib was interrupted due to diarrhea. On Day 95 (after 5 days of interruption), a Grade 2 AE of ventricular arrhythmia was reported, and the investigator assessed it as related to sunvozertinib. Sunvozertinib was resumed at same dose on Day 97, and then interrupted on Day 99 due to this event. On Day 110, the event was improved to Grade 1, and sunvozertinib was resumed with reduced dose of 200 mg. The event was recovered on Day 134. Sunvozertinib treatment continued until Day 212 and this event did not recur.

In conclusion, 36 subjects (8%) reported treatment emergent adverse events (TEAEs) of broad SMQ of "Torsade de pointes/QT prolongation". The TEAE of seizure (1%), syncope (0.6%), and ventricular arrhythmia (0.2%) were not likely caused by prolonged QTc. Twenty-nine subjects (6%) experienced TEAE of electrocardiogram QT prolonged. Five subjects (1%) experienced QTcF >500 msec and change from baseline >60 msec: 3 of them had electrolyte imbalance at the time of the QTc prolongation while the other two had no

relevant medical history, concomitant medication, or electrolyte imbalance to explain the events.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderderpqt@fda.hhs.gov

5 APPENDIX

5.1 EVALUATION OF THE APPLICANT'S CLINICAL QT STUDIES

1. QT Studies					
Study	ECG Quality	Treatments		Sample Size	ECG & PK Assessments
		Arms	Dose Coverage		
Protocol Number: WU-KONG1B (DZ2019E0001 Part B) Population: Patients Design: Other (Open label, randomized, two treatment arms with intensive PK in 44 patients)	Digital: Yes Central Read? Yes Blinded? Yes Replicates? Yes	Highest Dose: 300 mg QD Placebo: No Positive Control: No	Therapeutic	N=186 in Part B (Dose Expansion) are include in QT evaluation. Cohort 1: 200 mg (n = 83) Cohort 2: 300 mg (n = 103)	Baseline: Pre-dose baseline Matching PK/ECG Timing: Intensive PK patients (n = 44): C1D1 and C3D1: pre-dose, 2, 4, 6, 8 h post-dose. Sparse PK patients (rest): C1D1 and C3D1: pre-dose, 4 and 8 h post-dose. All patients: C1D8, C1D15, C2D1: pre-dose. Note: PK and ECG were collected at additional time points but were not matched.
Protocol Number: WU-KONG6 (DZ2020E0001)	Digital: Yes	Highest Dose: 300 mg QD	Therapeutic	104	Baseline: Pre-dose baseline Matching PK/ECG Timing:

Population: Patients	Central Read? Yes	Placebo: No			Intensive PK patients (n = 10):
Design: Other (Open label, randomized, one treatment arm with intensive PK in 10 patients)	Blinded? No	Positive Control: No			C1D1 and C3D1: pre-dose, 2, 4, 6, 8 h post-dose.
	Replicates? Yes				Sparse PK patients (rest): C1D1 and C3D1: pre-dose, 4 and 8 h post-dose.
					All patients: C1D8, C1D15, C2D1: pre-dose.
					Note: PK and ECG were collected at additional time points but were not matched.

5.2 EVALUATION OF THE APPLICANT'S CLINICAL QT ANALYSIS PLAN

1. Analysis plan	
1.1 Study Objectives Related to QT	
What QTc effect size is the analysis trying to exclude?	20 ms
<i>Reviewer's comments: The Applicant submitted two QT evaluation studies. Both were open-labeled studies without placebo controls.</i>	
1.2 Data Pooling	
Data pooling?	No
Did Applicant propose an assessment for heterogeneity?	N/A
Is the data pooling appropriate?	N/A

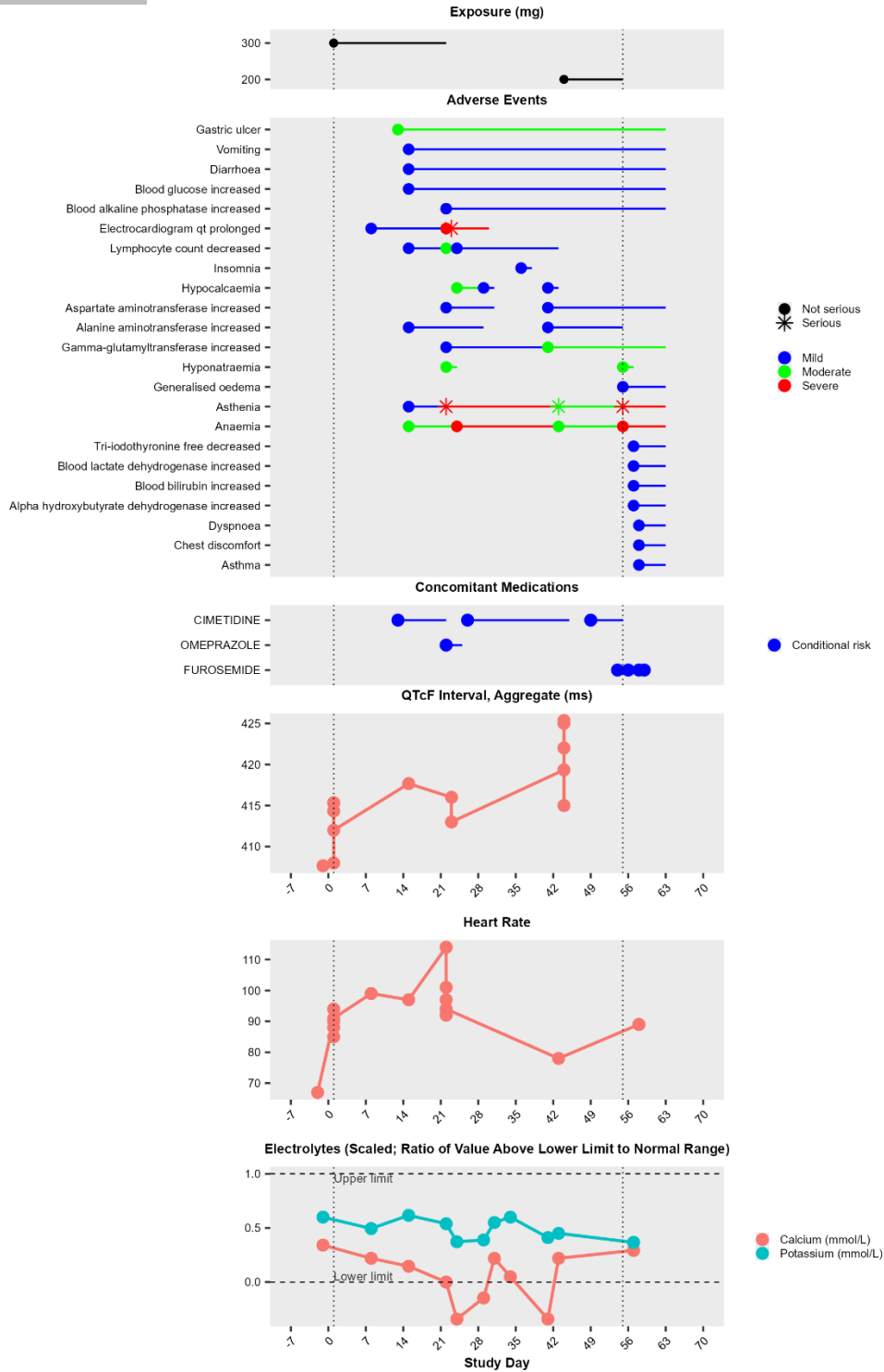
<i>Reviewer's comments: The Applicant analyzed the two QT evaluation studies separately, thus no pooling and assessment of heterogeneity, which is acceptable.</i>	
1.3 QT Correction Method	
Is an HR increase or decrease greater than 10 beats/min?	No
Primary method for QT correction	QTcF
<i>Reviewer's comments: No HR effect was observed. QTcF is appropriate for HR correction, thus acceptable.</i>	
1.4 Assay Sensitivity	
Assay sensitivity methods proposed by Applicant	☐ Moxifloxacin ☐ Exposure-margin ☐ QT bias assessment ☐ Other ☒ Not applicable (objective is large mean effects)
1.5 By-Time Analysis	
1.5.1 Investigational Drug	
Primary analysis	No
Did the Applicant use IUT or descriptive statistics?	Both
For IUT: Does the Applicant use MMRM to analyze longitudinal values that consider the correlation across time-points, or use ANCOVA by-time-point without considering correlation?	MMRM
For IUT: Is the MMRM model specified correctly with regard to covariance structure, covariates, or if ANCOVA, is the model specified correctly with regard to covariates?	Yes
By-time point analysis for QTcF interval was based on a mixed model for repeated measurements with Δ QTcF interval as the dependent variable, time (i.e., post-baseline time point with at least 3 patients within treatment: categorical), treatment (Dose 1 to Dose X of sunvozertinib) and time-by-treatment interactions as fixed effects, and baseline QTcF as a covariate. An unstructured covariance matrix was specified for the repeated measures at post-baseline time points within patients. If the model with an	

unstructured covariance matrix failed to converge, this by-time point analysis was performed using 2 separate models including data before Cycle 3 Day 1 and data on/after Cycle 3 Day 1, and other covariance matrices such as compound symmetry was considered, in this order, until convergence was achieved.			
<i>Reviewer's comments: The proposed model is acceptable.</i>			
1.5.2 Positive Control			
Primary analysis			N/A
Did the Applicant adjust for multiplicity?			N/A
1.6 Exposure-Response Analysis			
1.6.1 Investigational Drug			
Primary analysis		Yes	
What is the dependent variable in the Applicant's model?		Single delta	
White paper model?		Yes	
Which concentration covariate(s) are included in the model?		Multiple	
Which methods did the Applicant use for predicting the QT effect?		☒ Model-based confidence intervals ☐ Bootstrap-derived confidence intervals	
<i>Reviewer's comments: The proposed model for CQT analysis is consistent with the white paper model.</i>			
1.6.2 Positive Control			
Primary analysis		N/A	
Same model as investigational drug		N/A	
1.7 Categorical Analysis			
QTcF / Δ QTcF?	Yes	QRS?	Yes
PR?	Yes	HR?	Yes

5.3 GRAPHIC PATIENT PROFILE

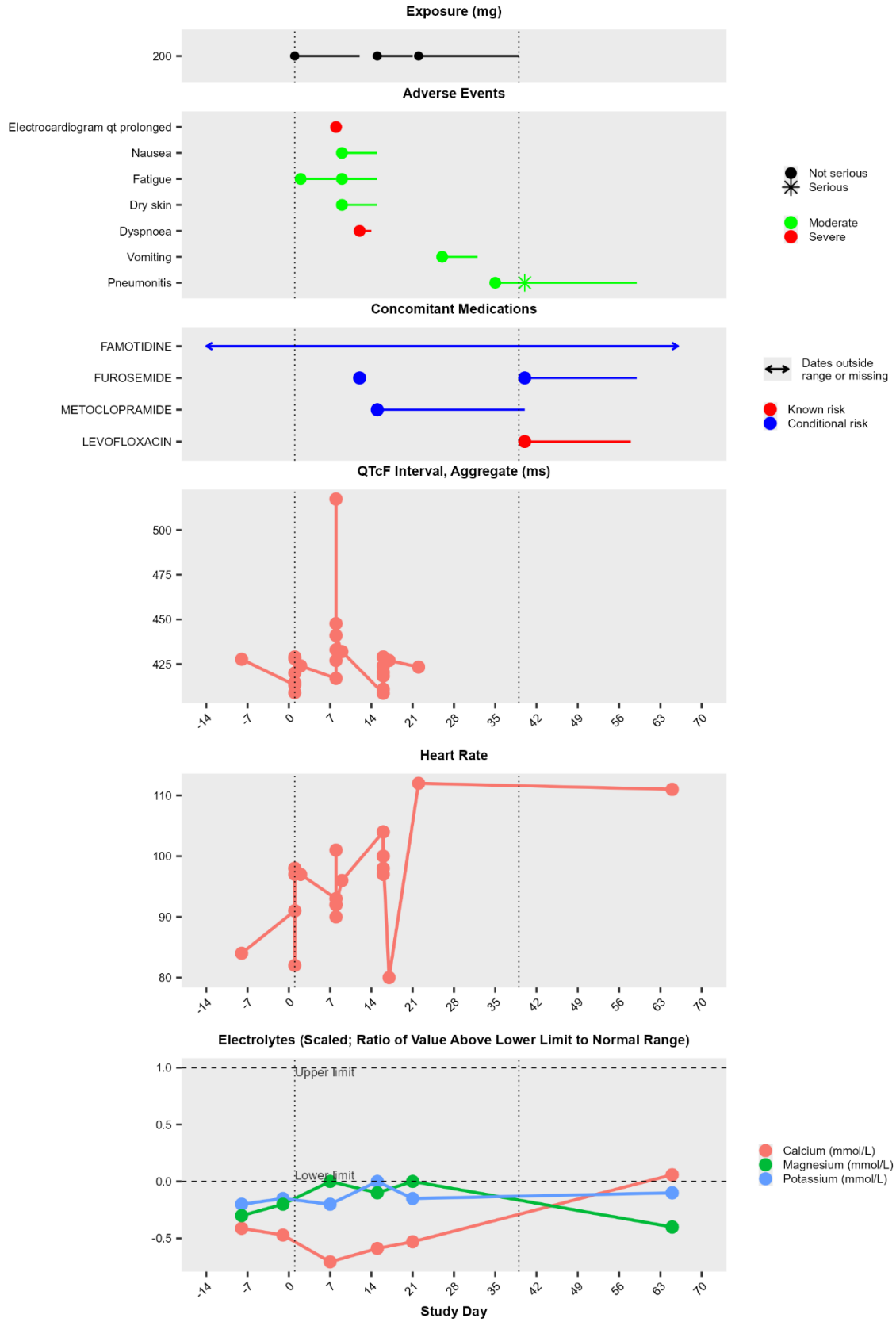
5.3.1 QTc Prolongation

(b) (6) Age: 50; Gender: M; Race: ASIAN; TRT01A: 300 mg



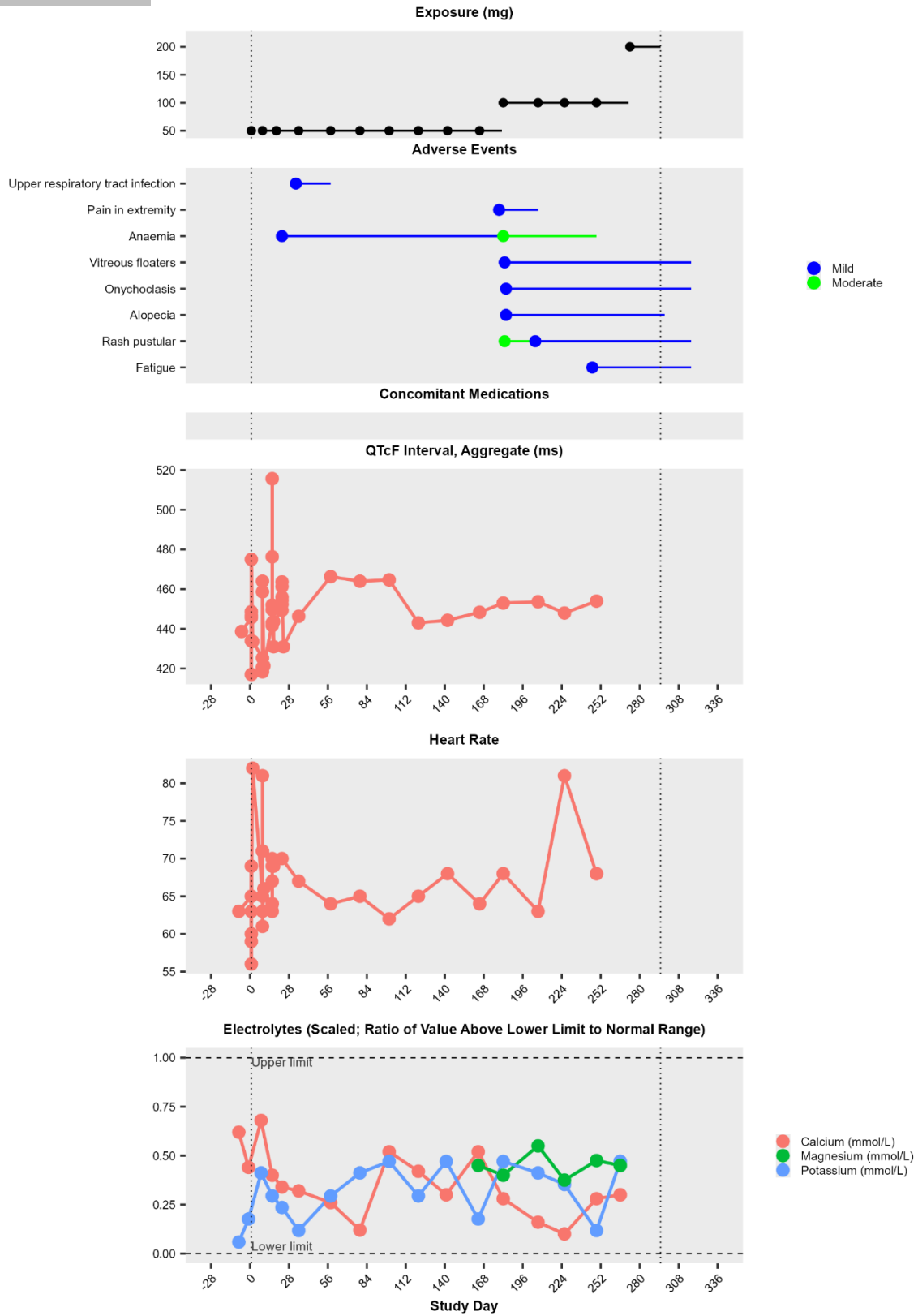
(b) (6)

Age: 65; Gender: F; Race: ASIAN; TRT01A: 200 mg



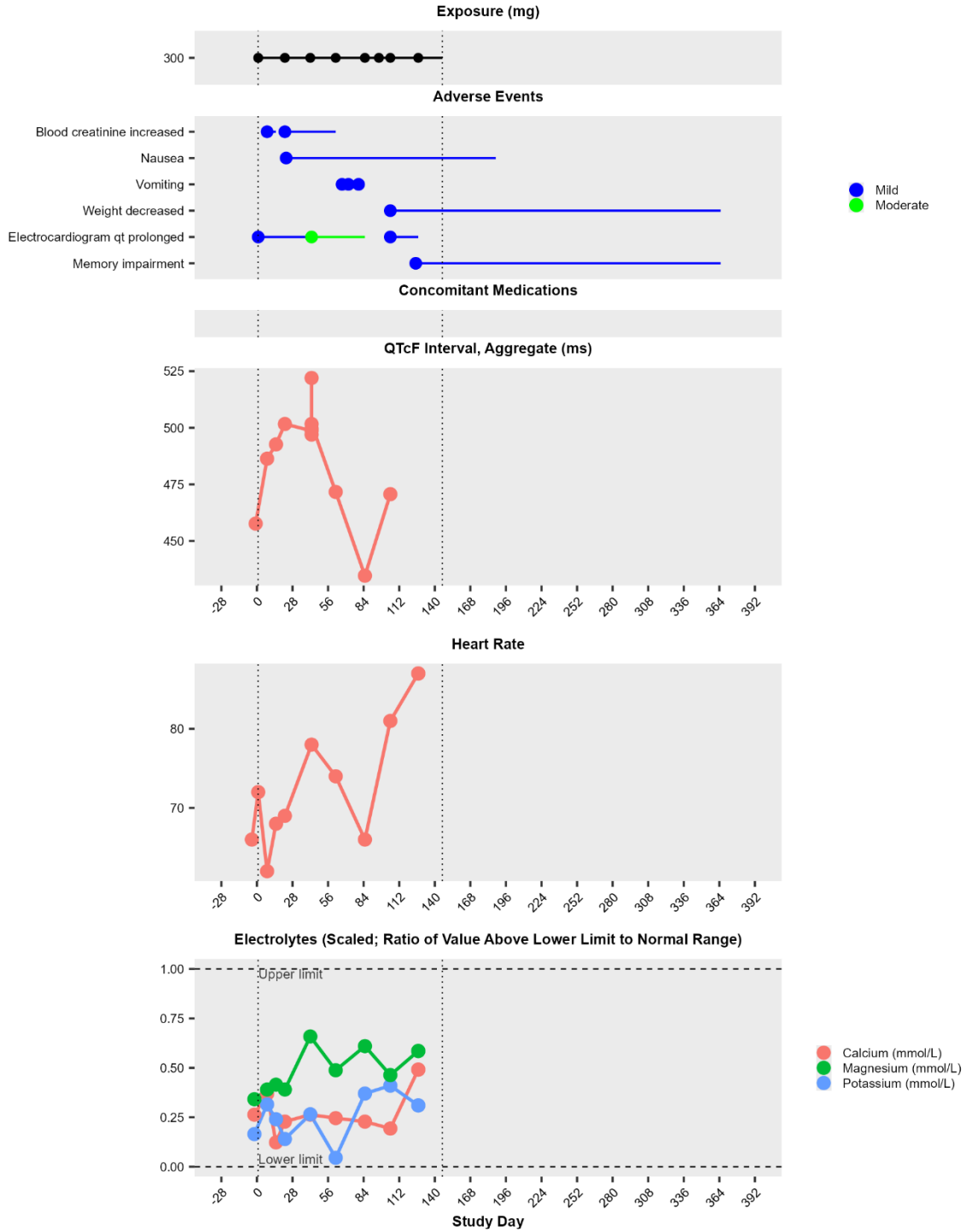
(b) (6)

Age: 38; Gender: F; Race: WHITE; TRT01A: 50 mg



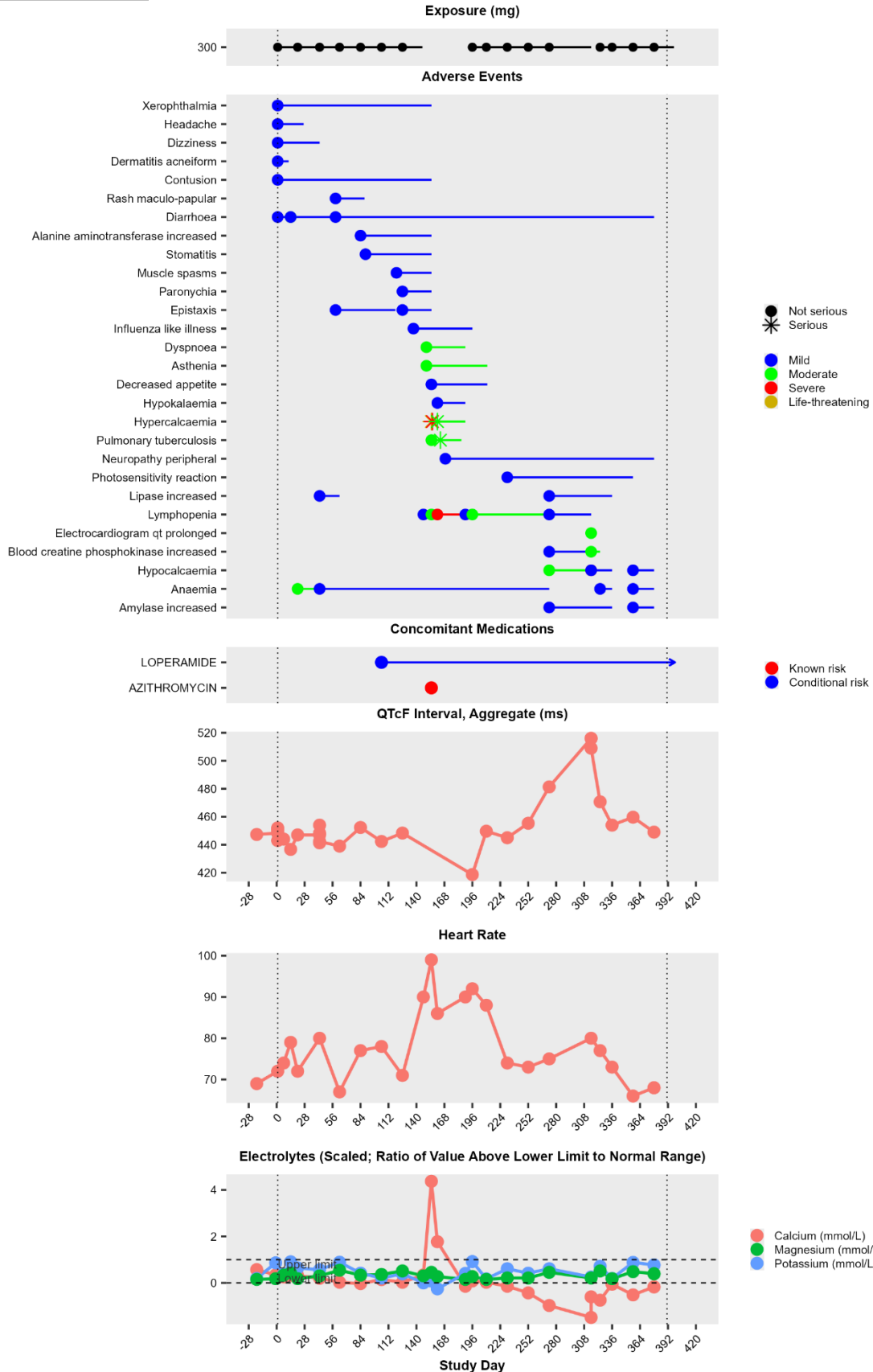
(b) (6)

Age: 73; Gender: F; Race: ASIAN; TRT01A: 300 mg

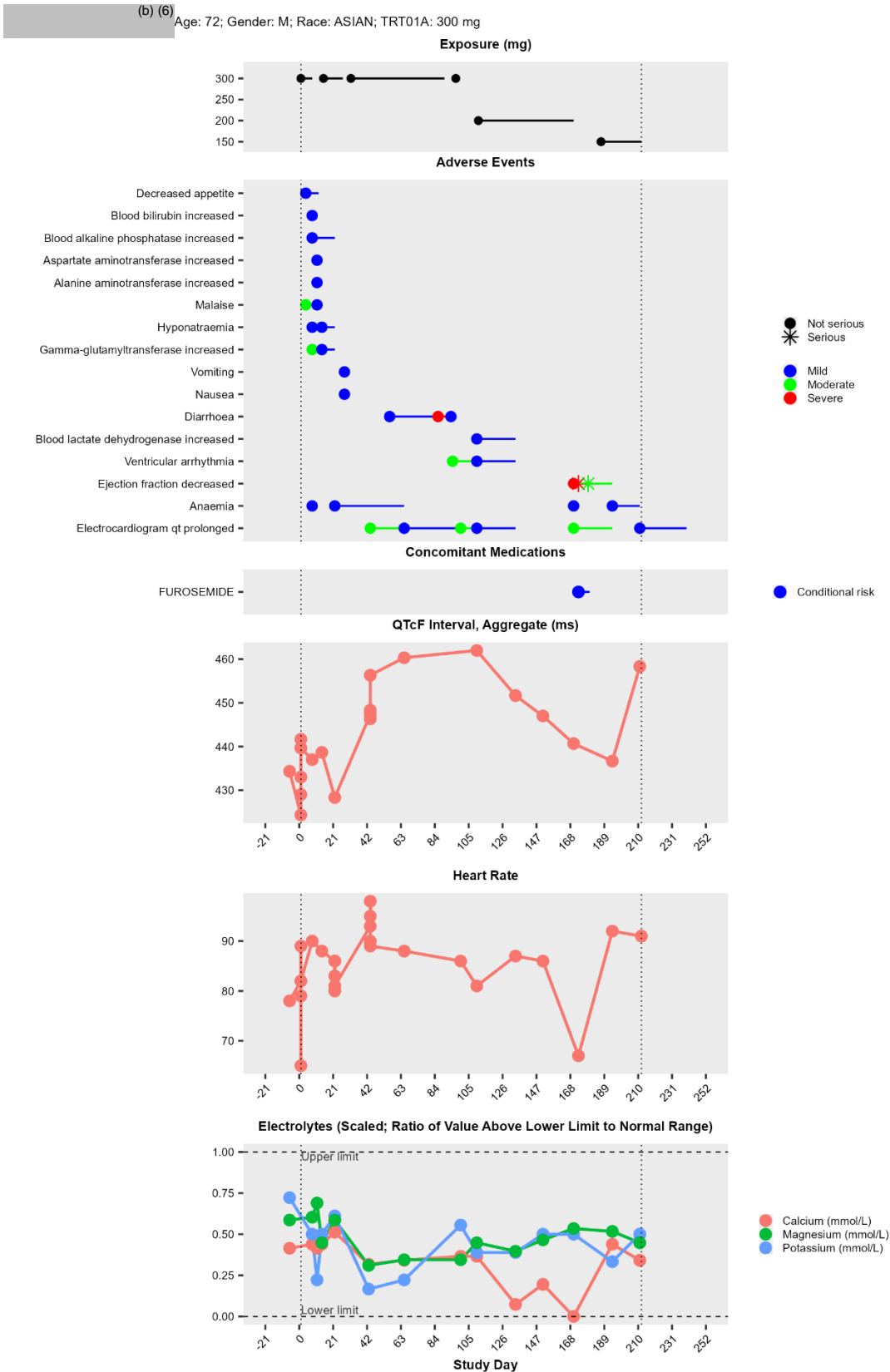


(b) (6)

Age: 72; Gender: F; Race: ASIAN; TRT01A: 300 mg



5.3.2 Ventricular Arrhythmia



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/s/

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