

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218944Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

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

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Date of This Review:	November 13, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 218944
Product Name, Dosage Form, and Strength:	Revuforj (revumenib) tablets, 25 mg, 110 mg and 160 mg
Applicant Name:	Syndax Pharmaceuticals, Inc. (Syndax)
FDA Received Date:	November 8, 2024 and November 12, 2024
TTT ID #:	2023-7014-2
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Syndax Pharmaceuticals, Inc. (Syndax) submitted revised Prescribing Information (PI), Medication Guide (MG), (b) (4) container labels and carton labeling received on November 8, 2024 and the Instructions for Use (IFU) on November 12, 2024 for Revuforj. We reviewed the revised PI, MG, (b) (4) IFU, container labels and carton labeling for Revuforj (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 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note the Applicant proposed to retain the 20 mL oral syringe for the reasons below:

- Experimental studies supporting tablet dispersion were all performed using a 20 mL syringe.
- Revumenib tablets contain insoluble excipients. Depending on the patient BSA and dose amount they may be crushing multiple tablets. The combined volume of insoluble excipients + 10 mL of water will exceed the volume of a 10 mL syringe. Therefore a syringe volume of greater than 10 mL is required.
- Revuforj will be distributed exclusively through Specialty Pharmacy and Specialty Distributor networks and not via retail pharmacies. Patients will be able to obtain 20 mL oral syringes from these networks.

As the proposed product and the supplies (e.g., 20 mL oral syringe) will be distributed through a Specialty Pharmacy, we find the Applicant's proposal to retain the 20 mL oral syringe in the labeling acceptable from a medication error perspective. In response to our clarification to provide the rationale for (b) (4) the Applicant revised the IFU to remove this information and replace with instructions to replace the oral syringe if there are signs of damage. We find this proposal acceptable from a medication error perspective.

We also note the Applicant proposed using a disposable plastic cup, which is not provided by the specialty pharmacy. Therefore, the Office of Pharmaceutical Quality (OPQ) sent an information request (IR) requesting the Applicant to provide the in-use stability/compatibility data of revumenib tablets dispersion with commonly available plastic cups (of different materials) and household cup. In response on November 6, 2024 and November 12, 2024, the Applicant stated that in-use stability/compatibility of the revumenib tablet dispersion was demonstrated through 2 hours after preparation in all four cup types including disposable plastic cups made of three commonly available plastic types (polypropylene, polystyrene or

^a Black, S. Review of Revised Label and Labeling for Revuforj (NDA 218944). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 NOV 08. TTT ID: 2023-7014-1.

PET) and household glass cups.^{bc} On November 12, 2024, OPQ found the submitted dose recovery data acceptable.

3 CONCLUSION

For the revised PI, MG, and (b) (4) we have no recommendations at this time.

For the container labels and carton labeling, Syndax implemented most of our recommendations. We note that the NDC number and net quantity are on the side panel rather than the principal display panel of the container label for the 25 mg strength; however, due to the small size of the label and space limitations, we find this acceptable and have no additional recommendations.

For the revised IFU, we find that it 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 Hematologic Malignancies 1 (DHM 1) in Section 4.

4 RECOMMENDATIONS FOR THE DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Instructions for Use (IFU)

1. As currently presented, reference to child is missing in the 4th bullet under the section “Important information you need to know before preparing to break apart the REVUFORJ tablets in water:”. As these instructions may be for adults or children who are unable to swallow whole tablets, we recommend revising the 4th bullet to “REVUFORJ tablets come in different strengths. Each strength is a different color. Your healthcare provider may prescribe more than 1 strength of REVUFORJ tablets for you or your child, so it is important that you understand how to take or give the medicine the right way. Be sure that you understand exactly how many tablets you need to take, and what strengths to take.”
2. As currently presented, Figure A does not specify which of the supplies are provided by the specialty pharmacy. Lack of adequate instruction on items needed for drug preparation may lead to preparation medication errors. We recommend including a statement to specify which supplies will be provided by the specialty pharmacy. In addition, as the supplies are to be provided by a specialty pharmacy, we recommend removing “(b) (4)” and revising the statement above Figure A to “Supplies needed to prepare and break apart the REVUFORJ tablets in water. You may need to get these supplies from your pharmacy.”

^b Response to Request for Information – 30Oct2024 (NDA 218944 and Revuforj). New York (NY): Syndax Pharmaceuticals, Inc.; 2024 NOV 06. Available from: <\\CDSESUB1\EVSPROD\nda218944\0094\m1\us\111-information-amendment\quality-resp-30oct2024.pdf>

^c Response to Request for Information – 06Nov2024 (NDA 218944 and Revuforj). New York (NY): Syndax Pharmaceuticals, Inc.; 2024 NOV 12. Available from: <\\CDSESUB1\EVSPROD\nda218944\0098\m1\us\111-information-amendment\quality-resp-06nov2024.pdf>.

3. As currently presented in Figure A, the image of the teaspoon contains “1 tsp”. Instructions indicate that 2 teaspoons of water are needed. To minimize confusion, we recommend removing the statement “1 tsp” from the image under Figure A.
4. As currently presented, room temperature water in a glass is depicted under Figure A. As Figure A depicts two different cups (small cup and glass of room temperature water), it may cause confusion on which type of cup a patient should use for product preparation. We defer to DMPP if an image of room temperature water is needed in Figure A.
5. As currently presented, Figure C depicts water being added to a cup (b) (4) which is inconsistent with the instructions in Step 2 (which states to add water to small cup then add the crushed tablets.) In addition, the spoon is labeled (b) (4) even though the instructions indicate that 2 teaspoons of water are needed. We recommend revising Figure C for consistency with Step 2 and removing (b) (4) .
6. As currently presented, the statement (b) (4) . To minimize redundancies, we recommend removing this statement from Step 2.
7. As currently presented, the statement “ (b) (4) .” is not presented in patient friendly language. We recommend revising the statement to “The medicine must be taken within 2 hours of preparation.”
8. As currently presented, Step 6 contains a dash symbol. Error prone symbols may lead to misinterpretation and medication error. We recommend replacing the symbols with its intended meaning “to”. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
9. As currently presented in Step 7, the statement (b) (4)) can be further simplified. We recommend revising this statement to “Place two teaspoons (10 mL) of room temperature water in the cup, rinsing down the sides (Figure H).”
10. As currently presented, the spoon is labeled “ (b) (4) ” in Figure H even though the instructions indicate that 2 teaspoons of water are needed. This inconsistency may lead to confusion on how much water is needed. We recommend removing “ (b) (4) ” in Figure H.
11. As currently presented in Step 8, it is not clear that steps 5 and 6 should be repeated until no medicine is in the cup. To ensure administration of all medication, we recommend revising Step 8 to state “Repeat Step 5 and Step 6 until no more medicine is left in the cup.”
12. As currently presented, Figure M (rinsing syringe under water) does not correspond to Step 12 (draw warm water into oral syringe and squirt). We recommend revising Figure M for consistency with Step 12.

13. As currently presented, Figure N ((b) (4)) does not correspond to Step 13 ((b) (4)). We recommend revising Figure N for consistency with Step 13.
14. As currently presented, the material of the small cup is not provided. To ensure the stability of product preparation, we recommend revising the label “ (b) (4) ” to “small plastic or glass cup” in Figure A.

APPENDIX A. LABELS AND LABELING RECEIVED ON NOVEMBER 8, 2024 AND NOVEMBER 12, 2024

A.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^d along with postmarket medication error data, we reviewed the following Revuforj labels and labeling submitted by Syndax Pharmaceuticals, Inc. (Syndax).

- Prescribing Information received on November 8, 2024, available from <\\CDSESUB1\EVSPROD\nda218944\0097\m1\us\114-labeling\draft\annotated\annotated-draft-label-text-word.doc>
- Medication Guide received on November 8, 2024, available from <\\CDSESUB1\EVSPROD\nda218944\0097\m1\us\114-labeling\draft\labeling\medication-guide-annotated-word.doc>
-  (b) (4)
- Instructions for Use received on November 12, 2024, available from <\\CDSESUB1\EVSPROD\nda218944\0099\m1\us\114-labeling\draft\labeling\instructions-for-use-word-redline.docx>
- Container labels received on November 8, 2024
- Carton labeling received on November 8, 2024

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

Container Labels:



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

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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:	November 8, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 218944
Product Name, Dosage Form, and Strength:	Revuforj (revumenib) tablets, 25 mg, 110 mg and 160 mg
Applicant Name:	Syndax Pharmaceuticals, Inc. (Syndax)
FDA Received Date:	November 1, 2024 and November 6, 2024
TTT ID #:	2023-7014-1
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Syndax Pharmaceuticals, Inc. (Syndax) submitted revised Prescribing Information (PI), Medication Guide (MG), (b) (4) container labels and carton labeling received on November 6, 2024 for Revuforj. The revisions are in response to recommendations that we made during a previous label and labeling review.^a In addition, Syndax submitted a new proposed Instruction for Use (IFU) for preparing the tablet for dispersion received on November 1, 2024. We reviewed the PI, MG, (b) (4) IFU, container labels and carton labeling for Revuforj (Appendix A) to determine if they are acceptable from a medication error perspective.

2 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

For the proposed IFU, we note Syndax proposed using a 20 mL oral syringe and a disposable plastic cup which may not be readily available in pharmacies for dispensing to patients. Therefore, the Office of Pharmaceutical Quality (OPQ) sent an information request (IR) requesting the Applicant to provide the in-use stability/compatibility data of revumenib tablets dispersion with commonly available plastic cups (of different materials) and household cup. In response on November 6, 2024, the Applicant stated that “the in-use stability/compatibility of revumenib tablet dispersions has been demonstrated in five different types of cups that are readily available to patients at home including disposable plastic cups made of three commonly available plastic types (polypropylene, polystyrene or PET) and household plastic or glass cups.”^b However, the Applicant did not provide potency data and plan to submit this information on a later date. We defer to OPQ regarding the acceptability of this data.

For the proposed container labels and carton labeling, we note the format of the expiration is MMM YYYY where the month is presented in alphabetical characters and the year is presented in numeric characters (e.g., FEB 2023). Syndax plans to implement the expiration format of YYYY-MMM using alphabetical characters for the month and separating the expiry date attributes using a hyphen in the next campaign after the initial product launch. We find this approach acceptable. Additionally, Syndax confirmed the location of the 2D data matrix barcode associated with the product identifier on the carton labeling.

3 CONCLUSION

Our evaluation of the revised MG and (b) (4) did not identify areas of vulnerability that may lead to medication errors, and we have no recommendations at this time. However, the proposed PI, IFU, container labels and carton labeling may be improved to promote the 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

^a Black, S. Label and Labeling Review for Revuforj (NDA 218944). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 OCT 30. TTT ID: 2023-7014.

^b Response to Request for Information – 30Oct2024 (NDA 218944 and Revuforj). New York (NY): Syndax Pharmaceuticals, Inc.; 2024 NOV 06. Available from: <\\CDSESUB1\EVSPROD\nda218944\0094\m1\us\111-information-amendment\quality-resp-30oct2024.pdf>

medication error for the Division of Hematologic Malignancies 1 (DHM 1) in Section 4 and for Syndax Pharmaceuticals, Inc. (Syndax) in Section 5.

4 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Prescribing Information

1. Section 2 Dosage and Administration

- a. As currently presented in Section 2.2 *Recommended Dosage*, the footnote at the bottom of Table 1 references (b) (4) for total tablet dosage; however, (b) (4) no longer exists. We recommend revising the footnote from “See (b) (4) for the total tablet dosage by BSA (body surface area) for patients weighing less than 40 kg.” to “See Tables 2 (b) (4) for the total tablet dosage by BSA (body surface area) for patients weighing less than 40 kg.”
- b. As currently presented in Table 2, the BSA is presented with a trailing zero (e.g., 1.0). Trailing zeros can lead to tenfold dosing errors when the decimal point goes unnoticed (e.g., 1.0 is seen as 10). We recommend revising the BSA to remove the trailing zero. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
- c. As currently presented Section 2.3 *Dosage Modifications for Adverse Reactions*, the statement before Table (b) (4), *Dose levels for dose reductions are listed in Table (b) (4) and Table (b) (4)* is inconsistent with the footnote at the bottom of Table (b) (4) (*See Tables 3, 4 and 5 for the reduced dose levels*). Inconsistent dosing information leads to confusion. We recommend revising the statement before Table 2 to state “Dose levels for dose reductions are listed in Table (b) (4) and Table 4, and Table 5.”

B. Instructions for Use

1. As currently presented, a 20 mL oral syringe and small plastic disposable cup is recommended when preparing the tablet for dispersion; however, 10 mL of water is recommended for tablet dispersion. Additionally, a pharmacy may not stock a 20 mL oral syringe and small plastic disposable cup for dispensing to patients. Lack of adequate instruction on items needed for drug preparation may lead to preparation medication errors. We recommend revising references of 20 mL oral syringe to 10 mL oral syringe.
2. We note the statement “(b) (4) However, a pharmacy may not stock a 20 mL oral syringe. Please provide the rationale for use of 20 mL oral syringe.
3. As currently presented, the instructions state “(b) (4) and to use a 20 mL oral syringe to measure the amount of water. The use of an oral syringe is needed for accuracy in measuring and administration of the drug

product rather than water. For patient ease, we recommend use of a teaspoon to measure the amount of water and limiting the use of the oral syringe to administration of the drug product. For example, revise Step 2 to state “Use two teaspoons to measure 10 mL of room temperature water.” and revise the image accordingly. In addition, remove the statement (b) (4)

and add “teaspoon” to Figure A.

4. As currently presented, Step 3 states to add crushed tablets to the cup containing water, (b) (4). For clarity, we recommend revising Figure D to depict adding crushed tablets to the cup of water.
5. As currently presented, Step 5 instructs user to draw up the entire content of the cup into a 20 mL oral syringe. As a 20 mL oral syringe is not readily available, we recommend revising to
 - a. “Draw up the medicine into the 10 mL oral syringe right away.”
 - b. “Push the plunger of the oral syringe all the way up towards the tip. Place the tip of the oral syringe in the small cup. Pull the oral syringe plunger to draw up all of the medicine in the small cup.”
 - c. “Turn the oral syringe upside down and back several times before taking or giving the medicine.”
6. As currently presented, Figure G (b) (4) does not accurately depict all the intended patient ages for the proposed indication which include older pediatric patients (e.g., 1 years and older). Inaccurate images in the IFU may lead to confusion concerning appropriate product administration. Revise Figure G to depict the oral syringe being squirted into the side of cheek only (b) (4)
7. As currently presented, Step 7 states (b) (4). For patient ease, we recommend use of a teaspoon to measure the amount of water (b) (4). For example, revise to “Use two teaspoons (b) (4) 10 mL of room temperature water. (b) (4) cup, rinsing down the sides.” In addition, revise Figure H to depict measuring additional water and placing into the cup in addition to swirling the cup.
8. We note the statement “(b) (4), throw away the oral syringe in your household trash. Use a new 20 mL oral syringe (b) (4).” Please provide the rationale (b) (4)

5 RECOMMENDATIONS FOR SYNDAX PHARMACEUTICALS, INC. (SYNDAX)

A. Container Labels

1. The terminology within the statement of dosage statement (i.e., package insert) is inconsistent with the terminology in the Prescribing Information. To ensure consistency with the terminology in the Prescribing Information, we recommend revising the dosage statement to read, "Recommended Dosage: See Prescribing Information."
2. As currently presented on the container label for 25 mg strength, the NDC number continues to be on the side panel. The human-readable NDC is often used for product verification and identification prior to dispensing or administering a drug. Therefore, we recommended relocating the NDC number to the top of the principal display panel above the proprietary name for prominence.
3. As currently presented, the net quantity statement does not appear on the principal display panel of the container label for the 25 mg tablet. Failure to include the net quantity statement on the principal display panel may result in confusion regarding the contents of the container. We recommend including a net quantity statement (e.g., 30 tablets) on the principal display panel and ensure it is located away from and less prominent than the product strength. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

B. Carton Labeling

1. As currently presented on the carton labeling, the NDC number is on the side panel. The human-readable NDC is often used for product verification and identification prior to dispensing or administering a drug. Therefore, we recommended relocating the NDC number to the principal display panel for prominence.

APPENDIX A. LABELS AND LABELING RECEIVED ON NOVEMBER 1, 2024 AND NOVEMBER 6, 2024

A.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Revuforj labels and labeling submitted by Syndax Pharmaceuticals, Inc. (Syndax).

- Prescribing Information (Image not shown) received on November 6, 2024, available from <\\CDSESUB1\EVSPROD\nda218944\0093\m1\us\114-labeling\draft\annotated\annotated-draft-label-text-word.docx>
- Medication Guide (Image not shown) received on November 6, 2024, available from <\\CDSESUB1\EVSPROD\nda218944\0093\m1\us\114-labeling\draft\labeling\medication-guide-word-annotated.docx>
-  (b) (4)
- Instructions for Use (Image not shown) received on November 1, 2024, available from <\\CDSESUB1\EVSPROD\nda218944\0091\m1\us\114-labeling\draft\labeling\inst-for-prep-revumenib-tab-disp.pdf>
- Container labels received on November 6, 2024
- Carton labeling received on November 6, 2024

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

Container Labels:



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

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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 6, 2024

To: Rachel McMullen
Regulatory Project Manager
Division of Hematologic Malignancies I (DHM1)

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

From: Maria Nguyen, MSHS, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Valerie Guerrier, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): REVUFORJ (revumenib)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 218944

Applicant: Syndax Pharmaceuticals, Inc.

1 INTRODUCTION

On January 26, 2024, Syndax Pharmaceuticals, Inc., submitted for the Agency's review a 505(b)(1) for their New Drug Application (NDA) 218944 for REVUFORJ (revumenib) tablets (b) (4)

The proposed indication for REVUFORJ (revumenib) is treatment for adult and pediatric patients with relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) rearrangement.

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 Hematologic Malignancies I (DHMI) on February 7, 2024, for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for REVUFORJ (revumenib) tablets, for oral use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU is forthcoming.

2 MATERIAL REVIEWED

- Draft REVUFORJ (revumenib) IFU received on January 26, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 30, 2024.
- Draft REVUFORJ (revumenib) Prescribing Information (PI) received on January 26, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 7, 2024.

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. In our review of the IFU, the target reading level is at or below and 8th grade 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 MG document using the Arial font, size 10.

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the PI

- removed unnecessary or redundant information
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFU 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 IFU 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 IFU.

Please let us know if you have any questions.

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DMPP-OPDP review of revumenib (REVUFORMJ) NDA 218944 IFU

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Consult Memorandum

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Date: 06/04/2024

To: Donna Przepiorka, Supervisory Physician, CDER/OND/OOD/DHM1
Rachel McMullen, Senior Regulatory Health PR, CDER/OND/ORO/DROOD

From: Deblina Banerjee, Ph.D., Lead Reviewer, CDRH/OPEQ/OHT7/DMGP/MGB

Through: Karen Bijwaard, M.S., Senior Policy Advisor, CDRH/OPEQ/OHT7/DMGP,
Donna Roscoe, Ph.D., Acting Director, CDRH/OPEQ/OHT7/DMGP,
Reena Philip, Ph.D., Associate Director, OCE

Subject: NDA 218944

Drug Name: Revumenib (SNDX-5613)

Drug Sponsor: Syndax Pharmaceuticals

Subject A Phase 1/2, Open-label, Dose-Escalation and Dose-Expansion Cohort Study of
SNDX-5613 in Patients with Relapsed/Refractory Leukemias, Including Those
Harboring an MLL/KMT2A Gene Rearrangement or Nucleophosmin 1 (NPM1)
Mutation

Biomarker(s): KMT2A

Device Name: (b) (4)

Device Sponsor: (b) (4)

CDRH Tracking ICCR # 00989010, ICC2400446

Number:

Related Submissions: (b) (4)

I. BACKGROUND and PURPOSE

Background: CDER is currently reviewing Syndax Pharmaceuticals' application for NDA 218944 for Revumenib (SNDX-5613). Revumenib is being developed for the treatment of patients with relapsed or refractory (R/R) acute leukemia.

All 57 efficacy evaluable patients in the pivotal cohort had *KMT2A* rearrangements centrally confirmed by FISH diagnostic testing at a Clinical Laboratory Improvement Amendments certified (CLIA) central lab (b) (4) using the Clinical Trial Assay (CTA) which is an ASR (b) (4). The test utilizing ASRs was developed and its performance characteristics was determined by (b) (4) as required by CLIA '88 regulations. The test has not been cleared or approved for specific uses by the FDA. Syndax's is working with the device collaborator, (b) (4) to bridge the CTA to the CDx that is currently progressing through validation steps (Submission (b) (4)).

Purpose: CDER is requesting CDRH's feedback on the adequacy of the Clinical Trial Assay (CTA) used in the trial for identification of *KMT2Ar* in patients with acute leukemias.

The submission was received on May 6, 2024.

II. BIOMARKER/ANALYTE

KMT2Ar in Acute Leukemias

III. DEVICE USE IN THE TRIAL

The NDA is supported by data from the pivotal Phase 1/2 AUGMENT-101 trial (NCT04065399), which evaluated the menin inhibitor as monotherapy in adult and pediatric patients with *KMT2A* -rearranged acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL). Findings showed that the study met its primary end point with a complete remission (CR)/CR with partial hematologic recovery (CRh) rate of 23% (95% CI, 12.7%-35.8%; one-sided $P=0.0036$) among evaluable patients in the pooled *KMT2A*-rearranged AML/ALL population ($n=57$).

The [REDACTED] (b) (4) was used as the CTA device to confirm the *KMT2Ar* status of the patients enrolled in the trial.

IV. CDRH RESPONSE TO CDER

CDRH has the following response to CDER's questions:

CDER Question 1

With regard to Item (D), you requested "[REDACTED]" (b) (4)

[REDACTED] (b) (4)

(b) (4). The applicant stated that "[REDACTED]" (b) (4)

[REDACTED] (b) (4). Please clarify whether this is still a deficiency.

CDRH Response

The subjects in the pivotal trial were enrolled based on local diagnostic testing (LDT) at the site showing a rearrangement involving the 11q23 region by conventional cytogenetic analysis, and/or FISH analysis. Confirmation of *KMT2Ar* for efficacy eligibility is subsequently performed using confirmatory FISH

(b) (4)

(b) (4)

S

submission was not required.

CDER Question 2

Please see the applicant's validation summary report with line listings and figures. Based on the original response from the applicant and the additional information now provided, please comment on the adequacy of the central laboratory assay for identification of *KMT2Ar* in patients with acute leukemias.

CDRH Response

CDRH has reviewed the MLL FISH ASSAY Validation Report provided by the applicant. In response to CDRH's information request to support the analytical validation of the central laboratory assay, the sponsor provided the following:

with acute leukemias.

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/

RACHEL S MCMULLEN
11/01/2024 01:51:03 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:	October 30, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 218944
Product Name, Dosage Form, and Strength:	Revuforj (revumenib) tablets, 25 mg, 110 mg and 160 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Syndax Pharmaceuticals, Inc. (Syndax)
FDA Received Date:	October 27, 2023, December 29, 2023, February 27, 2024, July 25, 2024, October 4, 2024, October 11, 2024, and October 17, 2024, October 29, 2024
TTT ID #:	2023-7014
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 REASON FOR REVIEW

As part of the approval process for Revuforj (revumenib) tablets, we reviewed the proposed Revuforj Prescribing Information (PI), Medication Guide (MG), (b) (4) container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 218944.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C
Information Requests	D

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container labels, carton labeling, (b) (4) PI, and MG for Revuforj tablets to determine whether there are significant concerns in terms of safety related to preventable medication errors.

We note the PI was unclear on how doses are administered that do not correspond to one of the proposed tablet strengths (b) (4)

Therefore, we sent an Information Request (IR) to the Applicant for clarification on their dosing strategy for BSA dosing (b) (4)

See Appendix D for full information request and response.

We also note the requirement of different strengths needed to achieve certain doses (e.g., 1 x 110 mg tablet plus 1 x 160 mg tablet to achieve a 270 mg dose) may be prone to medication dosing and administration errors. Therefore, after further discussion with the review team, we sent an IR recommending that the Applicant co-package one bottle of the 110 mg tablet and one bottle of the 160 mg tablet in one box (with the appropriate labels/labeling) to make the 270 mg dose to mitigate the potential for error. (see Appendix D). On June 14, 2024, the Applicant responded that the “potential errors can be adequately addressed through provisions that are currently in place without co-packaging for the 270 mg dose (e.g., dispensing through a specialty pharmacy, differentiation in tablets and packaging and instructions in the MG.”. We find the Applicant’s proposed mitigations acceptable and we will address any remaining medication error concerns through labels and labeling.

Lastly, we note the discrepancy in storage information (e.g., whether to store in original container until dispensing) between the PI, MG, IFU, container label and carton labeling. We reached out to Office of Pharmaceutical Quality (OPQ) to clarify this storage information. OPQ confirmed that based on their review of the data, they propose including the storage statement, "Keep in original container until dispensed".

(b) (4)

(b) (4)

was removed from the PI. In addition, OPQ found the data for the 25 mg tablet acceptable. We expressed our concern that pediatrics 1 to 2 years old may not be able to swallow the 25 mg tablet. Thus, the Division sent a consult to Division of Pediatric and Maternal Health (DPMH) to clarify if there are any FDA or CDER policies regarding limits in tablet size for pediatric patients, if a tablet of this size [0.18" (H) X 0.37" (D)] represents a choking hazard and in which age groups and if there is a

^a Response to FDA Request for Information (NDA 218944 and Revuforj). New York (NY): Syndax Pharmaceuticals, Inc.; 2024 MAY 29. Available from: <\\CDSESUB1\EVSPROD\nda218944\0053\m1\us\12-cover-letters\cover.pdf>.

(b) (4)

^c Response to Request for Information – 30Sep2024 (NDA 218944 and Revuforj). New York (NY): Syndax Pharmaceuticals, Inc.; 2024 OCT 04. Available from: <\\CDSESUB1\EVSPROD\nda218944\0082\m1\us\111-information-amendment\clin-resp-30sep2024.pdf>.

recommended age limit or BSA given the size of the tablet^d. In addition, the Division requested the Applicant provide the dimensions of the 25 mg tablet, whether data exists supporting these patients can swallow the 25 mg tablet and if no data is available, the youngest recommended age proposed to use the 25 mg tablet considering the choking hazard.

On October 15, 2024, the Applicant clarified the dimensions of the 25 mg tablet is 9.4 mm (L), 4.6 mm (W), and 3.5 mm (H), confirmed there is no clinical study data supporting 1 to 2 year old patients can swallow as all younger patients were administered the oral solution and that the youngest age for use of the 25 mg tablet is (b) (4) older based on patient's ability to swallow tablets.

On October 21, 2024, OPQ informed that an IR was sent to the Applicant for in-use stability data on crushing tablets and mixing with water as an alternative for pediatrics. In addition, DPMH clarified that FDA does not have guidelines on the youngest age to use tablets but recommended 4 years to 6 years of age^e. We remain concerned that the indicated population of 1 year and older are unable to swallow the tablet presentation.

On October 29, 2024, the Applicant stated that they performed studies for 4 tablet combinations spanning the full recommended dose range and using each of the 3 tablet strengths. They concluded the results of recovery, compatibility, pH and solubility studies support use of the preparation procedure to crush and disperse revumenib tablets for oral administration when prepared according to the proposed preparation instructions. The review team (OPQ, non-clinical, clinical pharmacology and clinical) found that the data provided support the alternative administration of tablets as an aqueous dispersion in water. Clinical pharmacology confirmed a dedicated bioequivalence study is not required to support labeling of this alternative administration of the tablet.

4 CONCLUSION

The proposed Revuforj Prescribing Information (PI), Medication Guide (MG), (b) (4) container labels and carton labeling for Revuforj 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 Hematologic Malignancies 1 (DHM 1) in Section 5 and for Syndax in Section 6.

5. RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Prescribing Information

1. Section 2 Dosage and Administration

^d McMullen, R. Division of Pediatric and Maternal Health Request for Consultation for REVUFORJ. Silver Spring (MD): FDA, CDER, OND, DHM1 (US); 2024 OCT 07. NDA 218944. Available from: <https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80773acf>.

^e Hausman, E. Memorandum to File. Silver Spring (MD): FDA, CDER, OND, ORDPURM, DPMH (US); 2024 OCT 23. NDA 218944. Available from: <https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8077897b>.

- a. As currently presented in Section 2.2 *Recommended Dosage*, the statement “40 kg or more” in Table 1 is not consistent with the statement “40 kg or greater” in Table (b) (4) 4. For consistency (b) (4) we recommend revising the statement “40 kg or more” to “40 kg or greater” in Table 1.
- b. As currently presented Section 2.2 *Recommended Dosage*, the footnote at the bottom of Table 1 references Table (b) (4) for combinations of tablet strengths to achieve a dose; however, Table (b) (4) depicts only the dose. Inconsistencies in dosing information may lead to confusion and dosing errors. We recommend revising the footnote from “ (b) (4) ” to “See Table 2 for BSA-based dosage (b) (4) ”
- c. As currently presented, administration instructions are presented under Section 2.2 *Recommended Dosage*, bullets 1 (*Administer twice daily fasted or with a low-fat meal...*) and 2 (*Administer orally around the same time each day...*) (b) (4) (Advise patients to swallow...) (b) (4) For clarity and to minimize administration errors, we recommend placing all the administration instructions together in Section 2.2 as a separate subsection (see screenshot below) and deleting (b) (4) In addition for consistency with the administration of the tablet, we recommended revising the statement (b) (4) .” to “Advise patients to swallow tablets whole and to not cut or chew tablets. If patients are unable to swallow tablets, they may be crushed and dispersed in water [see Instructions for Use].”

Administration:

- Administer REVUFORJ twice daily fasted or with a low-fat meal (e.g., meals with approximately 400 calories, 25% or less fat) (b) (4)
- Administer REVUFORJ orally around the same time each day.
- Advise patients to swallow tablets whole and to not cut or chew tablets. If patients are unable to swallow tablets, they may be crushed and dispersed in water [see Instructions for Use].
- If a dose of REVUFORJ is missed or not taken at the usual time, administer the dose as soon as possible on the same day and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours.

- d. As currently presented in Table (b) (4) under “Differentiation Syndrome”, the (b) (4) bullet does not specify whether to resume at the same dose or reduced dose level. Unclear dose modification instructions may lead to dosing errors. We recommend specifying whether to resume at the same dose or reduced dose level in the (b) (4) bullet.
- e. As currently presented in (b) (4) ,

(b) (4)

we recommend removing the reference (b) (4)

- f. As currently presented, (b) (4)
- Presenting dosing information together minimizes the risk of dosing errors. We recommend relocating (b) (4)

In addition, we recommend revising the table headers and columns (b) (4) and relocating the administration instruction "If needed, attain the desired dose by combining different strengths of REVUFORJ tablets." as a footnote under Tables 2 and (b) (4) for clarity.

Section 2.2

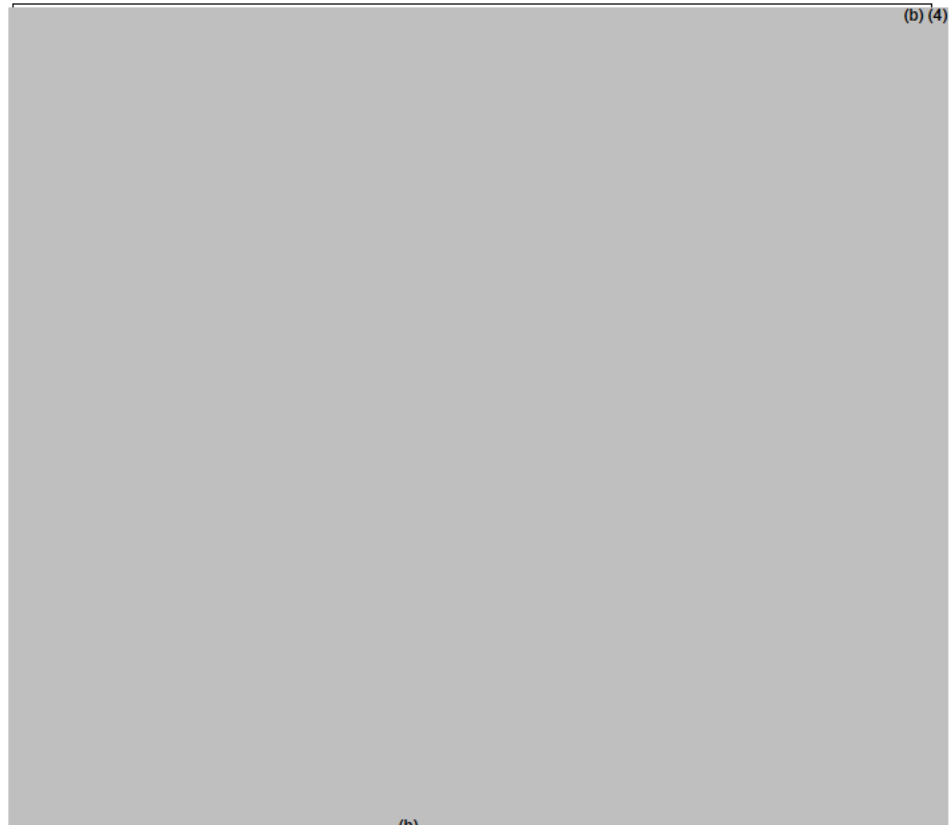
Table 1. REVUFORJ Recommended Dosage for Patients 6 Months and Older		
Patient Weight	Without Strong CYP3A4 Inhibitors	With Strong CYP3A4 Inhibitors
40 kg or more	270 mg orally twice daily	160 mg orally twice daily
Less than 40 kg	160 mg/m ² orally twice daily*	95 mg/m ² orally twice daily*

(b) (4)

Table 2: Recommended Dosage for Patients weighing less than 40 kg with 160 mg/m² and 95 mg/m² BSA-Based Dosing

BSA (m ²)	Dosage for 160 mg/m ²	Dosage for 95 mg/m ²
1.4	220 mg twice daily	135 mg twice daily
1.3	220 mg twice daily	135 mg twice daily
1.2	185 mg twice daily	110 mg twice daily
1.1	185 mg twice daily	110 mg twice daily
1.0	160 mg twice daily	100 mg twice daily
0.9	135 mg twice daily	75 mg twice daily
0.8	135 mg twice daily	75 mg twice daily
0.7	110 mg twice daily	50 mg twice daily
0.6	100 mg twice daily	50 mg twice daily
0.5	75 mg twice daily	50 mg twice daily
0.4	50 mg twice daily	25 mg twice daily

Section 2.3



- g. As currently presented, Table (b) (4) Recommended Dose Modifications for (b) (4) Adverse Reactions does not reference the reduced dosage information. For clarity, we recommend including a footnote with references to reduced dosage tables when “reduced dose level” is mentioned.

2. Section 16 How Supplied/Storage and Handling

- a. As currently presented, (b) (4) To minimize unnecessary information, we recommend removing (b) (4)

3. Section 17 Patient Counseling

- a. As currently presented under Dosing instructions, the statement (b) (4) “ is inconsistent with the proposed administration. For consistency with the proposed administration, we recommend revising to “Advise patients to swallow tablets whole with a cup of water and not to cut, or chew tablets. If patients are unable to swallow the tablets, they may be crushed and dispersed in water [see Instructions for Use].”

B. Medication Guide (MG)

1. As currently presented, the proprietary name is denoted by the placeholder “PROPRIETARY NAME”. Replace all presentations of the placeholder “PROPRIETARY NAME” with the conditionally acceptable proprietary name, Revuforj.
2. As currently presented, the statement (b) (4) “ is inconsistent with the administration of the tablet. For consistency with the proposed administration of the tablet, we recommend revising to “Swallow REVUFORJ tablets whole with a cup of water. If you are unable to swallow tablets, crush the tablets and dissolve them in water. See the Instructions for Use for detailed instructions on how to prepare and give REVUFORJ tablets. Do not cut or chew tablets.”
3. As currently presented, the storage statement is incomplete and inconsistent with the Prescribing Information. For clarity, we recommend revising the storage statement to present the °F before the °C and include “room temperature”. (b) (4)
4. As currently presented under “How should I take REVUFORJ?” section, the statement “ (b) (4) is unclear that different strengths may be needed to achieve a dose. Unclear instructions may lead to administration errors. We recommend removing the statement “ (b) (4) ” and creating a separate bullet with the statement “REVUFORJ tablets come in different strengths. Each strength is a different color. Your healthcare provider may prescribe more than 1 strength of REVUFORJ tablets for you, so it is important that you understand how to take your medicine the right way. Be sure that you understand exactly how many tablets you need to take, and what strengths to take.”

C. (b) (4) (b) (4)

6. RECOMMENDATIONS FOR SYNDAX PHARMACEUTICALS, INC. (SYNDAX)

A. General Comments for Tablet (Container labels & Carton Labeling)

1. The placement of the graphic (b) (4) competes with the legibility of the proprietary name, which may lead to misinterpretation of the proprietary name. Placing a logo immediately before, within, or after the proprietary name can lead to misinterpretation because logos may look like an additional letter in the proprietary name or detract from legibility. Furthermore, see 21 CFR 201.10(a) which states that the ingredient information required by section 502(e) of the Federal Food, Drug, and Cosmetic Act shall appear together, without any intervening written, printed, or graphic matter, except the proprietary names of ingredients, which may be included with the listing of established names, and such statements that are specifically required for certain ingredients by the act or regulations in this chapter. Delete the graphic (b) (4) and revise the color of the letter “o” to be consistent with the rest of the proprietary name.
2. The (b) (4) color of the established name lacks contrast. We recommend increasing the prominence of the established name. Consider the use of different font type or size, bolding, color, or other means to achieve increased prominence. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
3. The terminology within the statement of dosage statement (i.e., “(b) (4)” and (b) (4)”) is inconsistent with the terminology in the Prescribing Information. To ensure consistency with the terminology in the Prescribing Information, we recommend revising the dosage statement to read, “Recommended Dosage: See Prescribing Information.”
4. As currently presented, the format for the expiration date is not defined (e.g., XX/XX) on the container labels for the 110 mg and 160 mg tablets. We are unable to assess the proposed expiration date format from a medication safety perspective. In addition, the format of the expiration date on the container labels for the 25 mg tablet and the carton labeling for all strengths is MMM YYYY. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See Guidance for

Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

5. The placement of the graphic (b) (4) competes is prominent. Delete, move, and/or decrease the prominence of the graphic (b) (4)

B. Container Labels

1. As currently presented on the container label for 25 mg strength, the NDC number lacks prominence and on the side panel. The human-readable NDC is often used for product verification and identification prior to dispensing or administering a drug. Therefore, we recommended relocating the NDC number to the top right of the principal display panel for prominence.
2. The net quantity statement is in close proximity to the product strength. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Product selection or dosing errors can occur if the net quantity statement is mistaken for the product strength, leading to under- or over-dosing. We recommend relocating the net quantity statement away from and less prominent than the product strength, such as to the top left of the principal display panel. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022). To allow room on the 110 mg and 160 mg bottles, relocate the “Rx Only” statement to where the net quantity currently is.
3. The administration technique is missing from the container labels. For consistency with the carton labeling and to minimize wrong technique errors, we recommend including the statement “Swallow tablets whole or crush and disperse in water. Do not cut or chew tablets.” on the side panel.

C. Carton Labeling

1. As currently presented, the warning statement “ (b) (4) ” is inconsistent with the administration of the proposed tablet. This may lead to drug administration errors. We recommend revising the statement to Swallow tablets whole or crush and disperse in water. Do not cut or chew tablets.”).
2. 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 place holder to the carton labeling.

5 APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Revuforj received on October 17, 2024 from Syndax Pharmaceuticals, Inc. (Syndax).

Table 2. Relevant Product Information for Revuforj	
Initial Approval Date	N/A
Active Ingredient	revumenib
Indication	REVUFORJ is a menin inhibitor indicated for the treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients (b) (4) and older (b) (4)
Route of Administration	Oral
Dosage Form	tablets
Strength	25 mg, 110 mg and 160 mg

Table 2. Relevant Product Information for Revuforj

Dose and Frequency	(b) (4)
How Supplied	(b) (4) 25 mg: Pink modified oval film-coated tablet debossed with "S" on one side and "25" on the other side. • 30-count bottles with a child resistant closure (NDC 73555-500-00) 110 mg: Beige modified oval film-coated tablet debossed with "S" on one side and "110" on the other side. • 30-count bottles with a child resistant closure (NDC 73555-501-00) 160 mg: Purple modified oval film-coated tablet debossed with "S" on one side and "160" on the other side. • 30-count bottles with a child resistant closure (NDC 73555-502-00)
Storage	Store tablets at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Keep in original container until dispensed.

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,^f along with postmarket medication error data, we reviewed the following Revuforj labels and labeling submitted by Syndax Pharmaceuticals, Inc. (Syndax).

- Prescribing Information (Image not shown) received on October 17, 2024 , available from <\\CDSESUB1\EVSPROD\nda218944\0085\m1\us\114-labeling\draft\annotated\annotated-draft-label-text-word.doc>
- Medication Guide received on December 29, 2023, available from <\\CDSESUB1\EVSPROD\nda218944\0009\m1\us\114-labeling\draft\labeling\medication-guide-pdf.pdf>

(b) (4)

- Container labels received on December 29, 2023 (160 mg and 110 mg) , October 11, 2024 (25 mg)
- Carton labeling received on July 25, 2024 (160 mg and 110 mg) and October 11, 2024 (25 mg)

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

(b) (4)

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

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

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/s/

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10/30/2024 04:34:14 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ORDPURM
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Version: October 23, 2024
From: Ethan D. Hausman, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)
Through: Shetarra Walker, MD, MSCR, Clinical Team Leader, DPMH
NDA #: 218,944
Applicant: Syndax Pharmaceuticals
Drug: Revumenib
Indication: Treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older.
Dosage Form: Tablets for oral administration. A 25 mg tablet is ready for approval.

(b) (4)

Consult Request: The Division of Hematologic Malignancies 1 (DHM1) requests DPMH-Pediatrics input regarding oral tablet administration for pediatric dosing. The questions asked are:

1. Please clarify if there are any FDA or CDER policies (or any national society guidelines) regarding any limits in tablet size for pediatric patients.
2. There are no data on use of this tablet in pediatric patients. Please clarify whether a tablet of this size would have a choking hazard and which age groups would have that hazard.
3. Given the size of the tablet, what would you recommended be age limit or BSA for use of the oral tablet?

Background

Revumenib is under development for treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older. A solid, tablet formulation is ready for approval “for use down to 1 year of age”. The smallest to be marketed product a 25 mg tablet with a length of 0.18 inches (~4.6 mm) and diameter of 0.37 inches (~9.4 mm). (b) (4)



Notable safety issues with the candidate product include a narrow therapeutic index for QTc prolongation, and differentiation syndrome (i.e., a syndrome associated with treatment of certain hematologic malignancies with symptoms of dyspnea, fever, peripheral edema, hypotension, weight gain, pleuro-pericardial effusion, acute renal failure, musculoskeletal pain, and hyperbilirubinemia).¹

This review will discuss the suitability of administration of the tablet formulation only and will not address other safety issues or dosing.

Introductory comment

The suitability of solid oral dosage forms for pediatric or adult patients depends multiple factors including age, developmental stage, cognitive maturity, nature of the underlying condition, and physical and chemical attributes of the product.

FDA has no guidance on the matter of choking or swallowability of pediatric dosage forms. The American Academy of Pediatrics has no specific practice guidelines but states that children younger than 3 years are at greatest risk of choking from hard/solid objects.² As discussed in the response to Question 1 below, the European Medicines Agency (EMA) states that the youngest age at which most patients should be able to swallow solid formulations is affected by multiple product characteristics (e.g., shape, size, taste, and texture).

While the responses below should serve as a guide, it is the responsibility of the Applicant/Sponsor to provide justification for the youngest pediatric age for which the product may be indicated.

Responses and Discussion

Question 1. Please clarify if there are any FDA or CDER policies (or any national society guidelines) regarding any limits in tablet size for pediatric patients.

Response: FDA Guidance on physical attributes of generic tablets and capsules acknowledges potential difficulty of swallowing related to product dimensions (e.g., flat tablets may adhere to the esophagus and have longer transit times than round/ovoid

¹ Larson RA, Bag R. Differentiation syndrome associated with treatment of acute leukemia. UpToDate. Original publication Date July 31, 2023. Reference update: September 2024.

² American Academy of Pediatrics Policy Statement: Prevention of choking among children. Pediatrics (2010) 125 (3): 601–607.

products);³ however, the guidance does not address swallowing or choking in pediatric patients. EMA consensus recommendations regarding appropriate sizes of oral formulations have been published:⁴

- Small tablets (3 to 5mm in largest dimension) are not considered acceptable for children below the age of 2 years.
- Medium tablets (5 to 10mm in largest dimension) are not considered acceptable below the age of 6 years.
- Large tablets (10 to 15mm in largest dimension) are not considered acceptable for children younger than 12 years.

However, product texture and taste, developmental stage, and criticality of the drug administration should be considered when applying these guidelines.

Based on the above EMA framework, the candidate may be appropriate for children approximately 4 to 6 years of age and older; however, the applicant should provide justification for the suitability of the product for the youngest ages for whom the product would be indicated. The justification should address all relevant factors.

Question 2. There are no data on use of this tablet in pediatric patients. Please clarify whether a tablet of this size would have a choking hazard and which age groups would have that hazard.

Response: Several studies below exemplify the limitations of available data relating to this question.

Study 1: (Radhakrishnan et al):⁵ In this study of 152 adults, 18 to 65 years of age, 32% of subjects reported a prior history of difficulty swallowing tablets or capsules. The study was comprised of a questionnaire regarding history of difficulty swallowing oral dosage forms, followed by administration of one size 000 capsule followed by one size 4 capsule; lengths of 1.029 inches (26.1 mm) and 0.563 inches (14.3 mm), respectively.⁶ Subjects with history of swallowing difficulties were more likely to report memory of prior choking than the subjects without a history of difficulty swallowing solid dosage forms (OR=7.25, $p < 0.05$). Four participants failed to swallow size 000 capsules: one declined to attempt the task, one attempted the task but failed due to choking sensation, and two attempted but then declined because they stated they needed food to aid in swallowing. Success rates for swallowing size 4 capsules were not identified in the publication.

Comment: Limitations of the study include lack of inclusion of pediatric patients and lack of reporting (or studying) the success rate of the smaller, size 4, capsules.

³ FDA Guidance for Industry: Size, shape, and other physical attributes of generic tablets and capsules. June 2015.

⁴ European Medicines Agency committee for medicinal product for human use, 2011. Draft guideline on the pharmaceutical development of medicines for paediatric use. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/06/WC500107908.pdf.

⁵ Radhakrishnan C, Forough AS, Cicher J. A difficult pill to swallow: An investigation of the factors associated with medication swallowing difficulties. Patient Preference and Adherence. 2021;15: 20-40

⁶ <https://www.lfacapsulefillers.com/capsule-size-chart>. Website accessed October 23, 2024.

Study 2 (Bracken et al):⁷ A recent study assessing the ability of pediatric patients, ages 4 to 12 years, to swallow 6-, 8-, and 10-mm tablets, enrolled 55 of 1077 screened patients. Reasons for exclusion were predominantly failure to provide consent. Of enrolled patients, 30 (55%) were 4- to 8-years old, and 25 (45%) were 9- to 12-years old. Male-to-female ratio and history of prior ingestion of tablets (yes/no) were each approximately even; however, those characteristics were not reported by age group. Each patient was offered each sized tablet. Denominators for success are reported as subjects in each age group who attempted to swallow the tablets.

In the 9- to 12-year-old group, 100% were able to swallow the 6- (n=25) and 8-mm (n=25) tablets, and 24 (96%) were able to swallow the 10-mm tablets.

In the 4- to 8-year-old group 67% of 30 patients were able to swallow the 6-mm tablet, 91% of 23 patients were able to swallow the 8-mm tablet, and 95% of 21 patients were able to swallow the 10-mm tablet.

The article comments that participants comment that both taste and size affected the ability to ingest the product, underscoring the need for data-collection in pediatric age groups.

Comment: The article does not address attempt at care giver instruction or coaching; however, these data support that the candidate product *may be safely administered to patients approximately 4 years and older*. The small study size limits generalizability.

Study 3 (van Riet-Nales et al):⁸ A recent study assessed “pleasantness” of ingestion of placebo formulations (4-mm tablets, powders, suspensions, syrups) in children from 1 to 4 years of age, without stratification by age. Secondary outcome was number of successful fully swallowed administrations. Products were administered twice on day one, and once daily for days 2, 3, and 4. Parents were instructed to provide the placebo products “as usual”; no additional coaching/instruction efforts were employed. No choking events were reported. While number of completed ingestions was highest for tablets, the mean rates were less than 50% in all groups (Table 1). There is no data regarding partially swallowed doses or skipped doses.

⁷ Bracken L, McDonough E, Ashleigh S. Can children swallow tablets? Outcome data from a feasibility study to assess the acceptability of different-sized placebo tablets in children (creating acceptable tablets (CAT)). BMJ Open 2020; 10:e036508.

⁸ Riet-Nales, de Neef B, Schobben A, et al. Acceptability of different oral formulations in infants and preschool children. Arch Dis Child 2013;98:725-731.

Table 1: Acceptability of four different oral formulations (n: 148 children): Source: van Riet-Nales DA, et al. Arch Dis Child 2013;98:725–731

	VAS score		Result of the intake All four days Mean† (95% CI)
	First day (four different groups) Mean* (95% CI)	All four days (cross-over design) Mean* (95% CI)	
Numerical data			
Tablet	9.39 (8.85 to 9.93), n=32	9.01 (8.75 to 9.28)	1.96 (1.92 to 2.00)
Powder	8.84 (8.19 to 9.49), n=45	8.20 (7.84 to 8.56)	1.58 (1.44 to 1.71)
Suspension	8.26 (7.47 to 9.04), n=34	7.90 (7.42 to 8.38)	1.70 (1.57 to 1.83)
Syrup	8.35 (7.45 to 9.25), n=37	8.19 (7.73 to 8.64)	1.67 (1.54 to 1.80)
	p Value‡	p Value‡	p Value§
Testing for any differences			
Tablet versus powder	<0.001	0.054	<0.001
Tablet versus suspension	<0.001	0.001	<0.001
Tablet versus syrup	<0.001	0.027	<0.001
Powder versus suspension	0.378	0.060	0.081
Powder versus syrup	0.869	0.611	0.168
Suspension versus syrup	0.164	0.302	0.513

* Estimate of the mean acceptability as expressed on a 10 cm visual analogue scale (VAS score).
† Estimate of the mean number of administrations of a formulation that were fully swallowed, maximum n=2.00.
‡p Values of the Mann-Whitney/Wilcoxon tests regarding any differences between the mean VAS scores of two different formulations.
§p Values of the Z tests comparing pairs of formulations regarding the mean number of administrations that were fully swallowed.

Comment: The absence of choking events is encouraging; however, the small dataset limits generalizability.

3. Given the size of the tablet, what would you recommended be age limit or BSA for use of the oral tablet?

Response: Patients as young as 4 to 6 years of age may be developmentally advanced enough to be taught to swallow the candidate tablets.^{9,10,11,12}

The decision regarding whether age or body surface area is the more appropriate criterion for pediatric dosing is deferred to DHM1 and Clinical Pharmacology.

⁹ Ben-Joseph E. Teaching your child how to swallow pills. Nemours Children's Health. August 2019. <https://kidshealth.org/en/parents/swallowing-pills.html>. Website accessed October 18, 2024.

¹⁰ Mutnick A. How to teach a child to swallow a pill. Columbia University Irving Medical Center. April 25, 2022. <https://www.cuimc.columbia.edu/news/how-teach-child-swallow-pill>. Website accessed October 18, 2024

¹¹ McCloskey A, Lunn A, Traynor M, et al. KidzMed e-learning to upskill student pharmacists to teach pill swallowing to children. PLoS One. 2023 Mar 16;18(3).

¹² Beck M, Cataldo M, Slifer K, et al. Teaching children with attention deficit hyperactivity disorder (ADHD) and autistic disorder (AD) how to swallow pills. Clin Pediatr (Phila). 2005 Jul-Aug;44(6):515-26.

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/s/

ETHAN D HAUSMAN
10/23/2024 08:30:39 AM

SHETARRA E WALKER
10/23/2024 01:36:58 PM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY PRODUCTS

Date: October 21, 2024

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead, Cardiac Safety IRT, DCN

To: Rachel McMullen
DHM1

Subject: QT Consult to NDA 218944 (SDN 85)

Note: Any text in the review with a light background should be inferred as copied from the Sponsor's document.

This memo responds to your consult to us dated 10/18/2024 regarding the Division's QT related question. We reviewed the following materials:

- Previous IRT review(s) for NDA 218944 dated [04/23/2024](#) and [10/02/2024](#) in DARRTS; and
- Drafted labeling (NDA 218944 / SN0085; [link](#)).

1 Responses for the Division

Question: Can IRT review the Applicant's proposed changes in Section 12.2 Cardiac Electrophysiology and provide feedback on whether to accept/reject the changes and/or have any other edits.

IRT's response: Our changes are highlighted ([addition](#), [deletion](#)) followed by a rationale for the changes made. Per the question in the Division's consult, we only looked at section 12.2. Please see our edits to section 2, 5, and 7 in our previous review dated [04/23/2024](#) in DARRTS.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of REVUFORJ on the QTc interval was evaluated across a dose range of 113 mg to 339 mg twice daily (1.2 times the highest adult approved recommended

dosage) with and without strong CYP3A4 inhibitors in patients with relapsed or refractory acute leukemia with KMT2Ar.

The increase in QTc interval was concentration-dependent with an increase in QTc predicted to be 27 msec (upper bound of 90% confidence interval: 30 msec) at the mean steady-state maximum concentration (C_{max}) observed in patients (b) (4) at the highest (b) (4) approved recommended dosage without (b) (4)-CYP3A4 inhibitors. The increase in QTc interval was predicted to be 19 msec (upper bound of 90% confidence interval: (b) (4) 22 msec) at steady-state C_{max} after administration of 163 mg twice daily with strong CYP3A4 inhibitors [see *Warnings and Precautions* (5.2)].

Reviewer's Comment:

(b) (4)

We agree with the Applicant to remove the word “ (b) (4) ”. Please refer to Table 24 in Summary of Clinical Pharmacology ([link](#)).

We agree with the Applicant to modify the upper bound of 90% CI of QTc prolongation to 22 msec following 160 mg BID with strong CYP3A4 inhibitors. It appears that (b) (4) msec was a typo from our previous review.

2 BACKGROUND

Refer to our previous review under NDA 218944 dated [04/23/2024](#) in DARRTS.

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/s/

YANYAN JI
10/21/2024 03:58:59 PM

CHRISTINE E GARNETT
10/21/2024 04:00:15 PM

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

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

Memorandum

Date: October 17, 2024

To: Rachel McMullen, Senior Regulatory Project Manager,
Division of Hematologic Malignancies 1 (DHM1)

From: Valerie Guerrier, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Samia Alam, Regulatory Review Officer, OPDP
Jina Kwak, Team Leader, OPDP

Subject: OPDP Labeling Comments for REVUFORJ® (revumenib) tablets, for oral use

NDA: 218944

Background:

In response to DHM1's consult request dated October 7, 2024, OPDP has reviewed the proposed Prescribing Information (PI), (b) (4) Medication Guide, and carton and container labeling for the original NDA submission for REVUFORJ® (revumenib) tablets, for oral use.

PI/ (b) (4) Medication Guide:

OPDP's review of the proposed PI and (b) (4) are based on the draft labeling and material accessed from SharePoint on October 8, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on October 15, 2024.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on October 8, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Valerie Guerrier at (240) 402-2162 or Valerie.Guerrier@fda.hhs.gov.

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/s/

VALERIE GUERRIER
10/17/2024 06:45:58 AM

**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: October 11, 2024

To: Rachel McMullen
Regulatory Project Manager
Division of Hematologic Malignancies I (DHM1)

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

From: Maria Nguyen, MSHS, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Valerie Guerrier, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): REVUFORJ (revumenib)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 218944

Applicant: Syndax Pharmaceuticals, Inc.

1 INTRODUCTION

On January 26, 2024, Syndax Pharmaceuticals, Inc., submitted for the Agency's review a 505(b)(1) for their New Drug Application (NDA) 218944 for REVUFORJ (revumenib) tablets (b) (4)

The proposed indication for REVUFORJ (revumenib) is treatment for adult and pediatric patients with relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) rearrangement.

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 Hematologic Malignancies I (DHMI) on February 7, 2024, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for REVUFORJ (revumenib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft REVUFORJ (revumenib) MG received on January 26, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 7, 2024.
- Draft REVUFORJ (revumenib) Prescribing Information (PI) received on January 26, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 7, 2024.

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%.

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 MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG 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 MG 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 MG.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
10/11/2024 06:10:38 PM
DMPP-OPDP review of revumenib (REVUFORMJ) NDA 218944 MG

VALERIE GUERRIER
10/15/2024 07:42:20 AM

LASHAWN M GRIFFITHS
10/15/2024 08:11:38 AM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY PRODUCTS

Date: October 2, 2024

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead, Cardiac Safety IRT, DCN

To: Rachel McMullen
DHM1

Subject: QT Consult to NDA 218944 (SDN 79)

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

This memo responds to your consult to us dated 9/23/2024 regarding the Division's QT related question. We reviewed the following materials:

- Applicant's response dated 09/23/2024 to Division's IR dated 09/16/2024 (NDA 218944/ SN0079; [link](#));
- Previous IRT review(s) for NDA 218944 dated [04/23/2024](#) in DARRTS; and
- Summary of clinical pharmacology, including highlights of clinical pharmacology and cardiac safety (NDA218944 / SN0009; [link](#)).

1 Responses for the Division

Question: The clinical review team has observed an increased risk of QT prolongation for revumenib in patients of Asian descent. The Division is requesting QT-IRT's input and review to see if there is any plausible explanation for this unusual finding.

IRT's Response: In acute leukemia patients treated with revumenib at the labeled dosing regimen in study SNDX-5613-0700, Asian patients had higher incidence of QTc prolongation AEs than non-Asian patients (Table 4 and Table 5). We evaluated the following possible explanations for this observation:

1. **Mechanism:** Both revumenib and its M1 metabolite are hERG channel blockers. Drugs that inhibit hERG are usually associated with concentration dependent QTc prolongation, as observed in study SNDX-5613-0700. We conducted a literature search to understand whether studies have shown that Asians are more sensitive to QTc prolongation for drugs that inhibit

hERG. Our search indicated that there are no publications to support this hypothesis. No significant differences were found between Japanese and Caucasian subjects in concentration-QTc relationship for moxifloxacin^{1, 2} and amisulpride³. A study investigating the effect of quinidine on QT prolongation in healthy Caucasian and Korean subjects showed Korean subjects were less sensitive to quinidine-induced QTc prolongation⁴. And there was no significant difference between Korean and Japanese subjects in moxifloxacin induced QTc prolongations⁵.

2. **Exposure:** Population pharmacokinetic model indicated that patients with body weight < 40 kg would have > 1.3-fold higher peak concentrations (C_{max}) of both revumenib and M1 than patients weighting 70 kg. Asian patients had lower body weight and therefore were expected to have higher C_{max} than non-Asian patients (Figure 1 and Table 3). However, in study SNDX-5613-0700, mean C_{max} of revumenib and M1 were only numerically higher in Asian (n = 13) compared to non-Asian (n = 180) patients in the 163 mg BID group (with strong CYP3A4 inhibitors) (Figure 2). The 95% confidence intervals of mean C_{max} were overlapping between Asians and non-Asians possibly because of the small number of Asians in the study. Based on the developed concentration-QTc model a 30% increase in C_{max} would not translate to significantly higher QTc prolongation compared to the expected QT increase in the overall patient population.
3. **Risk factors:** No imbalances were observed between Asian or non-Asian patients in baseline risk factors that could impact QTc prolongation including concomitant QTc prolonging medication, cardiac medical history, and abnormal serum electrolytes (section 3.2).

In conclusion, we did not identify any reasons why Asian patients had higher incidence of QTc prolongation in study SNDX-5613-0700. It is plausible that the increased incidence was by chance due to the small number of Asian patients (n = 16).

¹ Taubel J, Ferber G, Lorch U, Batchvarov V, Savelieva I, Camm AJ. Thorough QT study of the effect of oral moxifloxacin on QTc interval in the fed and fasted state in healthy Japanese and Caucasian subjects. *Br J Clin Pharmacol*. 2014 Jan;77(1):170-9. doi: 10.1111/bcp.12168. PMID: 23713767; PMCID: PMC3895358.

² Morganroth, J., Wang, Y., Thorn, M., Kumagai, Y., Harris, S., Stockbridge, N., Kleiman, R., and Shah, R. (2015) Moxifloxacin-induced QTc interval prolongations in healthy male Japanese and Caucasian volunteers: a direct comparison in a thorough QT study. *Br J Clin Pharmacol*, 80: 446–459. doi: 10.1111/bcp.12684.

³ Täubel J, Ferber G, Fox G, Fernandes S, Lorch U, Camm AJ. Thorough QT study of the effect of intravenous amisulpride on QTc interval in Caucasian and Japanese healthy subjects. *Br J Clin Pharmacol*. 2017 Feb;83(2):339-348. doi: 10.1111/bcp.13128. Epub 2016 Oct 21. PMID: 27618796; PMCID: PMC5237697.

⁴ Shin JG, Kang WK, Shon JH, Arefayene M, Yoon YR, Kim KA, Kim DI, Kim DS, Cho KH, Woosley RL, Flockhart DA. Possible interethnic differences in quinidine-induced QT prolongation between healthy Caucasian and Korean subjects. *Br J Clin Pharmacol*. 2007 Feb;63(2):206-15. doi: 10.1111/j.1365-2125.2006.02793.x. Epub 2006 Nov 10. PMID: 17096683; PMCID: PMC2000575.

⁵ Hyang-Ki Choi, Jin Ah Jung, Tomoe Fujita, Hideki Amano, Jong-Lyul Ghim, Dong-Hwan Lee, Kenichi Tabata, Il-Dae Song, Mika Maeda, Yuji Kumagai, Boaz Mendzelevski, Jae-Gook Shin, Population Pharmacokinetic–Pharmacodynamic Analysis to Compare the Effect of Moxifloxacin on QT Interval Prolongation Between Healthy Korean and Japanese Subjects, *Clinical Therapeutics*, Volume 38, Issue 12, 2016, Pages 2610-2621, ISSN 0149-2918, <https://doi.org/10.1016/j.clinthera.2016.10.011>.

2 BACKGROUND

2.1 Product Information

Syndax Pharmaceuticals submitted revumenib under NDA 218944 for the oral tablet (b) (4). Revumenib (SNDX-5613, MW: 631 g/mol [free base]) is a menin inhibitor indicated for the treatment of adult and pediatric patients with relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) rearrangement. The recommended dose is by weight and age. For patients (b) (4) ≥ 40 kg, the recommended dose (fasted or with a low-fat meal) is 270 mg BID without strong CYP3A4 inhibitors or 160 mg BID with CYP3A4 inhibitors. Frequently, azole antifungals (CYP3A4 inhibitors) are concomitantly administered as prophylaxis for management of fungal infection.

2.2 Summary Results of Prior QT Assessment

The CS-IRT has reviewed the Applicant's QT assessment (04/23/2024). Revumenib is associated with concentration dependent QTc prolongation. The QT assessment was based on study SNDX-5613-0700, a phase 1/2, open-label, dose escalation and dose expansion study in patients with relapsed/refractory leukemia (see previous review for study design). The highest dose covers high clinical exposure for revumenib and clinical exposure for metabolite M1. Data were analyzed using exposure-response analysis as the primary analysis. Change from baseline QTcF was around 20 msec at the exposure following proposed therapeutic regimen.

(b) (4)

2.3 Applicant's Position Related to the Question

Division's question #2 in IR dated 9/16/2024:

Using the ISS data set submitted 12/29/2023, in an analysis of all patients with acute leukemia treated with revumenib at the proposed recommended dosage, approximately 73% of patients of Asian descent were reported in adae.xpt as having an event of prolonged QT, and this high rate of prolonged QT in Asians carried through later updates of the ISS. Please provide the biological basis for this high rate of prolonged QT in Asians treated with revumenib, and describe your mitigation strategy.

Applicant's response dated 9/23/2024:

Syndax acknowledges there was a trend towards increased rates of prolonged QT in the Asian subpopulation enrolled in Study SNDX-5613-0700. There were 15 patients with Asian race treated with revumenib at the proposed recommended dosage in the ISS data set submitted 12/29/2023, of which 11 (73%) reported at least one prolonged event of QTc. *A biological basis for the rate of prolonged QT was not identified upon review of relevant factors including demographics, medical history, lines of therapy, concomitant medications, as well as PK exposure.*

3 Reviewer's Analysis

3.1 Clinical Pharmacology

The clinical pharmacology of revumenib and its major metabolite (M1) is summarize in the [Applicant's summary of clinical pharmacology](#) and in the previous IRT review dated 04/23/2024. Briefly, the Applicant's analysis indicated that food, age, sex, race, mild to moderate

renal impairment or hepatic impairment did not have a clinically relevant impact on PK of revumenib and M1. However, body weight, CYP3A4 inhibition/induction, and plasma albumin level had clinically relevant impact on revumenib and M1 exposures. For example, patients weighing 14 kg (5th percentile) and 40 kg would have $\sim 2.3\times$, and $\sim 1.3\times$ higher C_{max} than patients weighing 70 kg if they received the same revumenib dose.

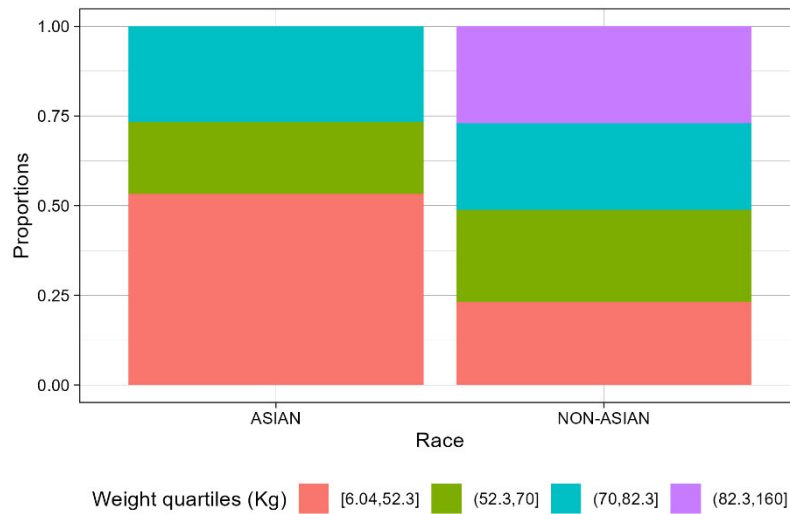
In this memo, the reviewer's independent analysis was performed on the most recent ISS dataset (adsl.xpt and adae.xpt from [SN0076](#) and adpc.xpt from [SN0072](#)) in the acute leukemia patients receiving label recommended dosage (276 mg BID without strong CYP3A4 inhibitors [Phase 1 Arm A] or 163 mg BID with strong CYP3A4 inhibitors [Phase 1 Arm B and Phase 2]) in study SNDX-5613-0700.

Figure 1 shows that a larger proportion of Asians had body weight below the first (52 kg) and second quartiles (70 kg) compared to other races, implying that Asians are predisposed to higher revumenib exposure compared to other races.

As shown in Figure 2, Asian patients in the 163 mg BID group (with strong CYP3A4 inhibitors) exhibited numerically higher mean C_{max} values than their non-Asian counterparts. In both Asian and non-Asian patients in the 163 mg BID group, exposures on day 7 were higher than day 1 due to steady state accumulation ($T_{1/2} = 7.5$ hours, accumulation factor = 1.5). It should be noted that the mean C_{max} in Asian patients is estimated with high uncertainty (i.e., wide error-bars) due to the small number of Asians in the study (3 Asians in Arm A [267 mg BID], and 13 Asians in Arm B and Phase 2 [163 mg BID]).

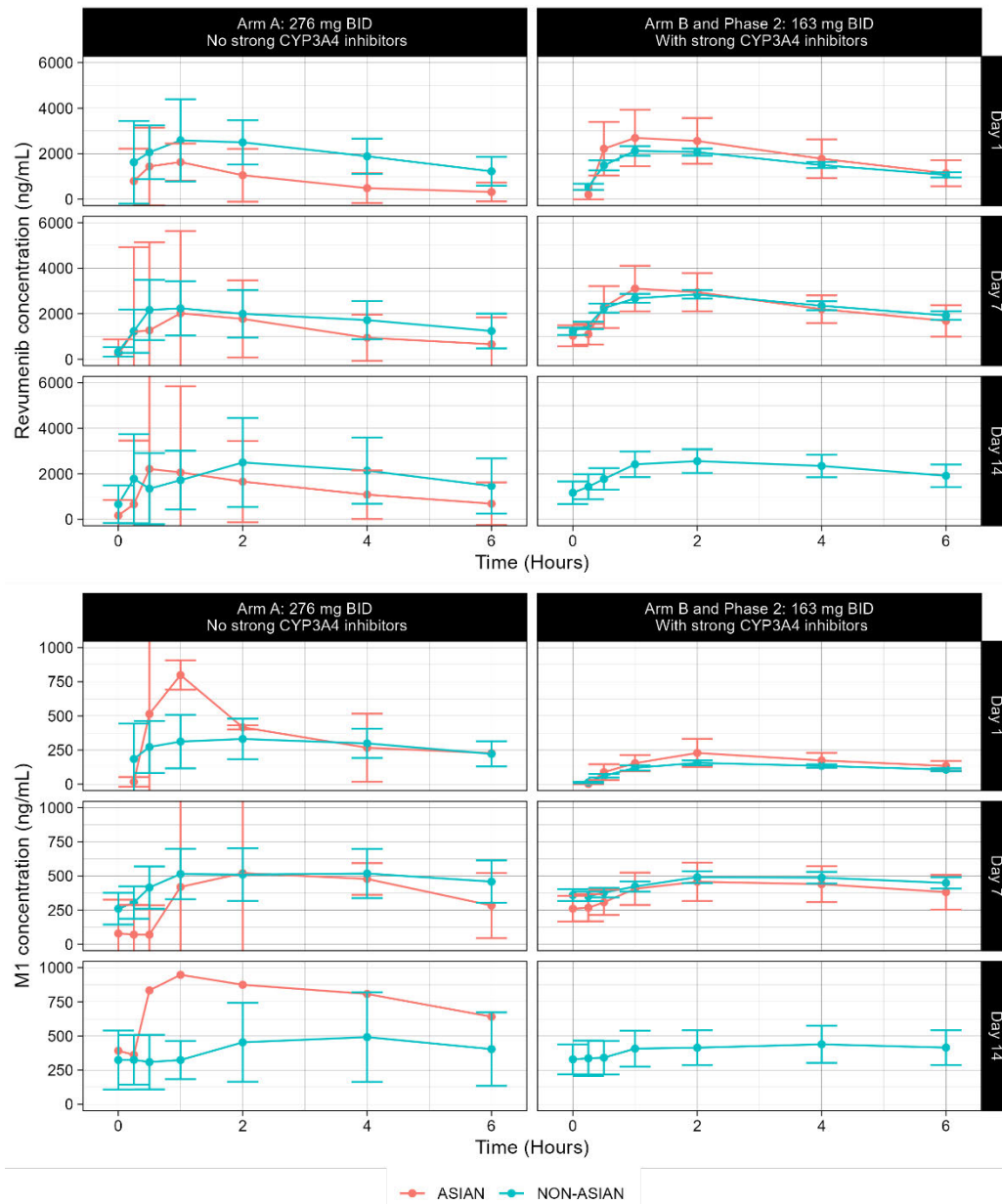
In total, 12 out of 16 (75%) Asian patients and 121 out of 208 (58%) non-Asian patients had drug interruption/withdrawal or dose reduction due to AEs (based on adae.xpt). The leading cause of drug interruption/withdrawal or dose reduction was QT prolongation (10 vs 32 patients in Asian and non-Asian). Higher proportion of Asian patients had drug interruption/withdrawal or dose reduction compared to non-Asian over time (Figure 3), possibly explaining the similar levels of C_{max} between the two populations. The time profile of proportion of patients with QT events is consistent with drug interruption/withdrawal or dose reduction (Figure 4). There is no trend in QT prolongation by body weight quantile (Figure 5).

Figure 1. Proportions of Patients in Different Weight Quartiles Stratified by Race (Asian or non-Asian)



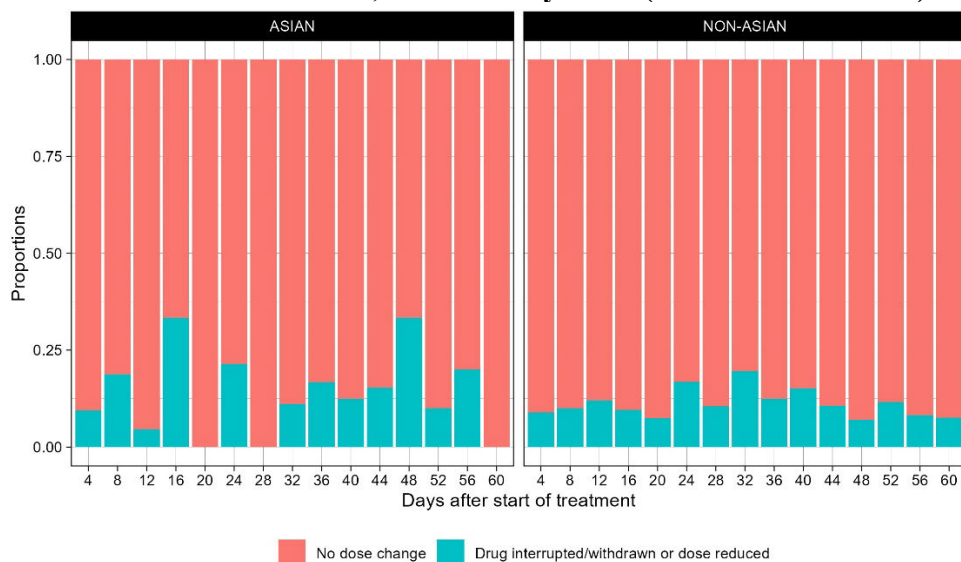
Source: Reviewer's independent analysis on adsl.xpt (SN0076)

Figure 2. Revumenib and M1 mean concentration-time profiles on Days 1, 7 and 14 in Cycle 1 of Treatment in Asian and Non-Asian Patients



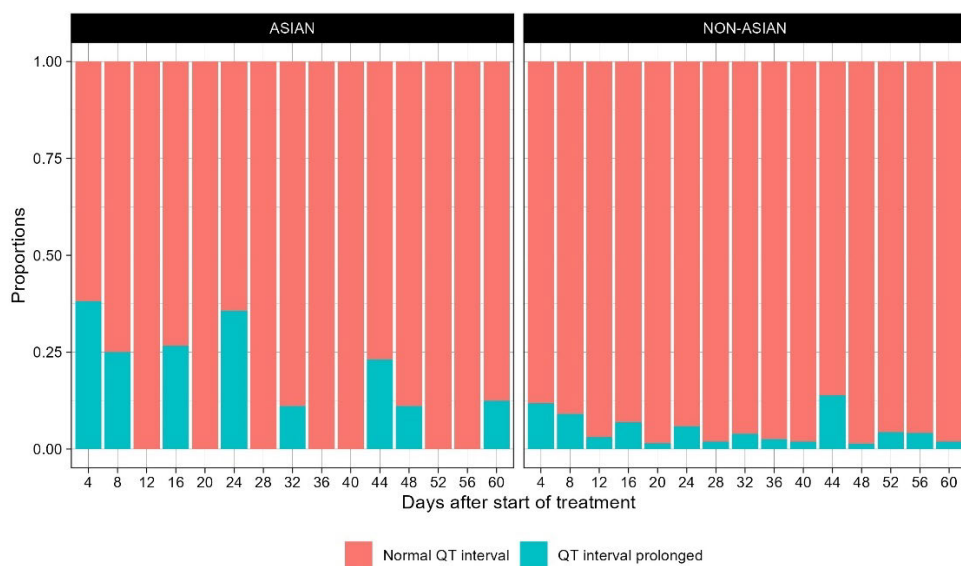
Source: Reviewer's independent analysis on adpc.xpt (SN0072)

Figure 3. Proportions of Patients with and without Drug Interruptions, Reductions, or Withdrawal Over Time, Stratified by Race (Asian vs non-Asian)



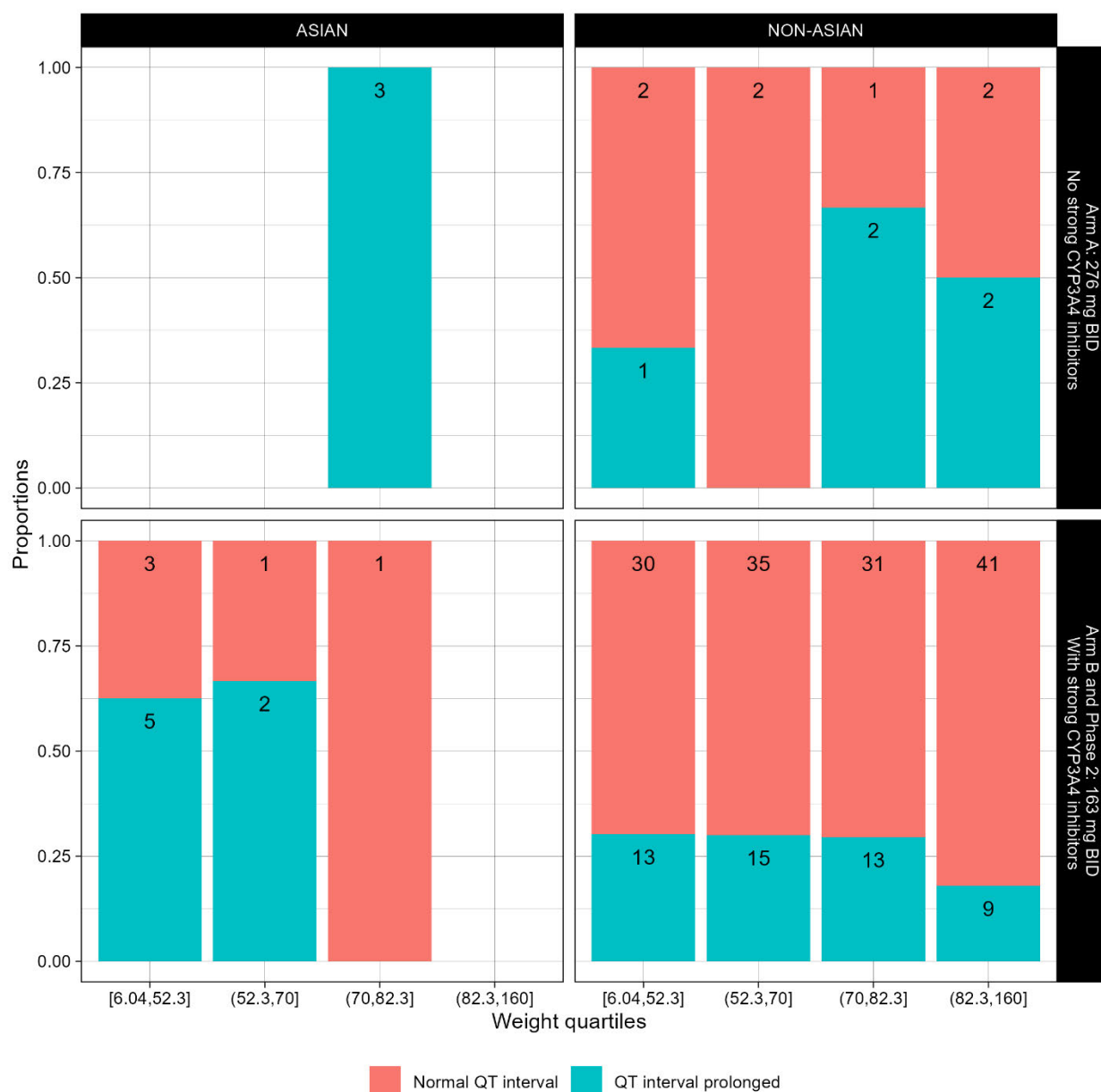
Source: Reviewer's independent analysis on adae.xpt (SN0076)

Figure 4. Proportions of Patients with and without QT prolongation Over Time, Stratified by Race (Asian vs non-Asian)



Source: Reviewer's independent analysis on adae.xpt (SN0076)

Figure 5. Proportions of Patients with QT prolongation in Different Weight Quartiles Stratified by Dosing Group and Race (Asian vs non-Asian). Numbers Inside the Bars Represent Patients with or without QT Prolongation.



Source: Reviewer's independent analysis on adae.xpt (SN0076)

3.2 Cardiac Safety Analysis

The reviewer's cardiac safety analysis was based on the most recent ISS dataset ([SN0076](#)). In total, 224 patients with acute leukemia treated with revumenib at the proposed recommended dosage (276 mg BID without strong CYP3A4 inhibitors [Phase 1 Arm A] or 163 mg BID with

strong CYP3A4 inhibitors [Phase 1 Arm B and Phase 2]) in study SNDX-5613-0700, of whom 16 were Asian and 208 were non-Asian.

Demographics, baseline characteristics, and treatment dosage were in general similar between Asians and non-Asians except for body weight at baseline. The Asians had lower body weight (Table 3). For patients who experienced electrocardiogram QT prolonged event, the median body weight was 53 (n=12) vs 71 kg (n=70) in the Asian vs non-Asian group. Five out of 12 patients in the Asian group who had QT prolongation had baseline weight > 53 kg. Age was not significantly different between Asians and non-Asians. Seven out of 12 patients in the Asian group who had QT prolongation were older than 50 years at baseline. All the Asian patients were from Western countries (US, Canada, Australia). There's no meaningful difference in baseline QTcF between Asian and non-Asian patients (mean QTcF 418 msec vs 410 msec).

Table 1. Demographics and Baseline Characteristics, Safety Population at Recommended Dose, Study SNDX-5613-0700

Characteristic	Asian N=16 n (%)	Non-Asian N=208 n (%)
Sex, n (%)		
Male	6 (37.5)	84 (40.4)
Female	10 (62.5)	124 (59.6)
Age, years		
Mean (SD)	49.4 (18.8)	45.4 (22.7)
Median (min, max)	49.5 (4.0, 79.0)	46.0 (1.0, 84.0)
Age groups (years), n (%)		
age<18	1 (6.2)	31 (14.9)
18<=age<65	12 (75.0)	121 (58.2)
age>=65	3 (18.8)	56 (26.9)
Weight (kg)		
Mean (SD)	54.6 (16.8)	68.2 (28.1)
Median (min, max)	51.4 (14.4, 81.0)	71.0 (6.0, 160.0)
Missing	1.0 (6.2)	1.0 (0.5)
BMI		
Mean (SD)	21.4 (3.8)	25.0 (7.2)
Median (min, max)	20.1 (14.8, 29.5)	24.6 (12.6, 58.8)
Missing	1.0 (6.2)	12.0 (5.8)
LVEF		
Mean (SD)	59.5 (7.1)	60.7 (6.5)
Median (min, max)	59.5 (43.0, 71.0)	60.0 (40.0, 78.0)
Missing	0	1.0 (0.5)
Arm		
163 mg Q12H with strong CYP3A4 inhibitor	13 (81.2)	194 (93.3)
276 mg Q12H without strong CYP3A4 inhibitor	3 (18.8)	14 (6.7)

Source: Reviewer's analysis based on adsl.xpt (SN0076)

There was no imbalance between the Asian (69%) and the non-Asian (76%) group in receiving concomitant medication with known QT prolongation risks (based on crediblemeds). There's no imbalance between the Asian (25%) and the non-Asian (21%) group in medical history of cardiac arrhythmias.

Higher percentage of patients in the Asian group experienced TdP/QT prolongation adverse events (customized query, Table 4), driven by the preferred term electrocardiogram QT prolonged. There were no imbalances in SAEs or AEs leading to discontinuation. Higher percentage of patients in the Asian group had severe QT prolongation events, confirmed by outlier analysis on the ECG data (Table 5). No patients in the Asian group had seizure, significant ventricular arrhythmias, or sudden cardiac death. One subject was younger than 1 year and he did not have QT prolongation.

There was no difference in change from baseline or outlier in electrolytes (potassium, calcium, and magnesium) between the Asian and the non-Asian group (data not shown).

Table 2. Customized Query of QT prolongation/TdP, Safety Population at Recommended Dose, Study SNDX-5613-0700

Adverse Event Category	Asian N=16 n (%)	Non-Asian N=208 n (%)
Any AE in group	12 (75.0)	80 (38.5)
Electrocardiogram QT prolonged	12 (75.0)	70 (33.7)
Cardiac arrest	0	6 (2.9)
Cardio-respiratory arrest	0	1 (0.5)
Death	0	1 (0.5)
Seizure	0	2 (1.0)
Sudden death	0	2 (1.0)
Syncope	0	4 (1.9)
Ventricular arrhythmia	0	1 (0.5)
Ventricular tachycardia	0	1 (0.5)
Maximum severity		
Death	0	10 (4.8)
Life-threatening	0	3 (1.4)
Severe	11 (68.8)	23 (11.1)
Moderate	1 (6.2)	29 (13.9)
Mild	0	15 (7.2)
Serious	2 (12.5)	17 (8.2)
Resulting in discontinuation	0	6 (2.9)

Source: Reviewer's analysis based on adae.xpt (SN0076)

Table 3. Patients With QTcF Values Exceeding Specified Levels, Safety Population at Recommended Dose, Study SNDX-5613-0700

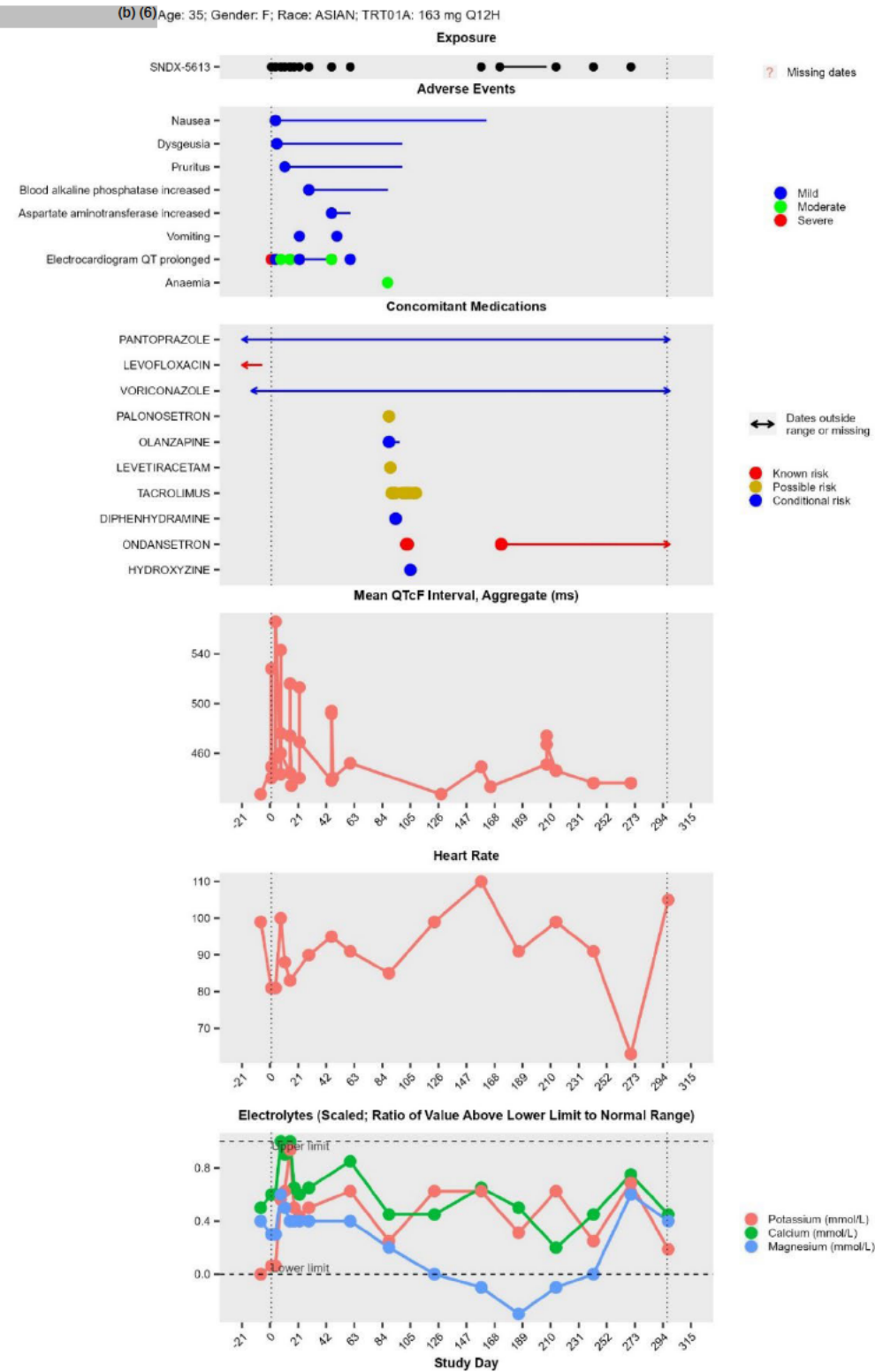
Parameter Level	Asian N=16 n/Nw (%)	Non-Asian N=208 n/Nw (%)
QTcF, high, (msec)		
Level 1 (>480)	8/15 (53.3)	41/193 (21.2)
Level 2 (>500)	3/15 (20.0)	19/193 (9.8)
Level 3 (>500 & CFB > 60)	3/15 (20.0)	18/193 (9.3)
QTcF, high (delta), (msec)		
Level 1 (>30)	14/15 (93.3)	120/193 (62.2)
Level 2 (>60)	9/15 (60.0)	40/193 (20.7)

Source: Reviewer's analysis based on adeg.xpt (SN0076)

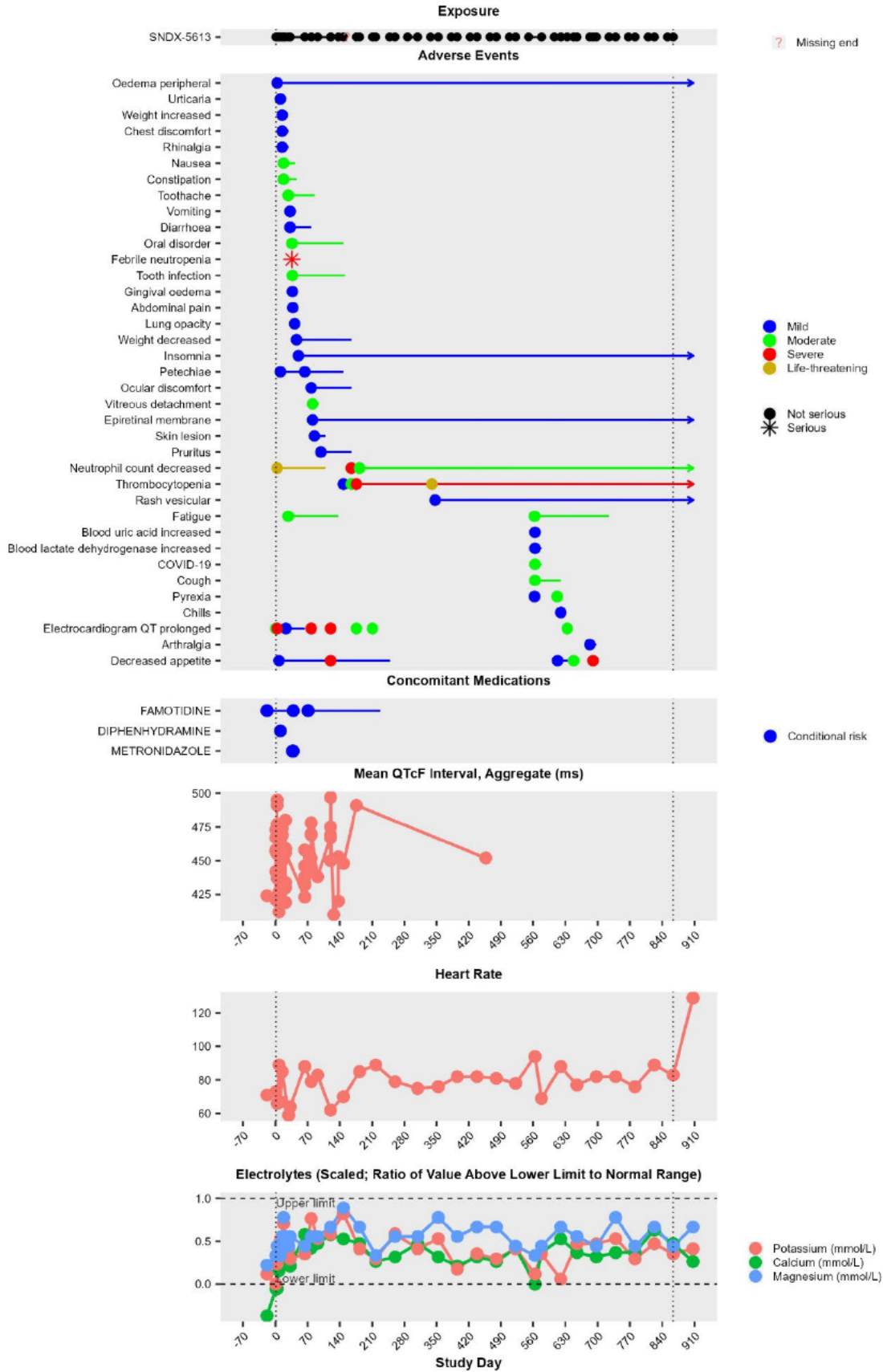
We reviewed the graphic patient profiles of the 9 Asian patients reported AE of electrocardiogram QT prolonged with QTcF > 480 msec (see section 4). One subject had QTcF > 480 msec before treatment started (ID: (b) (6)). Two patients ((b) (6)) received ondansetron during the QT prolongation. Ondansetron has a known QT prolongation risk ([label](#)). However, in general, there's no difference in the percentage of patients receiving concomitant QT prolonging drugs in Asians and non-Asians. All 9 patients had electrolytes within normal limits during the QT prolongation.

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 cdcrpqt@fda.hhs.gov

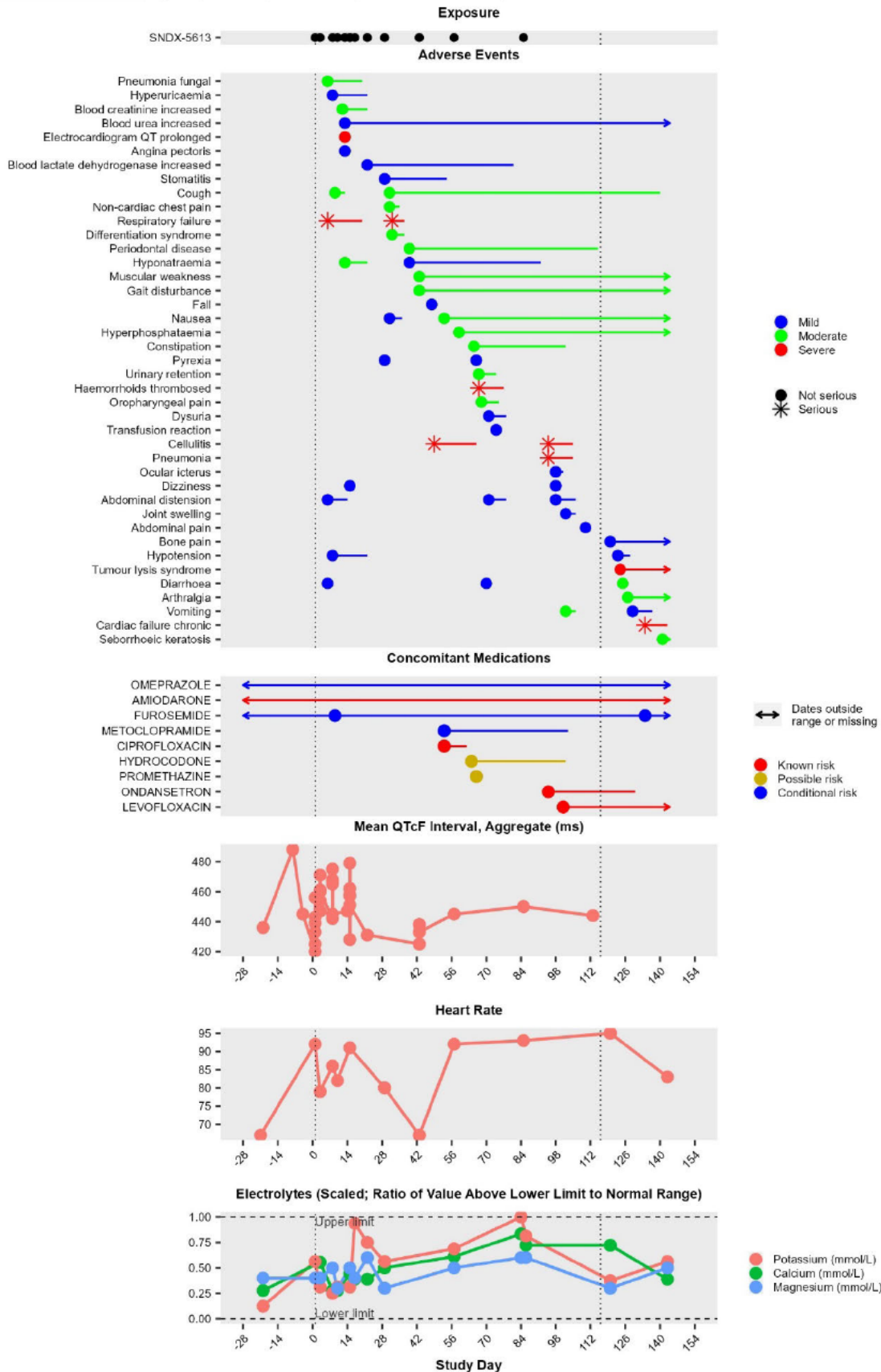
4 Graphic Patient Profile of Asian Patients with AE of Electrocardiogram Prolonged and QTcF > 480 msec



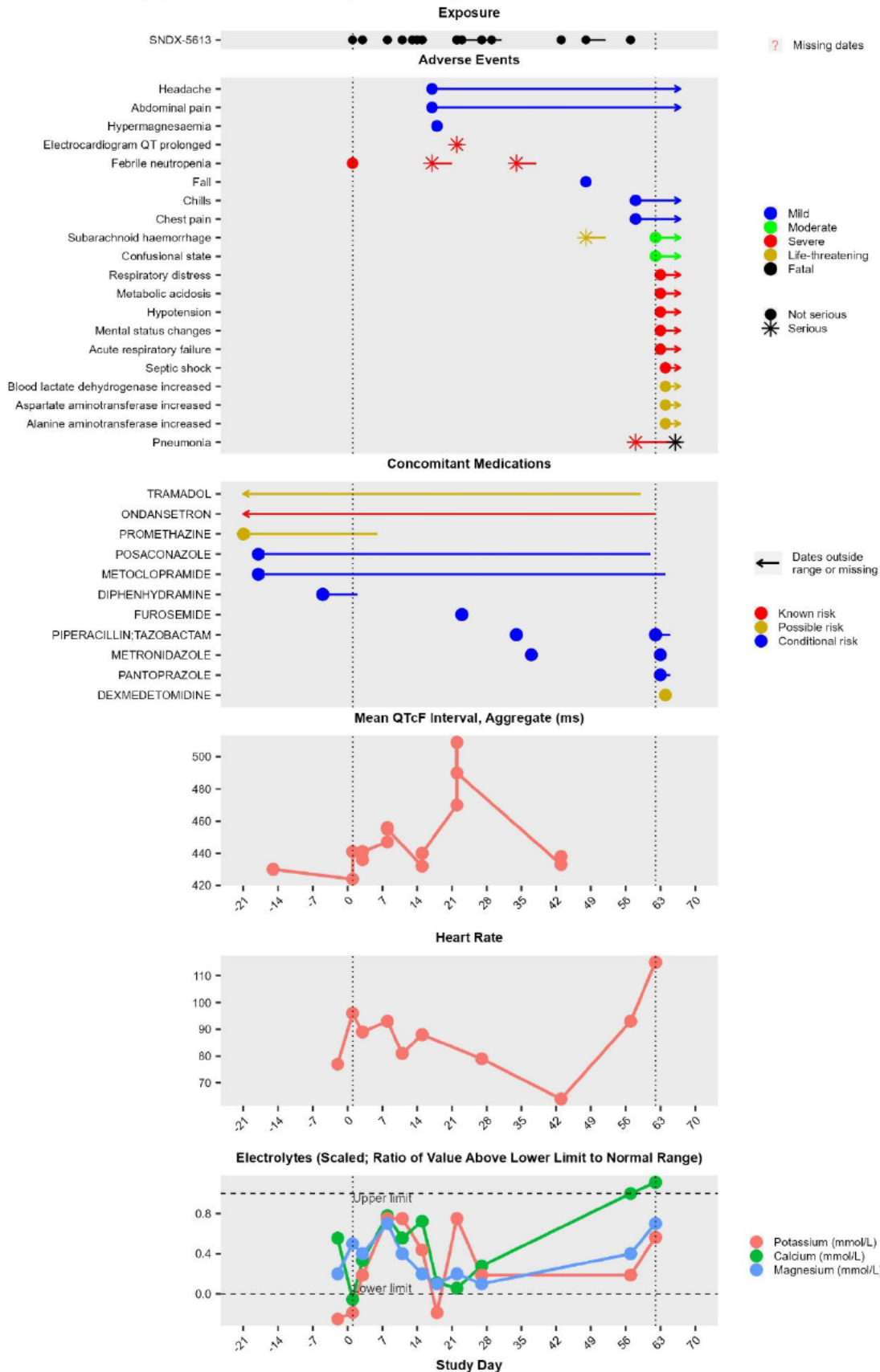
(b) (6) Age: 79; Gender: M; Race: ASIAN; TRT01A: Arm A: 276 mg Q12H



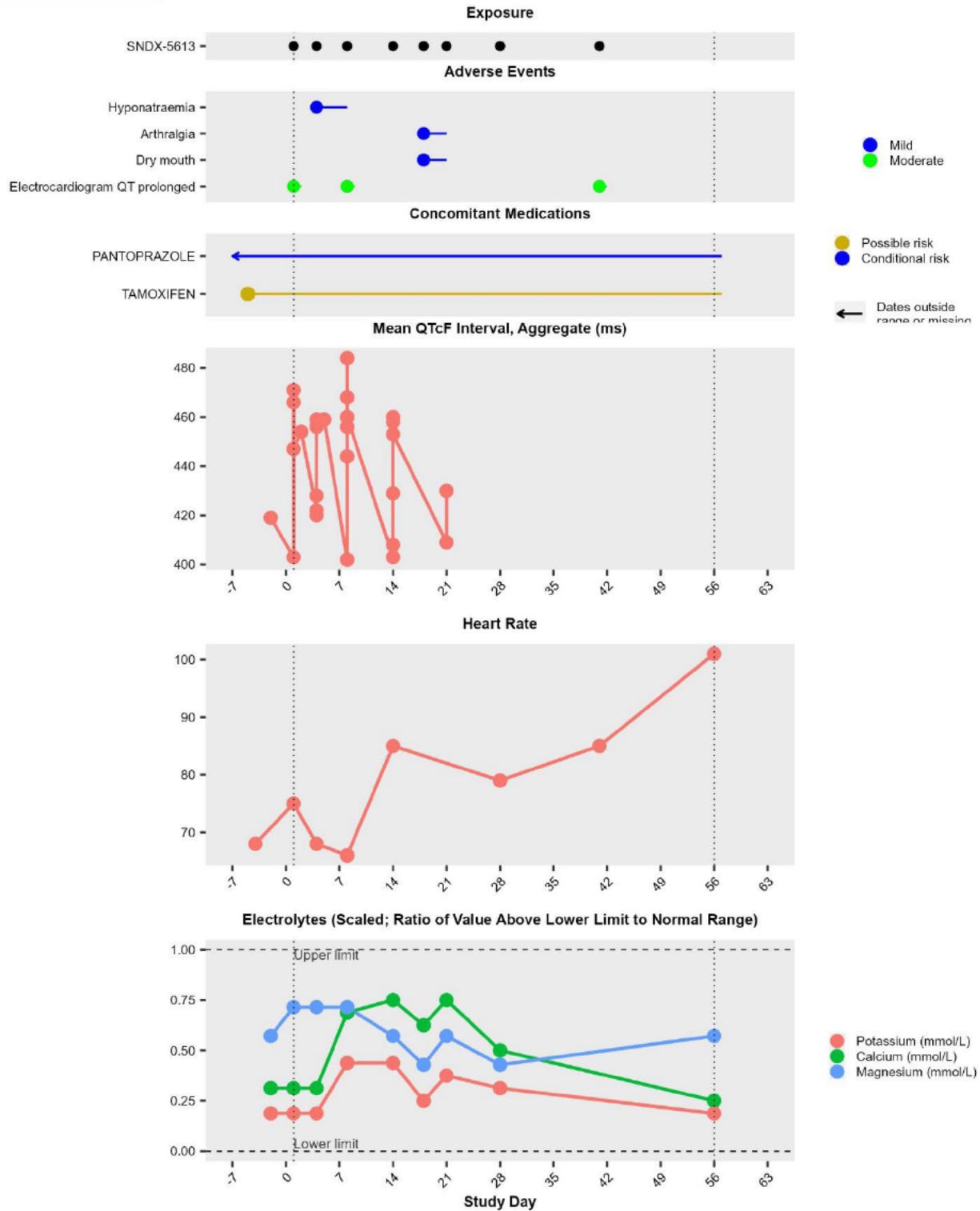
(b) (6) Age: 66; Gender: M; Race: ASIAN; TRT01A: Arm A: 276 mg Q12H



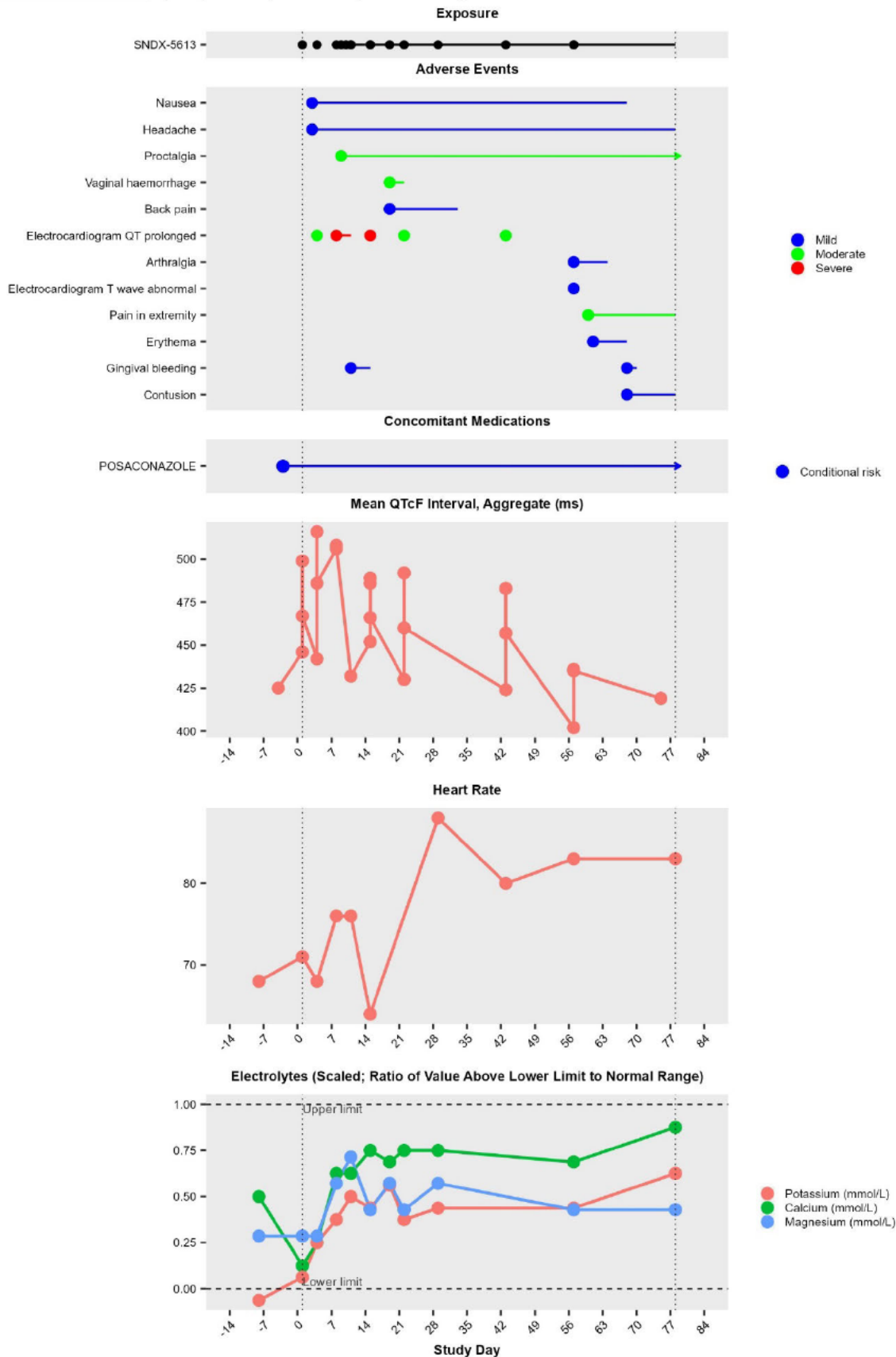
(b) (6), Age: 63; Gender: F; Race: ASIAN; TRT01A: 163 mg Q12H



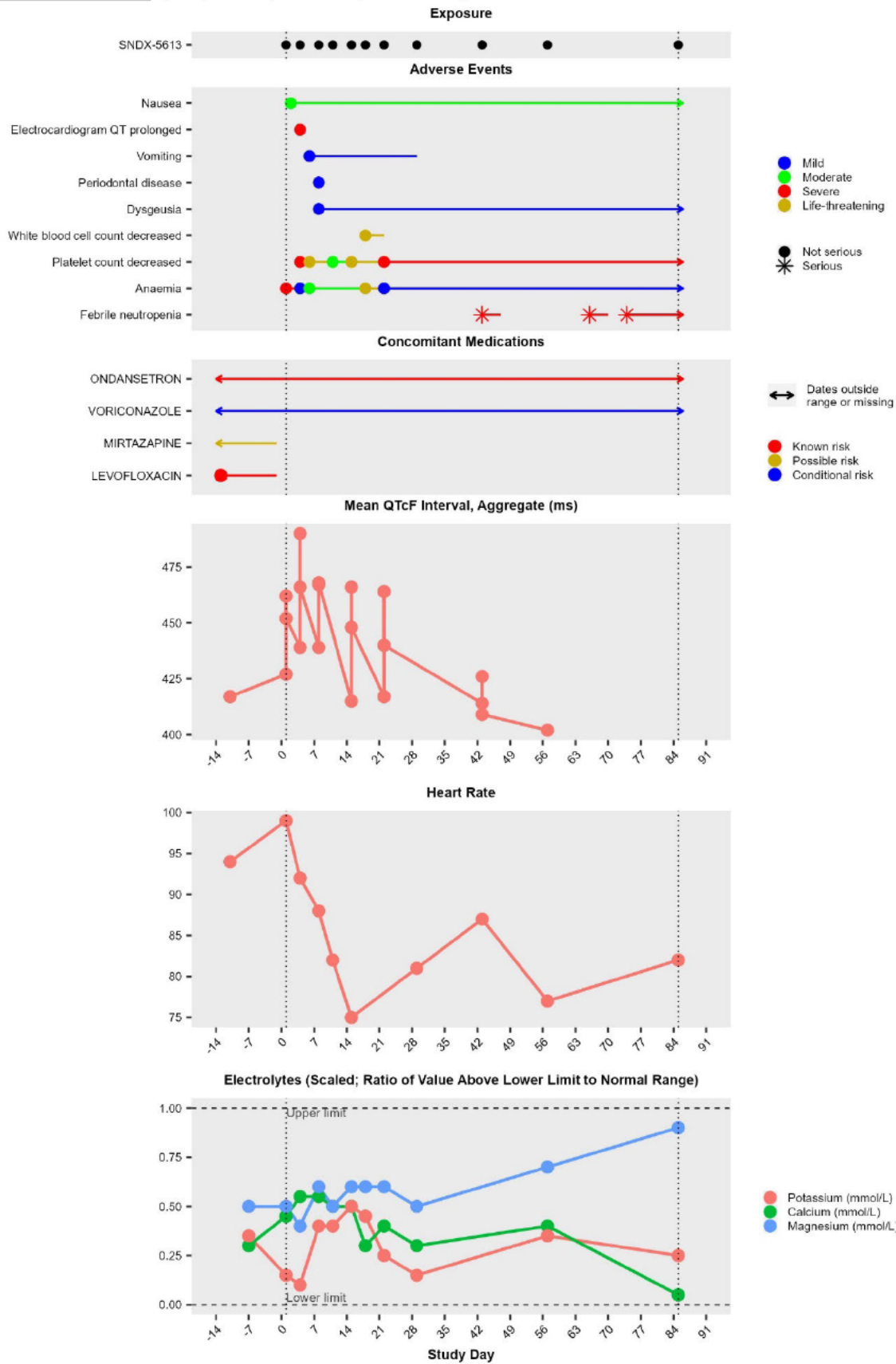
(b) (6), Age: 50; Gender: F; Race: ASIAN; TRT01A: Arm A: 276 mg Q12H



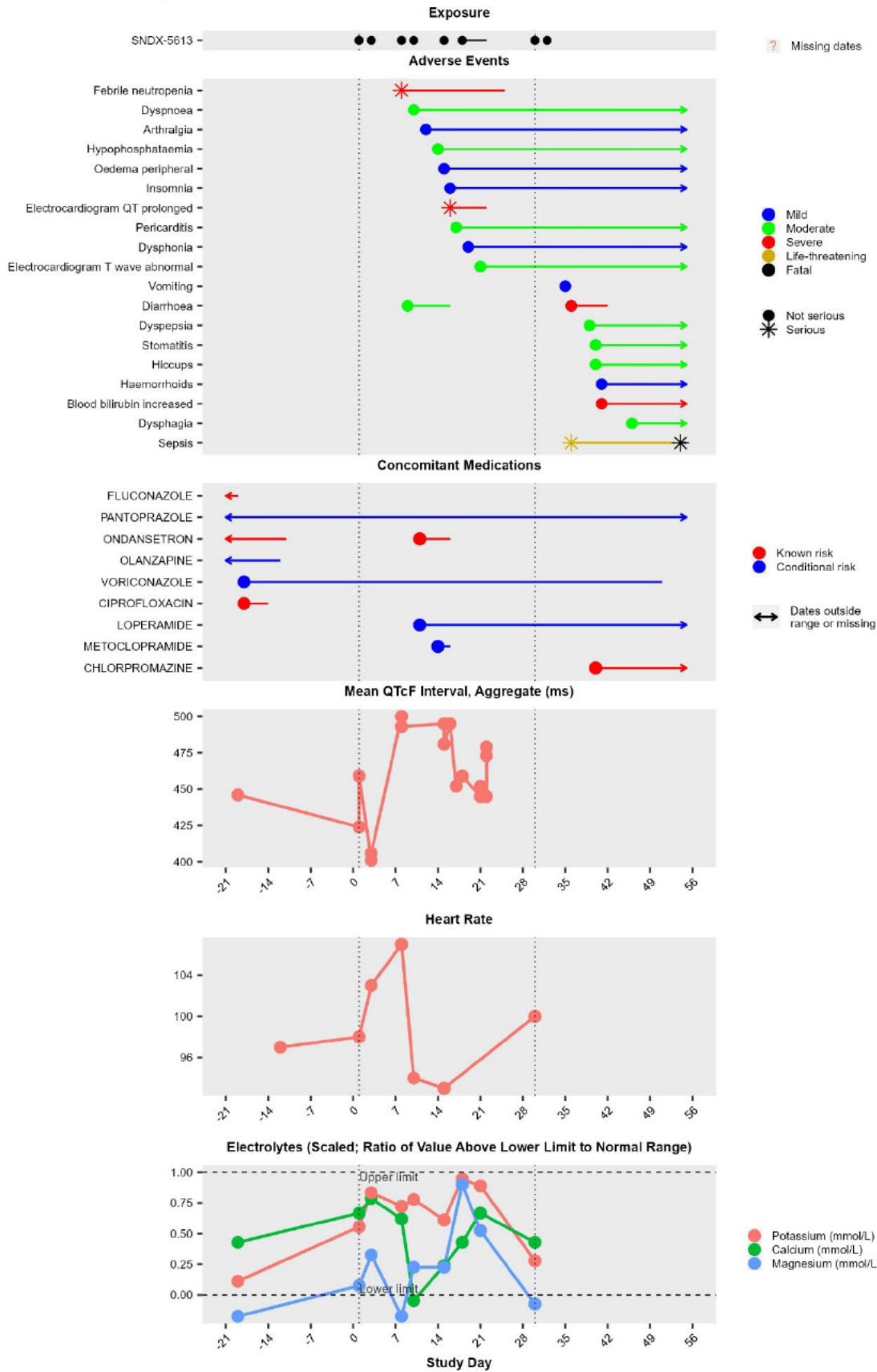
(b) (6) Age: 22; Gender: F; Race: ASIAN; TRT01A: 163 mg Q12H



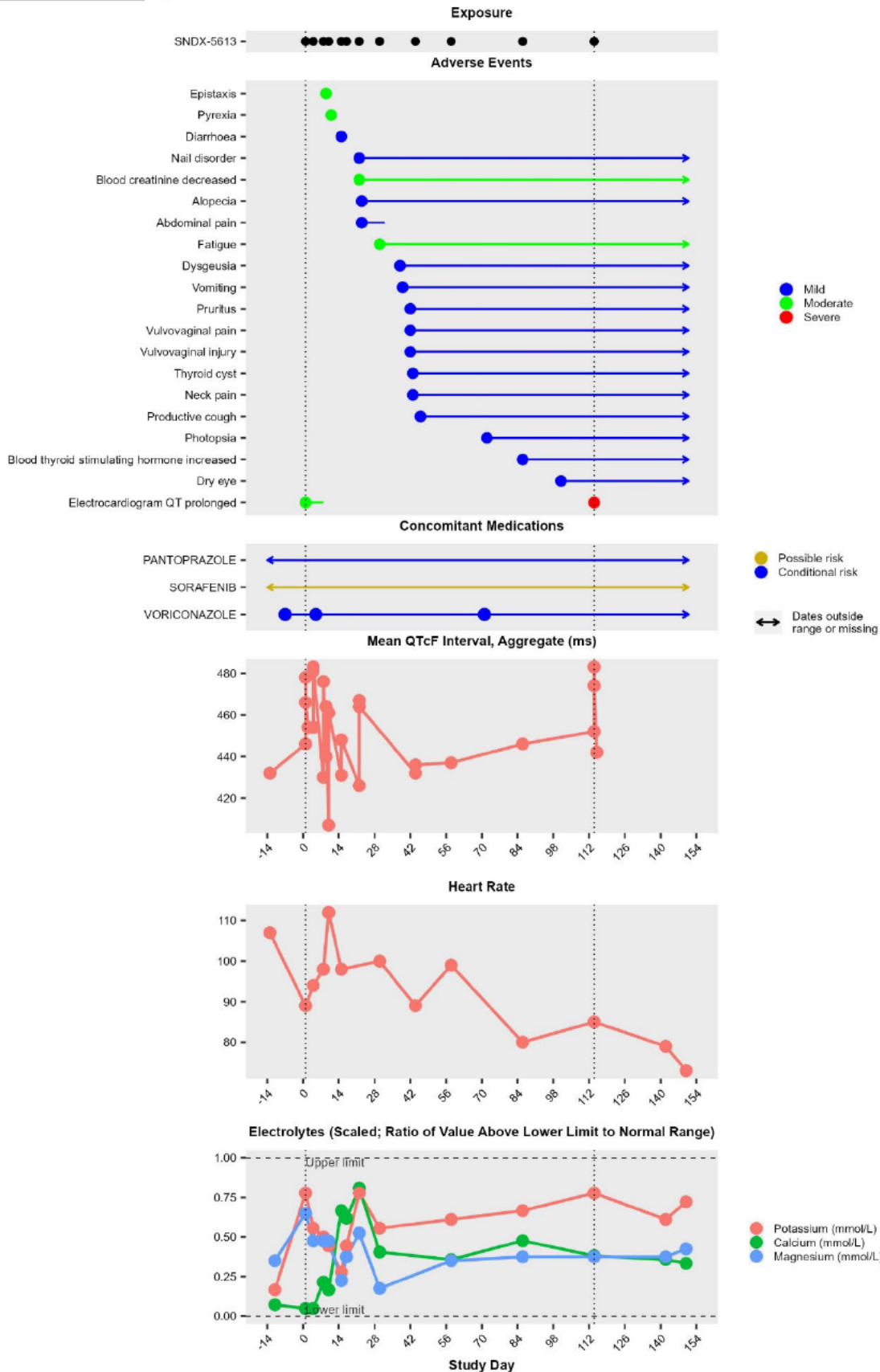
(b) (6) Age: 49; Gender: F; Race: ASIAN; TRT01A: 163 mg Q12H



(b) (6) Age: 71; Gender: M; Race: ASIAN; TRT01A: 163 mg Q12H



(b) (6) Age: 63; Gender: F; Race: ASIAN; TRT01A: 163 mg Q12H



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/s/

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LARS JOHANNESSEN
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CLINICAL INSPECTION SUMMARY

Date	August 29, 2024
From	Anthony Orencia, M.D., Ph.D., F.A.C.P., Senior Physician Min Lu, M.D., M.P.H., Medical Team Leader Jenn Sellers, M.D., Ph.D., F.A.A.P., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Chatchada Karanes, M.D., Clinical Reviewer Donna Przepiorka, M.D., Ph.D. Clinical Team Leader Rachel McMullen, MPH, MHA, Senior Regulatory Health Project Manager R. Angelo de Claro, M.D., Division Director Division of Hematologic Malignancy I Office of Oncology Drugs
NDA	NDA 218944
Applicant	Syndax Pharmaceuticals, Inc.
Drug	Revuforj™ (revumenib)
NME	Yes
Classification	Mutation KMT2A rearrangements, menin inhibitors
Proposed Indications	Treatment for adult and pediatric patients with relapsed or refractory acute leukemia with a KMT2A rearrangement.
Review Type	Priority Review
Consultation Request Date	February 7, 2024
Summary Goal Date	September 16, 2024
Action Goal Date	September 19, 2024
PDUFA Date	September 26, 2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study SNDX-5613-0700 were submitted to the Agency in support of a New Drug Application, for revumenib as proposed treatment for adult and pediatric patients with relapsed or refractory acute leukemia with a KMT2A rearrangement.

Four clinical investigators (Drs. Stein, Thirman, Issa, and Aldoss) and the sponsor, Syndax Pharmaceuticals, Inc., were inspected.

Based on the inspection results, the study data derived from the above clinical investigator sites and the sponsor's oversight appear to be acceptable. In general, the clinical data submitted to the Agency for assessment are acceptable in support of the proposed indication.

II. BACKGROUND

Revumenib (SNDX-5613) is a small molecule inhibitor of the binding of menin to wild-type (wt) lysine methyltransferase 2A (KMT2A) and KMT2A fusion proteins. It is being developed by Syndax Pharmaceuticals, Inc. (Syndax) for the treatment of adult and pediatric patients with relapsed or refractory (R/R) acute leukemias with a KMT2A rearrangement. Therapeutic alternatives to address AML mutations KMT2A rearrangements and NPM1 mutations, such as targeted menin inhibitors, could potentially involve 40% to 50% of all acute myeloid leukemias. Cellular programs hijacked by KMT2A rearrangements and NPM1 gene changes require menin, a compound that binds to the protein produced by KMT2A, called MLL1. The complex formed by these proteins binds to chromatin, and aberrant cellular communication pathways. Menin inhibitors stop the genes affected by the altered KMT2A or NPM1 from being expressed in the first place.

The Sponsor submitted data from Study SNDX-5613-0700 to support the proposed indication of revumenib for treatment of adult and pediatric patients with relapsed or refractory acute leukemia with a KMT2A rearrangement.

Study SNDX-5613-0700

Study SNDX-5613-0700 is an ongoing, multicenter, Phase 1 to Phase 2, open-label, dose-escalation and expansion study. Each phase of the study consisted of a screening period, treatment period and follow-up period, including an end-of-treatment visit (within seven days of the last dose), a safety follow-up visit (within 30 + 5 days of the last dose) and a survival follow-up or study termination visit.

Patients who were 30 days or older with relapsed/refractory acute leukemia were eligible for inclusion in the study, including those with KMT2 rearrangement. Patients with active diagnosis of acute promyelocytic leukemia, or active central nervous system disease were excluded. Patients with presence of central nervous system disease at their most recent relapse could be included if “cleared” prior to enrollment. Patients who developed post-transplant relapse were able to enroll as early as 60 days after prior hematopoietic stem cell transplant.

After Amendment #12 (April 14, 2022) of the study protocol, all patients were required to have a white blood count below 25,000/ μ L at the time of enrollment.

Throughout the study, the Safety Review Committee and Independent Data Monitoring Committee monitored safety and efficacy parameters as specified in the Charters.

Phase 1:

Patients in Arm A and Arm B must have had active acute leukemia with KMT2 rearrangement or NPM1 mutation, meeting criterion for full hematologic relapse (bone marrow blasts at least 5% or reappearance of blasts in peripheral blood).

Patients in Arm C through Arm F must have had either active acute leukemia or acute leukemia, with KMT2 rearrangement, Nucleoporin 98 rearrangement, or NPM1 mutation with detectable disease in the bone marrow which did not meet criterion for active leukemia.

Phase 2:

Patients must have had documented relapsed/refractory acute leukemia, defined by presence of at least 5% blasts in the bone marrow and/or persistence or reappearance of blasts in peripheral blood:

- Cohort 2A: Documented R/R ALL/MPAL with KMT2 rearrangement
- Cohort 2B: Documented R/R AML with KMT2 rearrangement
- Cohort 2C: Documented R/R AML with NPM1 mutation

Treatment was administered in 28-day cycles, with the first study drug dose, administered on treatment Cycle #1 Day #1 (C1D1) until disease progression or unacceptable toxicity.

For Phase 1, the primary objective for this study was to determine the safety, tolerability, maximum tolerable dose, and recommended Phase 2 dosing of revumenib in patients with relapsed/refractory acute leukemia in each of the arms studied. And, to characterize the pharmacokinetic parameters of revumenib and relevant metabolites in each of the arms studied.

For Phase 2, the primary objective for this study was to evaluate short- and long-term safety and tolerability of revumenib, and to assess the complete remission and complete remission with partial hematologic recovery.

In Phase 1, the study endpoints were assessed by dose level and overall, for each arm unless otherwise stated. No formal hypothesis testing was performed in Phase 1.

In Phase 2, the primary study endpoint was the combined treatment subject response in complete remission and complete remission with partial hematologic recovery and continued comprehensive subject safety assessment.

For Phase 1, 11 study sites enrolled patients in the United States only. For Phase 2, 22 study sites enrolled patients in 5 countries (Australia, Canada, France, the Netherlands, and the US).

For Phase 1, first patient enrolled on November 5, 2019. For Phase 2: first patient enrolled on October 1, 2021. The interim analyses were based on a database cut-off date of July 24, 2023.

III. RESULTS

1. Eytan Stein, M.D. /Site #01

530 E. 74th Street
New York, NY 10021-3459

Inspection dates: March 25 - 29, 2024

For Phase I study, 43 subjects were screened; 34 subjects were enrolled and received treatment, and one subject withdrew from study. Phase II study was open, 27 subjects were screened; 12 subjects enrolled, and the study was ongoing at the time of the inspection. The enrolled subjects' records were reviewed.

Records reviewed for the study comprised the electronic source records, regulatory documentation, inclusion/exclusion criteria, adverse events and serious adverse events, physical exams, review of informed consent forms, primary efficacy endpoints, and the investigational agent accountability record (b) (4)

The primary efficacy endpoint was verifiable.

No discrepancies were noted after a comprehensive review to all reported adverse events and serious adverse events. There was no evidence of under-reporting of adverse events.

The study data derived from Dr. Stein's site are considered acceptable.

2. Michael Thirman, M.D. /Site #04

5841 South Maryland Ave., MC 2115
Chicago, IL 60637

Inspection dates: April 2 – 9, 2024

For the Phase I study, 11 subjects were screened; 8 subjects were enrolled and received on-study treatment.

For the Phase II study, 20 subjects were screened; 13 subjects were enrolled and received on-study treatment.

Source records for all enrolled subjects (8 subjects in Phase I and 13 subjects in Phase II) were reviewed, including printed medical records in the subjects' binders and the medical data recorded in (b) (4) the electronic medical record deployed on site.

Records reviewed for the study comprised study protocol and amendments, institutional review board and regulatory authority approvals/acknowledgments, correspondence, regulatory documents, investigational product accountability records, informed consent forms, the electronic medical record, subject binders, adverse events and serious adverse events reporting, and the primary efficacy data.

The primary efficacy study endpoint was verifiable.

The inspection noted that the following adverse events and corresponding start dates were not recorded in the electronic data capture form, or that information about adverse events needed to be revised in the electronic data capture form:

- Subject (b) (6); cerebrovascular accident (b) (6); obstructive hydrocephalus (b) (6); hypotension (b) (6); hyponatremia (b) (6); dysphagia (b) (6)
- Subject (b) (6); aspergillus pneumonia (b) (6)
- Subject (b) (6); bilateral intraretinal hemorrhages in temporal periphery (b) (6); shakiness (b) (6); syncope (b) (6)
- Subject (b) (6); decreased platelet count, intermittent (b) (6); decreased neutrophil count, intermittent (b) (6)

The above adverse events were provided electronically to the sponsor after this site inspection.

Reviewer's comments:

The site conducted voluntarily a data comparison between the source adverse event log records and the electronic data capture, as part of its corrective action. After the FDA inspection, the site contacted the marketing sponsor and updated the aforementioned information, for these adverse events not reported or missed by the clinical site. The review division may consider including the above adverse events in the safety evaluation.

3. Ghayas Issa, M.D./Site #07

1515 Holcombe Boulevard
Houston, TX 77030

Inspection dates: March 11-14, 2024

There were 78 subjects screened; 56 subjects were enrolled and received study treatment; 1 subject withdrew, and 42 subjects completed the study. Subjects' records were reviewed for 21 subjects in Phase 1. The Phase 2 study was open and enrolling study subjects at the time of the inspection. All enrolled subjects' records were reviewed in this ongoing Phase 2 study.

FDA inspection comprised evaluation of the following documents: informed consent forms, monitoring logs, delegation logs, enrollment logs, Institutional Review Board correspondence and approvals, sponsor correspondence, adverse events, serious adverse events, electronic medical records, electronic case report forms, investigational product, accountability records, and source documentation.

The primary efficacy endpoint was verifiable.

No discrepancies were noted after a comprehensive review to all reported adverse events and serious adverse events. There was no evidence of under-reporting of adverse events.

In general, the inspection verified adequate source data for the inspected study subjects.

4. Ibrahim Aldoss, M.D. /Site #09

1500 East Duarte Road
Duarte, CA 91010

Inspection dates: April 29 -May 3, 2024

There were 48 subjects screened; and 35 subjects were enrolled. The study was ongoing at the time of the inspection. No subjects completed the study. For an entire complete treatment file folder, there was one study subject (b) (6) whose comprehensive records were reviewed. Further, a targeted review of six study subjects' records were conducted (b) (6) (b) (6).

FDA inspection at this site comprised a review of available documents such as reporting of the clinical trial data, specifically consenting, eligibility, dosing administration, adverse events, bone marrow biopsy, laboratory tests for blasts, hemoglobin, leukocytes, and platelets.

Source documents and case report forms (where applicable) were comparable to sponsor line listings with respect to reported adverse events, protocol deviations, reported concomitant medications (relevant to screening), and subject study status. No discrepancies were noted.

The primary efficacy study endpoint was verifiable. There was no underreporting of nonserious or serious adverse events.

In general, the inspection verified adequate source data for the inspected study subjects, with no significant deficiencies reported.

5. Sponsor

Syndax Pharmaceuticals, Inc.
730 3rd Avenue – (9th Floor)
New York, NY 10017

Inspection dates: August 19 - 22, 2023

The sponsor inspection involved a comprehensive review of selection and monitoring of clinical investigators, selection of monitors, monitoring procedures and activities, quality assurance, reporting to FDA of significant adverse effects/safety oversight, data collection and handling, financial disclosure, and electronic records.

Monitoring files were reviewed during the inspection, in general, were found to be adequate. Procedure and documents for reviewing and processing of adverse and serious adverse events were evaluated. No discrepancies were observed for adverse event reporting.

Sponsor's documents were reviewed for the monitoring files of sites #01, #04, #09 and #32. The inspection found that sponsor monitoring for these study sites to be adequate.

Based on the preliminary inspection results, the sponsor's oversight and monitoring of this clinical study appear to be acceptable. An amendment will be made, if there are significant changes in final inspection report.

{See appended electronic signature page}

Anthony Orencia, M.D., Ph.D., F.A.C.P.
FDA Senior Physician
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Min Lu, M.D., M.P.H.
Medical Team Leader
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CONCURRENCE:

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Jenn Sellers, M.D., Ph.D., F.A.A.P.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

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JENN W SELLERS
08/29/2024 03:36:40 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 218944 / (b) (4)
Submission Number	008, 009 / (b) (4)
Submission Date	12/22/2023
Date Consult Received	1/8/2024
Drug Name	Revumenib, SNDX-5613
Indication	Adult and pediatric patients with relapsed or refractory acute leukemia with a KMT2A rearrangement
Therapeutic Dose	270 mg BID without and 160 mg BID with strong CYP3A4 inhibitors
Clinical Division	DHM1
Protocol Review	Link from DARRTS

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

This review responds to your consult dated 1/8/2024 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review dated [12/08/2020](#), [07/20/2021](#), [09/07/2021](#), [06/01/2022](#), [12/07/2022](#), [04/11/2023](#), [06/22/2023](#) under IND 142693 in DARRTS;
- Clinical study report for study SNDX-5613-0700 (NDA218944 / SN0008; [link](#));
- CQT report for study SNDX-5613-0700 (NDA218944 / SN0008; [link](#));
- PK report for study SNDX-5613-0700 (NDA218944 / SN0008; [link](#));
- Protocol for study SNDX-5613-0700 (NDA218944 / SN0004; [link](#));
- Drafted label (NDA218944 / SN0009; [link](#)); and
- Summary of clinical pharmacology, including highlights of clinical pharmacology and cardiac safety (NDA218944 / SN0009; [link](#)).

1 SUMMARY

Revumenib is associated with concentration dependent QTc prolongation in study SNDX-5613-0700 — see Table 1 for overall results.

The clinical study SNDX-5613-0700 was a phase 1/2, open-label, dose escalation and dose expansion study of SNDX-5613 in patients with relapsed/refractory leukemia. The highest dose covers high clinical exposure for revumenib and clinical exposure for metabolite M1. Data were analyzed using exposure-response analysis as the primary analysis, which suggests that revumenib is associated with large mean increases in the QTcF interval (refer to section 4.5). The findings of the primary analysis are further

supported by nonclinical studies (section 3.1.2), by-time analysis (section 4.3), and categorical analysis (section 4.4).

In Cohort 2A + 2B, the pivotal safety population, 94 patients with relapsed or refractory acute leukemia with KMT2Ar received at least one dose of revumenib. Twenty-nine subjects (31%) reported treatment emergent adverse events of electrocardiogram QTc prolonged/torsade de pointe (customized query). Five subjects (5%) experienced serious adverse events (SAE) (preferred terms: syncope [2], death, sudden death, and electrocardiogram QT prolonged) and two were fatal (death and sudden death). The SAE of electrocardiogram QT prolonged was likely related to the study drug. The relatedness of the other four events were confounded by disease progression and cardiac history (section 4.6). No ventricular arrhythmias were reported.

Table 1: Summary of findings

Table 15 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 geometric mean Cmax (PK dataset) is 2470 ng/mL for revumenib and 619 ng/mL for M1 following therapeutic dose of revumenib 270 mg BID oral tablet without strong CYP3A4 inhibitors. - The high clinical exposure scenario is co-administration of revumenib 160 mg BID oral tablet with strong CYP3A4 inhibitors (geometric mean Cmax is 2880 ng/mL for revumenib and 423 ng/mL for M1). - The highest Cmax (PK-ECG dataset) in study SNDX-5613-0700 was 3552 ng/mL for revumenib in Phase 1 Arm B following 226 mg BID with strong CYP3A4 inhibitors and was 510 ng/mL for M1 in Phase 2 Cohort 2C following 163 mg BID with strong CYP3A4 inhibitors. They cover clinical and high clinical exposure for revumenib and clinical exposure for M1. - Predictions of ΔQTcF following proposed therapeutic regimen are shown in below table. Predictions are made at plasma concentrations of revumenib and M1 at Tmax of either revumenib or M1, whichever resulted in higher ΔQTcF. <table><tr><th>ECG parameter</th><th>Treatment</th><th>Revumenib Concentration</th><th>M1 Concentration</th><th>ΔQTcF (msec)</th><th>90% CI (msec)</th></tr><tr><td>QTcF</td><td>276 mg BID without strong CYP3A4i</td><td>2060</td><td>619 (Cmax)</td><td>22.0</td><td>(18.0 to 26.0)</td></tr><tr><td>QTcF</td><td>163 mg BID with</td><td>2880 (Cmax)</td><td>383</td><td>17.7</td><td>(15.0 to 20.4)</td></tr></table>						ECG parameter	Treatment	Revumenib Concentration	M1 Concentration	ΔQTcF (msec)	90% CI (msec)	QTcF	276 mg BID without strong CYP3A4i	2060	619 (Cmax)	22.0	(18.0 to 26.0)	QTcF	163 mg BID with	2880 (Cmax)	383	17.7	(15.0 to 20.4)
ECG parameter	Treatment	Revumenib Concentration	M1 Concentration	ΔQTcF (msec)	90% CI (msec)																			
QTcF	276 mg BID without strong CYP3A4i	2060	619 (Cmax)	22.0	(18.0 to 26.0)																			
QTcF	163 mg BID with	2880 (Cmax)	383	17.7	(15.0 to 20.4)																			

		strong CYP3A4i					
In vitro/in vivo findings	Integrated assessment was not conducted.						

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

- In the sponsor's (b) (6) the predicted change from baseline QTcF (Δ QTcF) is based on the population-PK model predicted steady state C_{max}. The reviewer's independent analysis determined that observed steady state mean C_{max} values were similar to the predicted values for subjects on revumenib 276 mg BID without strong inhibitors and 163 mg BID with strong inhibitors. But there was significant discrepancy between model predicted versus observed steady state C_{max} values in subjects receiving revumenib 276 mg BID with moderate CYP3A4 inhibitors. Therefore, the reviewer's predicted Δ QTcF (Table 1 and Section 4.5.1) are based on observed steady state C_{max}.
- For safety analysis, we focused on Cohort 2A + 2B, (b) (6) which included 149 patients with relapsed or refractory acute leukemia treated with revumenib at the recommended dosage in study SNDX-5613-0700 (safety population 2). Safety population 1 is a subset of population 2. Safety population 2 had numerically higher incidence of QTc prolongation/TdP events (customized query); however, the profiles were similar between the two populations (see section 4.6). No ventricular arrhythmias were reported in safety population 2.
- Our suggestions for labeling and additional labeling comments for the Division are presented below in Section 2.2.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SN0009 ([link](#)) from the CS-IRT.

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

5 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Syndax Pharmaceuticals submitted revumenib under NDA 218944 for the oral tablet (b) (4). Revumenib (SNDX-5613, MW: 804.93) is a menin inhibitor indicated for the treatment of adult and pediatric patients with relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) rearrangement. The recommended dose is by weight (b) (4) (Table 2). Frequently, azole antifungals (CYP3A4 inhibitors) are concomitantly administered as prophylaxis for management of fungal infection.

Table 2. Recommended Dosing for Revumenib

(b) (4)			
(b) (4)	< 40 kg	160 mg/m ² BID	95 mg/m ² BID
(b) (4)	≥ 40 kg	270 mg BID	160 mg BID

In this submission, the sponsor submitted final results of their QTc evaluation using data from study SNDX-5613-0700.

Study SNDX-5613-0700 was a first in human, phase 1/2, open-label, dose-escalation and dose-expansion cohort study (Table 3) of SNDX-5613 in patients (age ≥30 days) with relapsed/refractory leukemias. The formulation used in this study was planned to be immediate-release capsule (25 and 113 mg free base equivalents) and oral solution (F1 & F2: 50 mg/mL free base equivalents) containing SNDX-5613 ((b) (4) form). Doses were administered in a 28-day cycle. Triplicate ECGs and PK collection time points were planned to be the same during the Phase 1 and Phase 2 portions but different for patients with weight ≥ 7 kg or < 7 kg (12/07/2022). The dose escalation phase was halted at Arm A 339 mg Q12H without and Arm B 226 mg Q12H with a strong CYP3A4 inhibitor due to DLTs of QT prolongation. The sponsor continued exploring the higher dose levels expecting to identify optimal doses and the study continued with intensive ECG monitoring and appropriate risk mitigation plan (12/08/2020). The sponsor's PK/ECG data confirmed that SNDX-5613 is a QTc prolonger and it exhibits a concentration-dependent QTc prolongation. We agreed to limit ECG monitoring to be around Tmax (07/20/2021). Subsequently, Arm A 276 mg Q12H without and Arm B 163 mg Q12H with a strong CYP3A4 inhibitor were selected to be the maximum dose continued into the phase 2 study based on acceptable safety and efficacy profile (09/07/2021). Since the sponsor's in vitro hERG assay indicated that M1 metabolite also contributed significantly to the QTc prolongation effect, the sponsor included M1 metabolite in future assessment. The sponsor also intended to utilize the monohydrate monohydrate form (MW: 840.95) for immediate-release tablet (25 mg, 110 mg, and 160 mg free base equivalents) (b) (4).

formulation in future clinical studies (06/01/2022). Capsules, tablets, and oral solution formulations were all used in study SNDX-5613-0700. Phase 1 subjects who were ≥ 16 years old and have not received the first dose of study drug on C2D1 when the SNDX-5613 tablet formulation was available took part in a capsule versus tablet evaluation. In addition, approximately 12 patients ≥ 16 years old who enrolled into Arm A, D, E, or F were required to take part in a food effect evaluation during which they received a low-fat breakfast 30 minutes prior to dosing on either C1D8 or C1D15 and needed to complete the breakfast prior to dosing.

The CS-IRT reviewed the QT assessment proposal and SAP (06/01/2022, 12/07/2022, 04/11/2023, 06/22/2023). Overall, the proposed study design and analysis plan appeared acceptable to exclude mean increases >20 msec in the QTc interval. See review on 12/07/2022 for more details. The primary analysis was concentration-QTc analysis using the white paper model. Three models were explored: (A) model with both analytes of SNDX-563 and M1 (B) model with SNDX-563 alone, and (C) metabolite M1 alone. Baseline was defined as the average of pre-dose on Cycle 1 Day 1. We noted the lack of matching ECG and PK data at Tmax of parent (1 hr post dose) and metabolite (3 hr post dose) and denoted this as a review issue. We also noted that ECGs were initially collected with site owned ECG devices and were recorded on paper (12/07/2022). The sponsor explained that digital collection of ECGs did not begin until well into Phase 1 dose escalation. We agreed with the sponsor's proposed approach to read/measure all digitally acquired and digitized ECGs centrally (04/11/2023).

The sponsor's concentration-QTc model used pooled data from Phase 1 and Phase 2. Inclusion of data from Phase 2 was added to version 2.0 of SAP (06/22/2023). All patients in Phase 2 received concurrent strong CYP3A4 inhibitors. Data from food effect evaluation under fed condition were not included.

In the reviewer's analysis, concentration-QTc was based on pooled data from Phase 1 and Phase 2 excluding Phase 1 Arm C (cobicistat), Arm D (food effect), Arm E (isavuconazole) and anyone from the other cohorts who received isavuconazole, ketoconazole, or cobicistat during treatment period.

By-time analysis was performed on Phase 2 data and was shown for cohort 2A + 2B only; unscheduled ECGs were not included in this analysis. Categorical analysis was performed (b) (4) Safety analysis was performed (b) (4). We also conducted sensitivity analysis using only automatic ECG measurements. Please see section 4 for more details.

Table 3. Study SNDX-5613-0700 Treatment Arms

Phase	Arm	Dose of revumenib (under fasting condition except for T1D dosing)
Dose Escalation	A: No strong CYP3A4 inhibitors	113 mg Q12H (n = 1), 226 mg Q12H (n = 11), 276 mg Q12H (n=16), 339 mg Q12H (n=8)

	B: Strong CYP3A4 inhibitors (itraconazole, ketoconazole, posaconazole, or voriconazole)	113 mg Q12H (n=16), 163 mg Q12H (n=8), 226 mg Q12H (n=7)
	C: Strong CYP3A4 inhibitors (cobicistat starting C1D2)	113 mg Q12H (n=10), 163 mg Q12H (n=13), 226 mg Q12H (n=6), 276 mg Q12H (n=2)
	D: Moderate CYP3A4 inhibitor (fluconazole)	163 mg Q12H (n=6), 226 mg Q12H (n=5)
	E: No CYP3A4 inhibitors/inducers	163 mg TID <i>with food</i> (n=5)
	F: Moderate CYP3A4 inhibitor (isavuconazole)	226 mg Q12H (n=3)
Dose Expansion	2A: KMT2Ar ALL/MPAL	163 mg Q12H (n=14)
	2B: KMT2Ar AML	163 mg Q12H (n=71)
	2C: NPM1mut AML	163 mg Q12H (n=28)

Abbreviation: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; KMT2Ar, lysine methyltransferase 2A gene rearrangement; MPAL, mixed phenotype acute leukemia; NPM1mut, Nucleophosmin 1 mutation.

3.1.1 Clinical pharmacology

Revumenib was the major component in the plasma (61% to 71%, based on total area response by mass spectrometry). The major metabolite in human plasma is M1 (6.1% to 25.9%, N-deethylation). CYP3A4 metabolism is the major metabolic pathway of revumenib elimination.

According to the sponsor, the steady state geometric mean (%GeoCV) C_{max} following 276 mg (capsule) Q12H without a strong CYP3A4 inhibitor was 2052 (78.9) ng/mL (n = 11) for parent and 549 (51) ng/mL (n = 9) for M1 (study 0700 phase 1, on C1D8). The geometric mean (%GeoCV) C_{max} following 163 mg Q12H with a strong CYP3A4 inhibitor was 3220 (33.8%) ng/mL (n = 63) for parent and 464 (59) ng/mL (n = 60) for M1 (study 0700 phase 2, on C1D8) (see [summary of clinical pharmacology](#)). The reviewer's analysis showed similar numbers (see Table 4). T_{max} ~ 1 hour for parent and ~3 hours for M1.

Based on population-PK (pop-PK) analysis, age, sex, race, mild to moderate renal impairment or hepatic impairment did not have a significant impact on PK.

There was no clinically meaningful effect of food on the PK of revumenib and M1 based on PK analysis in patients administered revumenib with a low-fat meal.

Based on pop-PK analysis, moderate CYP3A4 inhibitors had no clinically significant effect on revumenib and M1 exposure; strong CYP3A4 inhibitors (posaconazole, itraconazole, and voriconazole) increased the revumenib AUC and C_{max} by 2-fold and had no significant effect on M1 exposure; cobicistat increased the revumenib AUC and

C_{max} by 2.5-fold and decreased the M1 exposures by 96%. Doses will be modified when co-administered with strong CYP3A4 inhibitors (Table 2).

Based on PBPK model, co-administration of rifampin (strong CYP3A4 inducer) is predicted to decrease revumenib C_{max} by 4-fold and increase M1 C_{max} by 1.8-fold. Concomitant use of strong or moderate CYP3A4 inducers should be avoided according to label but is not contraindicated. This exposure is outside of the range of the QTc assessment.

There was no clinically meaningful effect of formulation (tablet vs. capsules vs. oral solution) on the PK of revumenib and M1. The dose strengths of the capsule and tablet (e.g., 113 mg capsule vs. 110 mg tablet) formulations are considered equivalent.

The PBPK model was used to predict the PK of revumenib in pediatric cancer patients following multiple oral doses of 160 mg/m² for 14 days. Results of simulations suggest similar revumenib exposure in pediatric patients aged (b) (4) to 16 years to adults when dosed on a mg/m² basis. (b) (4)

Table 4: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen¹	270 mg BID without strong CYP3A4 inhibitors, oral tablet, fasted or with low-fat meal.	2470 ng/mL for revumenib and 619 ng/mL for M1 (Study 0070 Phase 1 Arm A 273 mg BID)
High clinical exposure scenario¹	For revumenib: 160 mg BID with cobicistat, oral tablets	3390 ng/mL for revumenib and 18 ng/mL for M1 (Study 0070 Phase 1 Arm C 163 mg BID + cobicistat)
	160 mg BID with strong CYP3A4 inhibitor (posaconazole, itraconazole, and voriconazole), oral tablet	2880 ng/mL for revumenib and 423 ng/mL for M1 (Study 0070 Phase 1 Arm B and Phase 2A+2B+2C)
	For M1: 270 mg BID with strong CYP3A4 inducer (4-fold decrease for parent and 1.8-fold increase for M1)	617 ng/mL for revumenib and 1114 ng/mL for M1
Highest dose in QT assessment	For revumenib: Phase 1 Arm B 226 mg Q12H, with strong CYP3A4 inhibitor ²	3552 ng/mL for revumenib and 352 ng/mL for M1 on C1D7/8

For M1: Phase 2 Arm 2C 2667 ng/mL for revumenib
163 mg Q12H, with strong and 510 ng/mL for M1 on
CYP3A4 inhibitors³ C1D7/8

C_{max} Ratio

For revumenib: 1.4-fold of clinical exposure and 1.0-fold of high clinical exposure

For M1: 0.8-fold of clinical exposure and 0.5-fold of high clinical exposure

¹ C_{max} calculated by reviewer based on PK dataset (ADPC)

² Dose corresponds to the maximum C_{max} for revumenib in arms included in the reviewer's QTc assessment with more than 3 subjects based on the PK-ECG dataset (QTPK).

³ Dose corresponds to the maximum C_{max} for M1 in arms included in the reviewer's QTc assessment with more than 3 subjects based on the PK-ECG dataset (QTPK).

3.1.2 Nonclinical Safety Pharmacology Assessments

SNDX-5613 inhibited hERG channel activity with IC₅₀ values of 15.1, 10.58, and 22.9 μM in the non-GLP assays and 4.75 μM in the GLP assay. Although the mean IC₅₀ value from the GLP assay was 2- to 5-fold lower than those in other assays, the 95% confidence limits encompassed the IC₅₀ value from the non-GLP assays. *The IC₅₀ for hERG inhibition is therefore 4.75 μM, which is approximately 13-fold higher than the steady-state unbound C_{max} of 0.4 μM at the recommended dose of 270 mg Q12H.*

Inhibition of hERG channel current was also observed with the primary metabolite M1 as it significantly reduced the current amplitude from the 1 μM application. *The IC₅₀ was determined to be 3.46 μM, which is approximately 6-fold higher than the steady-state unbound M1 C_{max} of 0.6 μM at the recommended dose of 270 mg Q12H.*

The acute effect of orally administered SNDX-5613 on cardiovascular function was assessed in a non-GLP study in beagle dogs (Study 2017-4272). Three beagle dogs per treatment group were dosed with SNDX-5613 at doses of 0 (vehicle control), 10, 50, 20, and 100 mg/kg (in that order). There were no treatment-related effects with SNDX-5613 on heart rate, blood pressure, or body temperature in this study. Following dosing, an increase in Van de Water-corrected QT interval (QTcV) duration compared to baseline was observed at all dose levels of SNDX-5613; the QTcV duration returned to near pre-treatment levels at approximately 15 hours post dosing. The QTcV interval was significantly increased at the higher doses of 50 and 100 mg/kg (73.8 and 94.4 ms, respectively), and smaller increases were found at the lower doses of 10 and 20 mg/kg (33.7 and 39.3 ms, respectively). The no-observed-effect level (NOEL) for QTc interval prolongation in this study was less than 10 mg/kg. An increase in frequency of premature atrial complexes with aberrant conduction was observed in most, but not all dogs with SNDX-5613 at dose levels of 20 mg/kg and greater. No adverse cardiac arrhythmias were observed in this study.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for revumenib was based on exposure-response analysis, please see section 3.2.3 for additional details.

Per sponsor's report, the by-time analysis was performed for each arm in Phase 1 separately (not pooled) and for each cohort in Phase 2 separately (not pooled). These analyses were performed using the corresponding QT/QTc populations. Unscheduled ECGs were not included in this analysis. The by-time point analysis for QTcF was based on a mixed model for repeated measurements (MMRM). Data from food effect evaluation under fed condition were excluded from the by-time analysis with statistical modeling. The by-time analysis demonstrated that SNDX-5613 produces a dose dependent QTc increase and had no clinically significant effect on heart rate, PR, and QRS.

In Phase 1 Arm A, the LS mean change-from-baseline QTcF (Δ QTcF) ranged from -20.9 ms in the 226 mg Q12H dose group on C4D1/D15 to 45.4 ms in the 339 mg Q12H dose group at 1 hour post-dose on C1D3/D4. In Phase 1 Arm C, LS mean Δ QTcF ranged from -21.2 ms in the 113 mg Q12H dose group on at 1 hour post-dose C2D15 to 27.4 ms in the 226 mg Q12H dose group at 2 hours post-dose on C1D1. During Phase 2, LS mean Δ QTcF ranged from -3.8 ms in Cohort 2B at pre-dose on C5D1 to 30.6 ms in Cohort 2C at 2 hours post-dose on C1D7/D8. During Phase 2 Cohort 2A, the mean Δ QTcF 2 hours post-dose ranged from 9.9 to 17.4 ms; while during Cohorts 2B and 2C, the mean Δ QTcF 2 hours post-dose ranged from 12.9 to 20.1 ms and from 6.6 to 30.6 ms, respectively.

Reviewer's comment: *The reviewer used non-parametric method to conduct the by-time analysis. The by-time analysis is shown for pooled data of Phase 2 Cohort 2A + 2B and unscheduled ECGs were not included in this analysis. The trend shown in by-time analysis from reviewer's analysis is similar to the trend shown in sponsor's by-time analysis. The significant QTc prolonging effect is observed. Please see section 4.3 for details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

The fully automated measurements from the ECG machine algorithm generated with the site collected paper ECGs were compared to the results of the Clario measurement technique in Phase 1 data using the QT/QTc population. The BA slope (QTcF of Clario minus automatic vs average QTcF) for all pooled data was -0.11 ms per 100 ms, which means Clario's measurement underestimate longer QTc intervals.

Reviewer's comment: *The sponsor's bias analysis did not show significant bias (absolute value of BA slope < 10 ms per 100 msec). The reviewer did not perform a bias assessment. Instead, a sensitivity analysis using automatic measurements was performed for concentration-QTc analysis.*

3.2.2 Categorical Analysis

The categorical analysis from the sponsor was performed for each arm in Phase 1 separately (not pooled) and for each cohort in Phase 2 separately (not pooled). For Phase 1 portion of the study, the analysis included the food effect evaluation part and the non-food effect part in each arm, separately. These analyses were performed using the corresponding QT/QTc populations. Unscheduled ECGs were included in this analysis.

In the Phase 1 cohorts, 1 subject each in Arm B 113 mg Q12H and 226 mg Q12H and Arm D 226 mg Q12H had an absolute QTcF > 500 msec. ΔQTcF increases from baseline > 60 ms were observed in multiple treatment arms. During Phase 2, 10 subjects (14.1%) in Cohort 2B and 8 in Cohort 2C (28%) had an absolute QTcF > 500 msec. QTcF increases from baseline > 60 ms were observed in 13 subjects (18.3%) in Cohort 2B and 10 (35.7%) in Cohort 2C.

Per the sponsor's analysis, no patients met categorical outlier for HR (>100 beats/min and 25% over baseline), PR (>200 msec and 25% over baseline), and QRS (>100 msec and 25% over baseline).

Reviewer's comment: Since the outlier in the sponsor's (b) (4) was based on 149 subjects receiving either 267 mg BID without strong CYP3A4 inhibitor (Phase 1 Arm A 267 mg dose group, n = 16) or 163 mg BID with strong CYP3A4i (Phase 1 Arm B 163 mg dose group and all Phase 2 cohorts, n = 133), the reviewer's categorical analysis was based on this population as well, which shows consistent number (b) (4). Reviewer's analysis for PR and QRS were similar to sponsor's that no significant outliers were observed. However, the reviewer's analysis showed 22 subjects met the tachycardia outlier (defined by the sponsor as >100 beats/min and 25% over baseline), while the sponsor claimed no patients in any cohorts met these criteria. Please see section 4.4 for details

3.2.3 Exposure-Response Analysis

The sponsor used the model recommended in the white paper. The model used pooled data from Phase 1 and Phase 2, excluding Phase 1 Arm E under fed condition. The sponsor explored three models: with both revumenib and M1 (Model A), revumenib only (Model B), and M1 only (Model C). Model A had the lowest AIC value therefore was chosen as the final model. Model with M1 only fitted better than with revumenib only (with lower AIC). The estimated population slopes of the concentration-QTc relationship for Model A were 0.0019 ms per ng/mL (90% CI: 0.00105 to 0.00270; P = 0.0003) and 0.032 ms per ng/mL (90% CI: 0.0245 to 0.0388; P < 0.0001) for revumenib and M1, respectively, with a fixed intercept of 0.079 ms (90% CI: -1.7205 to 1.8793; P = 0.9419). The fixed intercept was not statistically significant at 10% significance level, while the slopes of revumenib and M1 plasma concentrations were both statistically significant at the 10% significance level. The model predicted QTc prolongation at clinically relevant concentrations (Table 5).

Table 5. Predicted ΔQTcF Interval at Geometric Mean Peak Concentrations, Sponsor's Results

Subgroups	Geometric mean C _{max} of SNDX-5613 (ng/mL)	Geometric mean C _{max} of M1 (ng/mL)	ΔQTcF Estimate (ms) (90% CI)
Strong CYP3A4i 163 mg Q12H	2860	441	19.40 (16.84, 21.97)
Moderate CYP3A4i 276 mg Q12H	1520	524	19.52 (16.45, 22.58)
No CYP3A4i 276 mg Q12H	2880	664	26.50 (22.73, 30.27)

Source: Sponsor's CQT report Table 14.3.8.23.3.3.

Reviewer's comment: *In the situation of revumenib 163 mg Q12H with strong CYP3A4i and 276 mg Q12H with no strong CYP3A4i, the reviewer calculated geometric mean C_{max} of revumenib and M1 are similar to the sponsor's (see Table 9). However, in the situation of co-administration with moderate CYP3A4i, the reviewer calculated C_{max} (2480 ng/mL for revumenib and 706 ng/mL for M1, following 226 mg BID with moderate CYP3A4i) are much higher than the sponsor's (1520 mg for revumenib and 524 ng/mL for M1, following 276 mg Q12H with moderate CYP3A4i). Based on population-PK analysis, moderate CYP3A4 inhibitors do not have clinically significant effect on exposures of revumenib and M1. Sponsor's numbers appear to be an underestimation.*

3.2.4 Safety Analysis

QTc prolongation is an AESI for revumenib.

In total, 132 subjects were included in the **Phase 1** safety population. Thirty-one subjects (23.5%) had at least one Grade ≥ 2 event of ECG QT prolonged in Phase 1. All events were either Grade 2 (19 subjects [61.3%]) or Grade 3 (12 subjects [38.7%]) in severity. None of the events led to study drug discontinuation. All events were reported by the investigator as recovered or resolved. The median initial time to onset for QTc prolongation events was 4.0 days (range: 1 to 47 days) and the median duration of the initial event was 1.0 day (range: 1 to 22 days). One SAE of ECG QT prolonged (Grade 3) was reported in a subject from Phase 1 Arm B with a starting dose of 113 mg q12h. The subject was hospitalized for evaluation and monitoring and was restarted upon resolution after dose reduction. There were no events of ventricular dysrhythmia associated with QTc prolongation reported.

In total, 125 subjects were included in the **Phase 2** safety population. Forty subjects (32.0%) had at least 1 event of QTc prolongation, most experienced events of either Grade 2 (11 subjects [27.5%]) or Grade 3 (21 subjects [52.5%]). Grade 4 event was reported in 1 subject (0.8%). QTc prolongation was managed per protocol with dose interruption and dose reduction (Grade 3). None of these events resulted in discontinuation from revumenib. Ten subjects (25.0%) reported a TEAE of QTc prolongation leading to dose reduction and 21 subjects (52.5%) reported a TEAE of QTc prolongation leading to dose interruption. All events were reported by the investigator as recovered or resolved. The median time to onset for QTc prolongation events was 11.5 days (range: 1 to 84 days), with a median duration of 2.0 days (range: 1 to 8 days).

Overall, there were 4 subjects with SAEs of QTc prolongation; all 4 events were Grade 3. Three of these subjects were hospitalized for evaluation and had the drug interrupted and restarted, while the fourth was deemed serious based on criteria of medically significant with study drug interrupted.

The database was reviewed to identify subjects who experienced potentially important QTc prolongation-related cardiac events, and 5 subjects with events were identified: sudden death (2 subjects [1.6%]), cardiac arrest (1 subject [0.8%]), cardio-respiratory arrest (1 subject [0.8%]), and ventricular tachycardia (1 subject [0.8%]).

Important cardiac events, including ventricular arrhythmias, were low in frequency and observed in subjects with confounding factors. In these complex cases, the underlying

cardiac history and the morbidity associated with late-stage leukemia limited interpretation of any association with revumenib treatment.

Reviewer's comment: *We agree with the sponsor that most QTc prolongation-related cardiac events are confounded by subjects' cardiac history and morbidity associated with late-stage leukemia. Please see section 4.6 for reviewer's safety analysis.*

4 REVIEWERS' ASSESSMENT

The reviewer's concentration-QTc analysis was based on pooled data from Phase 1 and Phase 2 excluding Phase 1 Arm C (cobicistat), Arm D (food effect), Arm E (isavuconazole) and anyone from the other cohorts who received isavuconazole, ketoconazole, or cobicistat during treatment period. These data were excluded for their confounding factors of QTc effect: significant QTcF shortening has been observed under fed condition ([Taubel 2012](#)), with use of cobicistat ([previous review](#)) or isavuconazole ([isavuconazole label](#)), and ketoconazole is associated with QTc prolongation ([ketoconazole label](#)). Other azoles used as prophylaxis in this study, including [itraconazole](#), [posaconazole](#), [voriconazole](#), and [fluconazole](#) do not have a significant QTc effect. The most commonly used antifungal was posaconazole in both Phase 1 (25 subjects, 19%) and Phase 2 (84 subjects, 67%). Pooling is appropriate. Models based on Phase 1 or Phase 2 data only showed similar slope estimations as well as QTcF predictions as model based on pooled data.

The reviewer's by-time analysis was performed on Phase 2 data only (n = 118 in the ECG dataset). One single dose level of 163 mg Q12H with strong CYP3A4 inhibitor was used in Phase 2. Data were shown for pooled Cohort 2A + 2B since they were conducted in label indicated population (acute leukemia with KMT2A gene rearrangement, n = 88). Cohort 2C (n = 30) was analyzed separately and did not show important difference from 2A + 2B (data not shown).

Categorical analysis was performed on 149 patients with relapsed or refractory acute leukemia treated with revumenib at the recommended dosage, (b) (4). This included Phase 1 Arm A 267 mg BID without strong CYP3A4 inhibitors, Arm B 163 mg BID with strong CYP3A4 inhibitors, and Phase 2 all cohorts 163 mg BID with strong CYP3A4 inhibitors. In this section, categorical analysis was performed on QTPK dataset, which was created by the reviewer by merging ADPC and ADEG1. ADEG1 is usually generated by the core lab.

Safety analysis focused on 94 patients in Phase 2 Cohort 2A + 2B, the label indicated population. (b) (4)

(b) (4) In this section, outlier analysis was performed on ADEG.

All the above analyses used semi-automatic ECG measurements. In addition, we conducted sensitivity analysis of concentration-QTc using only automatic ECG measurements and results are consistent.

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

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

4.2 ECG ASSESSMENTS

Both digital ECG waveforms and non-digital ECG waveforms (i.e., scanned or digitized ECGs) were submitted for review. Digitized ECG waveforms were semi-automatically read. Since the submission includes digitized ECG waveforms, sensitivity analysis was performed using the automatic measurements as provided by the ECG devices at the clinical sites. The sensitivity analysis showed consistent results from the primary analysis (data not shown). The reviewer did not conduct QT bias assessment.

4.3 BY-TIME ANALYSIS

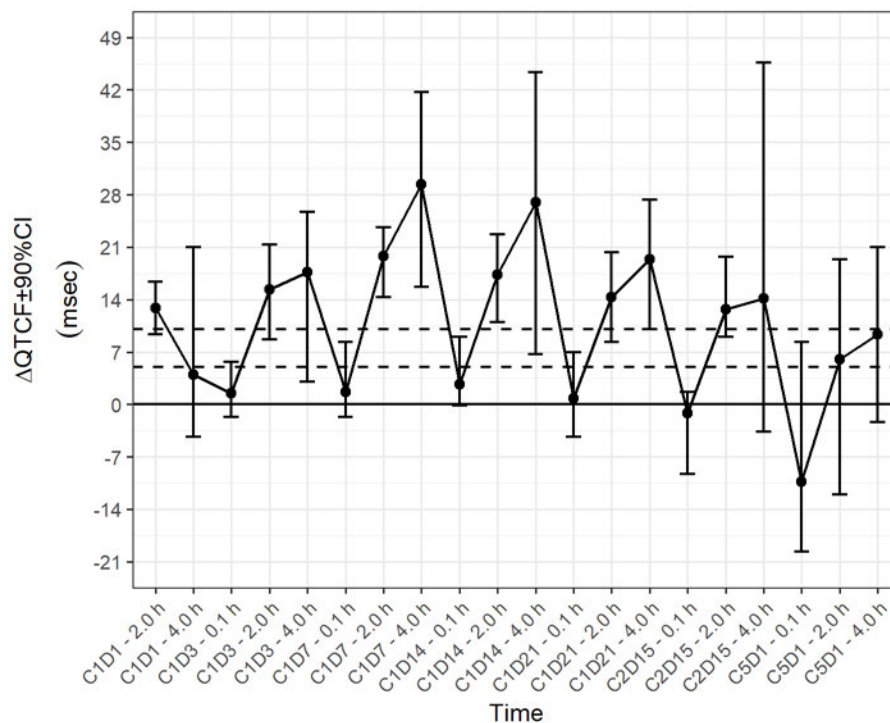
The analysis population shown here for by-time analysis included all subjects with a baseline, scheduling timepoint, and at least one post-dose ECG from Phase 2 Cohort 2A + 2B.

The statistical reviewer evaluated the Δ QTcF effect using descriptive nonparametric statistics.

4.3.1 QTc

Figure 1 displays the time profile of Δ QTcF for pooled Cohort 2A + 2B. Δ QTcF prolongation is consistently observed at 2-hour post-dose in multiple cycles. The variability is larger for the 4-hour post-dose time point, likely due to the lower number of observations. ECGs were only performed at 4-hour post-dose if the patient had a $\geq$ Grade 2 QTc prolongation at 2 hour post-dose.

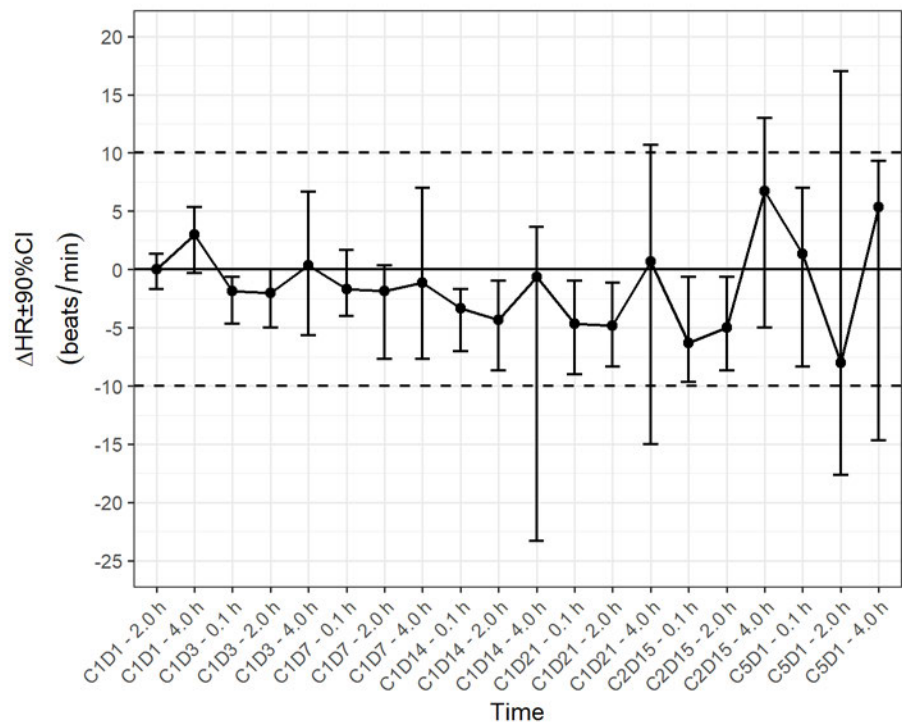
Figure 1: Median and 90% CI of Δ QTcF Time-course (unadjusted CIs).



4.3.2 HR

Figure 2 displays the time profile of Δ HR for revumenib 163 mg Q12H treatment group.

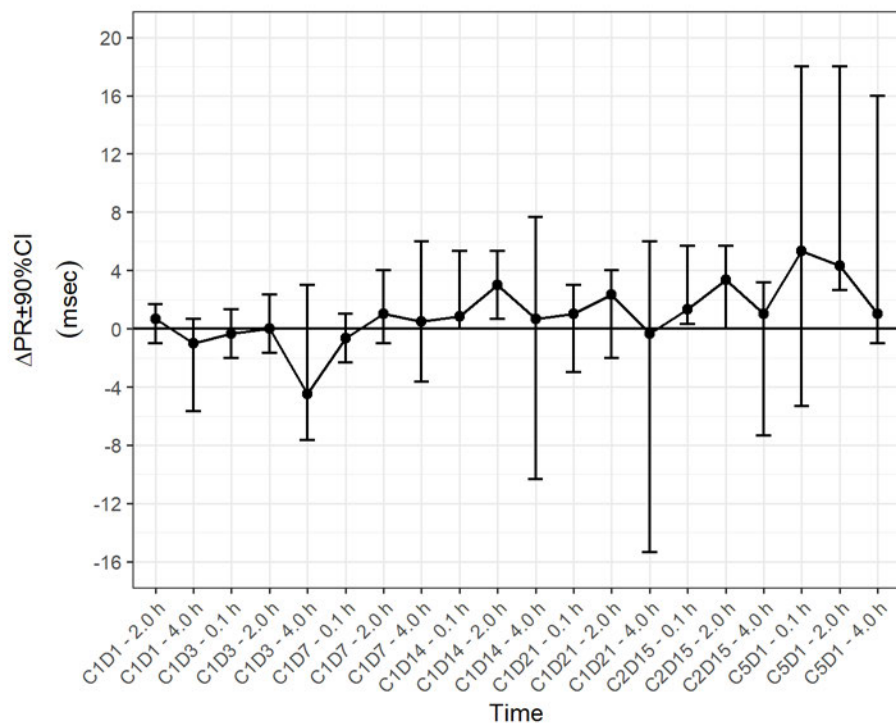
Figure 2: Median and 90% CI of Δ HR Time-course



4.3.3 PR

Figure 3 displays the time profile of Δ PR for revumenib 163 mg Q12H treatment group.

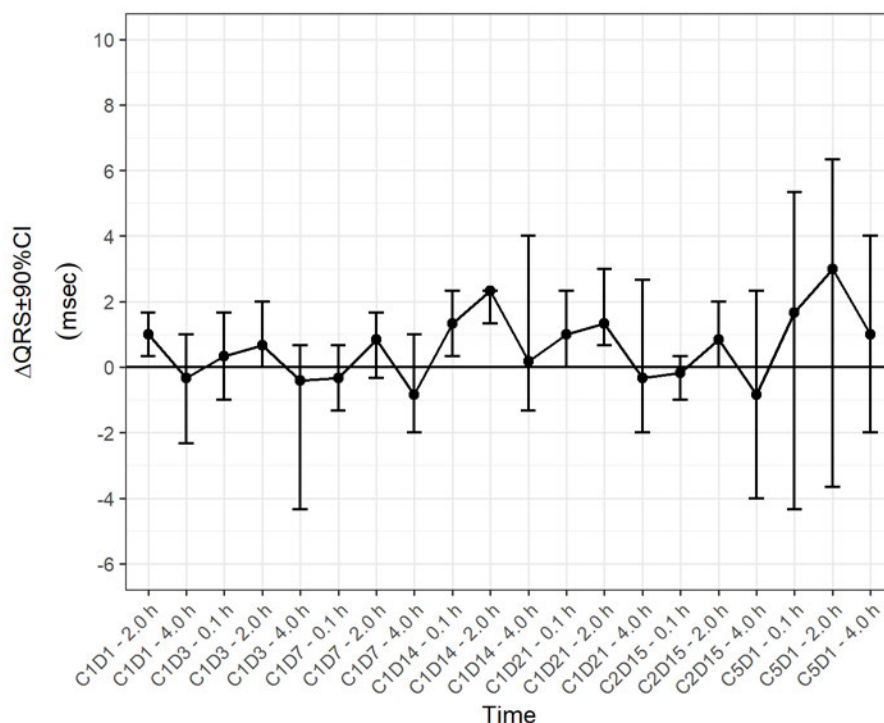
Figure 3: Median and 90% CI of Δ PR Time-course



4.3.4 QRS

Figure 4 displays the time profile of Δ QRS for revumenib 163 mg Q12H treatment group.

Figure 4: Median and 90% CI of Δ QRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population ^{(b) (4)} which includes both scheduled and unscheduled ECGs from Phase 1 Arm A with revumenib 276 mg Q12H treatment, Phase 1 Arm B with revumenib 163 mg Q12H treatment, and Phase 2 all cohorts with revumenib 163 mg Q12H treatment.

4.4.1 QTc

Table 6 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. There were 17 subjects having observed maximum QTcF above 500 msec with a change from baseline >60 msec in the revumenib 163 mg Q12H treatment group. This is consistent with safety outlier analysis (see section 4.6).

Table 6: Categorical Analysis for QTcF (maximum)

Actual Treatment	Total (N)		Value <=450 msec		450 msec < Value <=480 msec		480 msec < Value <=500 msec		Value >500 msec & ΔQTcF <=60 msec		Value >500 msec & ΔQTcF >60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Revumenib 163 mg Q12H	121	1846	61 (50.4%)	1441 (78.1%)	31 (25.6%)	292 (15.8%)	11 (9.1%)	79 (4.3%)	1 (0.8%)	5 (0.3%)	17 (14.0%)	29 (1.6%)
Revumenib 276 mg Q12H	16	459	7 (43.8%)	392 (85.4%)	5 (31.2%)	62 (13.5%)	4 (25.0%)	5 (1.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 7 lists the categorical analysis results for ΔQTcF (<30 msec, >30 and <60, and >60 msec). Thirty-three subjects (26 subjects in the revumenib 163 mg Q12H treatment group and 7 in the revumenib 276 mg Q12H treatment group) had maximum ΔQTcF above 60 msec. Note the categorical analysis was based on the QTPK dataset generated from ADEG1. From the ADEG dataset we observed 35 subjects in total with ΔQTcF > 60 msec, (b) (4) (see section 4.6).

Table 7: Categorical Analysis for ΔQTcF (maximum)

Actual Treatment	Total (N)		Value <=30 msec		30 msec < Value <=60 msec		Value >60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Revumenib 163 mg Q12H	121	1846	45 (37.2%)	1455 (78.8%)	50 (41.3%)	293 (15.9%)	26 (21.5%)	98 (5.3%)
Revumenib 276 mg Q12H	16	459	1 (6.2%)	318 (69.3%)	8 (50.0%)	122 (26.6%)	7 (43.8%)	19 (4.1%)

4.4.2 HR

Table 8 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). In total 79 out of 141 subjects (56%) had observed maximum HR above 100 beats/min. In addition, 22 subjects (16%) had HR > 100 beats/min and more than 25% increase over baseline (all in the revumenib 163 mg Q12H treatment group), thus meeting the sponsor defined tachycardia outlier, while the sponsor claimed that no subjects in any arms or cohorts met this criteria. See section 4.6 for discussion of AEs of tachycardia.

Note that even though more than half subjects had maximum HR > 100 bpm, the mean postbaseline HR (pooled across visits) was less than 100 beats/min for 276 mg Q12H (Phase 1 Arm A, mean baseline: 102 beats/min, mean postbaseline: 90 beats/min) and 163 mg Q12H (Phase 1 Arm B and three cohorts in Phase 2, mean baseline 90 beats/min, mean postbaseline 84 beats/min). Mean change from baseline HR was also less than 10 bpm in Phase 2 cohorts (see Figure 2).

Table 8: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value ≤100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Revumenib 163 mg Q12H	125	1863	57 (45.6%)	1509 (81.0%)	68 (54.4%)	354 (19.0%)
Revumenib 276 mg Q12H	16	459	5 (31.2%)	326 (71.0%)	11 (68.8%)	133 (29.0%)

4.4.3 PR

None of the subjects experienced PR >220 msec and 25% increase over baseline in the revumenib 163 mg Q12H and revumenib 276 mg Q12H treatment groups.

4.4.4 QRS

None of the subjects experienced QRS >120 msec and 25% increase over baseline in the revumenib 163 mg Q12H and revumenib 276 mg Q12H treatment groups.

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. In the reviewer's analysis, concentration-QTc was based on pooled data from Phase 1 and Phase 2 excluding Phase 1 Arm C (cobcistat), Arm D (food effect), Arm E (isavuconazole) and anyone from the other cohorts who received isavuconazole, ketoconazole, or cobcistat during treatment period. To be consistent with sponsor's analysis, treatment/time point combinations with less than 3 patients were excluded from the model. In addition, concentrations of both parent and metabolite were included as fixed effects in the CQT model.

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 ΔQTcF; and 3) absence of a nonlinear relationship.

Figure 2 shows the time-course of ΔHR, with an absence of significant ΔHR changes, thus supporting the use of QTcF.

Figure 5 offers an evaluation of the relationship between time-course of revumenib and SN-60165 and ΔQTcF, with no appearance of significant hysteresis. An increase in ΔQTcF closely follows the increase in concentrations of both parent and metabolite. For visualization purpose, only dose groups and visits with sufficient sample size were presented in this figure.

Figure 6 shows the relationship between drug concentration and $\Delta QTcF$ and supports the use of a linear model.

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

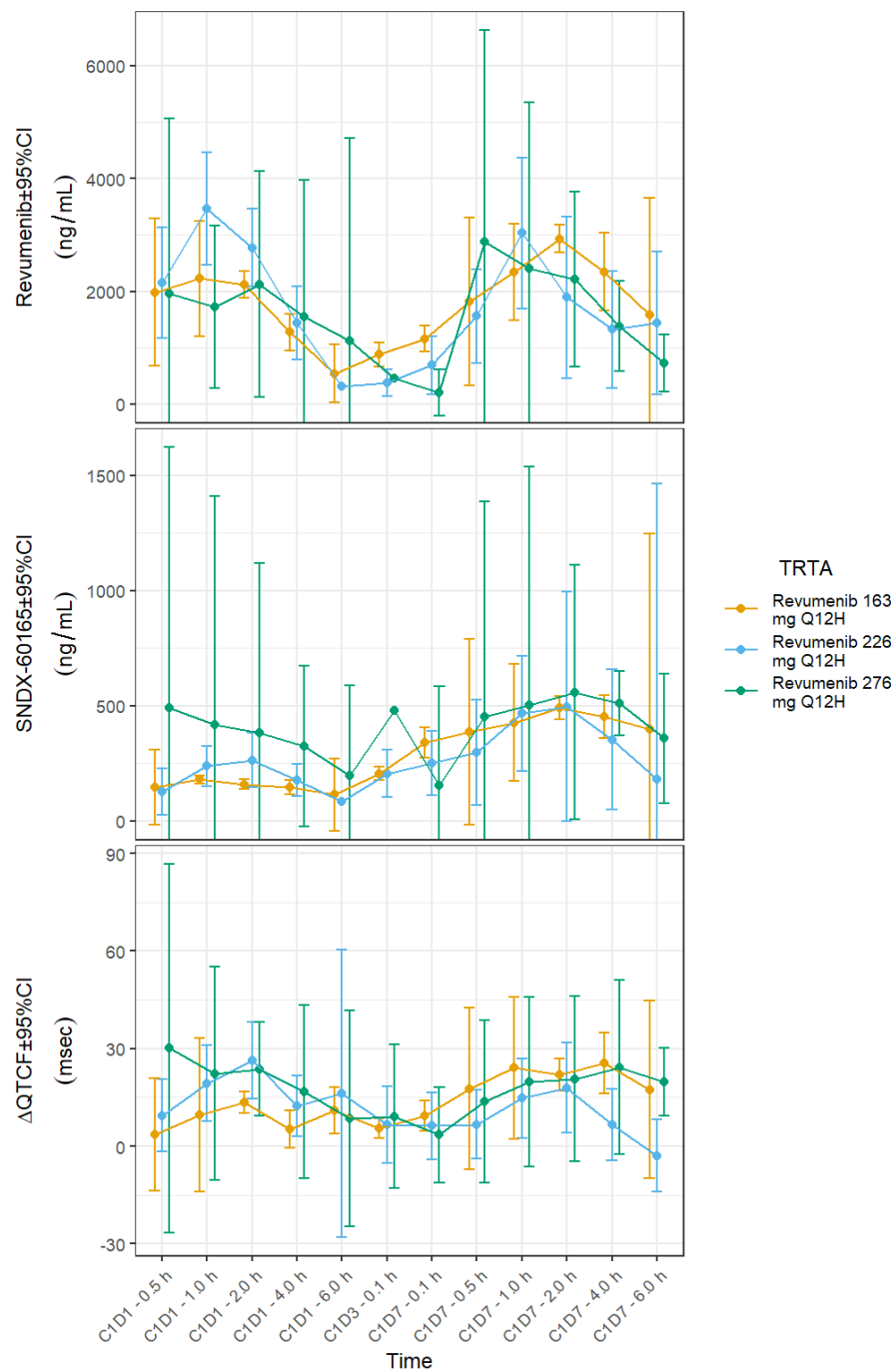
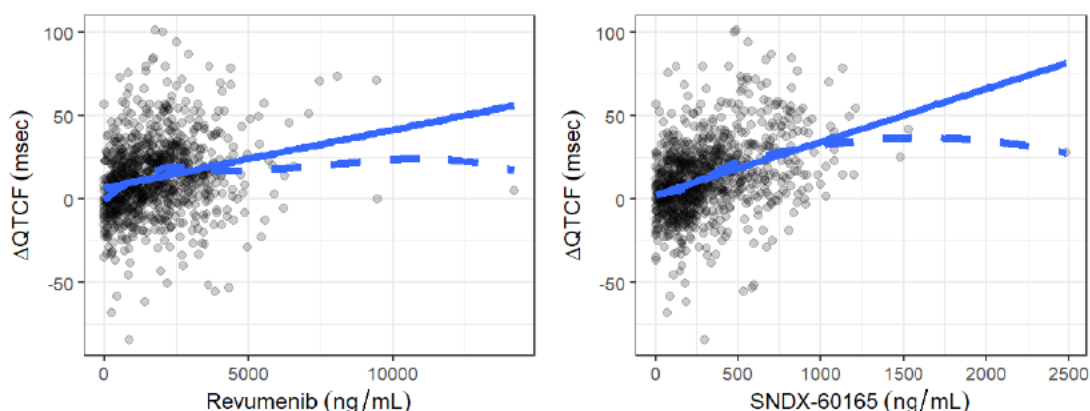


Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data. Predictions from the concentration-QTcF model are provided in Table 9. Since the model included both parent and metabolite and the two moieties have different T_{max}, predictions were made at geometric mean concentrations of revumenib and M1 at T_{max} of revumenib (scenario 1) and at T_{max} of M1 (scenario 2). The concentrations were calculated by the reviewer using observed data from the ADPC dataset. The predictions of ΔQTcF were similar between the two scenarios, and the maximum of the two predictions is presented in Table 1. A 20 msec increase in ΔQTcF cannot be excluded in any scenario where the proposed therapeutic regimen was given since the upper bound of 90% confidence interval were above 20 msec. Predictions of 276 mg BID with moderate CYP3A4 inhibitors are not included in Table 9 because population-PK analysis showed that moderate CYP3A4 inhibitors do not impact the exposure of revumenib or M1. Note that a goodness of fit plot cannot be generated for models with more than one moiety.

Table 9: Predictions from Concentration-QTcF Model at Concentrations Calculated by Reviewer

Actual Treatment	Revumenib (ng/mL)	M1 (ng/mL)	ΔQTcF (msec)	90.0% CI (msec)
276 mg BID with no strong CYP3A4i	2,060	C _{max} : 619.0	22.0	(18.0 to 26.0)
276 mg BID with no strong CYP3A4i	C _{max} : 2,470	544.0	21.0	(17.6 to 24.5)
163 mg BID with strong CYP3A4i	2,450	C _{max} : 423.0	17.7	(14.9 to 20.4)
163 mg BID with strong CYP3A4i	C _{max} : 2,880	383.0	17.7	(15.0 to 20.4)
163 mg BID with cobicistat*	2,740	C _{max} : 17.7	7.2	(4.1 to 10.4)
163 mg BID with cobicistat*	C _{max} : 3,390	15.8	8.9	(5.2 to 12.6)

*Predictions were made based on PK interaction between revumenib and cobicistat only and information regarding PD interaction was not included in the model since the CQT model did not include data from patients taking cobicistat.

In addition, the reviewer also predicted $\Delta QTcF$ using the developed model and concentrations provided by the sponsor. The predicted $\Delta QTcF$ in Table 10 are similar to those reported by the sponsor in Table 5. As noted before (see section 3.2.3), the concentrations calculated by the reviewer are similar to the sponsor's in the cases of 276 mg BID with no strong CYP3A4 inhibitors and 163 mg BID with strong CYP3A4 inhibitors, but the reviewer calculated concentrations in the case of 276 mg BID with moderate CYP3A4 inhibitors are higher than those reported by the sponsor. However, they are similar to concentrations after 276 mg BID without CYP3A4 inhibitors. This is consistent with the pop-PK findings that moderate CYP3A4 inhibitors do not have an effect on exposures of revumenib and M1.

Table 10. Predictions from Concentration- $QTcF$ Model at Concentrations Provided by Sponsor

Treatment Group	Revumenib (ng/mL)	M1 (ng/mL)	$\Delta QTcF$ (msec)	90.0% CI (msec)
Strong CYP3A4i 163 mg Q12H	2,860	441.0	19.2	(16.3 to 22.2)
Moderate CYP3A4i 276 mg Q12H	1,520	524.0	18.0	(14.6 to 21.4)
No CYP3A4i 276 mg Q12H	2,880	664.0	25.4	(21.2 to 29.7)

In the proposed label section 12.2, we used the sponsor's predictions of $\Delta QTcF$ for 276 mg BID without strong CYP3A4 inhibitors and 163 mg BID with strong CYP3A4 inhibitors. We did not recommend reporting $\Delta QTcF$ prediction in moderate CYP3A4 inhibitors since exposures in this group (and therefore predicted $\Delta QTcF$) is comparable to that with revumenib 276 mg BID without strong CYP3A4 inhibitors.

4.6 SAFETY ASSESSMENTS

The reviewer's safety assessment focused on Phase 2 Cohort 2A + 2B, (b) (4)
In total 94 subjects were included in this safety population. The median treatment duration was 10 weeks (range: 1-36 weeks).

Table 10 shows a customized query of treatment emergent adverse event (between 1st dose and 30 days after the last dose) of QTc prolongation/TdP. Five subjects (5%) experienced SAEs (PTs: syncope [2], death, sudden death, and electrocardiogram QT prolonged) and two were fatal (death and sudden death). One subject discontinued treatment (PT: sudden death). Seventeen subjects (18%) experienced TEAE with Grade $\geq$ 3 (PTs: death, sudden death, syncope [3], and electrocardiogram QT prolonged [13]). There were no ventricular arrhythmias reported.

Table 11. Customized Query of QT prolongation/TdP, Safety Population, Phase 2A + 2B

	163 mg Q12H N=94 n (%)
Adverse Event Category	
Any AE in group	29 (30.9)
Electrocardiogram QT prolonged	24 (25.5)
Syncope	3 (3.2)
Death	1 (1.1)
Seizure	1 (1.1)
Sudden death	1 (1.1)
Maximum severity	
Death	2 (2.1)
Life-threatening	1 (1.1)
Severe	14 (14.9)
Moderate	8 (8.5)
Mild	4 (4.3)
Serious	5 (5.3)
Fatal	2 (2.1)
Resulting in discontinuation	1 (1.1)

Source: Reviewer's analysis based on adae.xpt

Treatment emergent adverse event is defined as adverse events that start on or after the first administration of study drug and within 30 days of last dose date.

We reviewed the narratives of the 5 SAEs. The Electrocardiogram QT prolonged SAE (QTcF 486 msec, baseline 407 msec) was likely related to the study drug. The relatedness of the other four events were confounded by disease progression and medical history. The event of death was likely due to disease progression; the subject was discontinued from study treatment due to progressive disease 10 days prior to the event. The event of sudden death was likely related to disease progression; the subject had thrombocytopenia at screening and throughout the study, which increased her risk of bleeding, and had a Grade 4 haemorrhage intracranial 4 weeks prior to the sudden death. One syncope event in subject (b) (6) could be related to the atrioventricular block complete; the subject also reported a 20-year history of episodes of pre-syncope lightheadedness; the subject experienced a Grade 3 QTc prolongation but not at the same time as the syncope event. The other syncope event in subject (b) (6) was suspected to be vasovagal syncope unlikely arrhythmia as he had nausea and vomiting; the subject had been having poor appetite in the last few days and was dehydrated.

Death: Subject (b) (6) was a 36-year-old white male. The subject was hospitalized on Day 8 for pneumonia (SAE, Grade 3). The event was resolved on Day 16. No action was taken with the study because of the event. On Day 117, the subject was discontinued from study treatment due to progressive disease and the last dose was administered on Day 114. The most recent disease response assessment prior to death was during end of treatment on Day 112 and showed progressive disease with 45% marrow blasts (79% at baseline). On Day 127, the subject was found dead at home. There was no other information known surrounding the details of the death.

The subject's QTcF values were all below 450 msec.

The sponsor assessed that death was likely due to progressive disease.

Sudden death: Subject (b) (6) was a 55-year-old white female. At screening (Day -10), the subject showed low platelet count ($22 \times 10^9/L$, reference range: $150-400 \times 10^9/L$), low

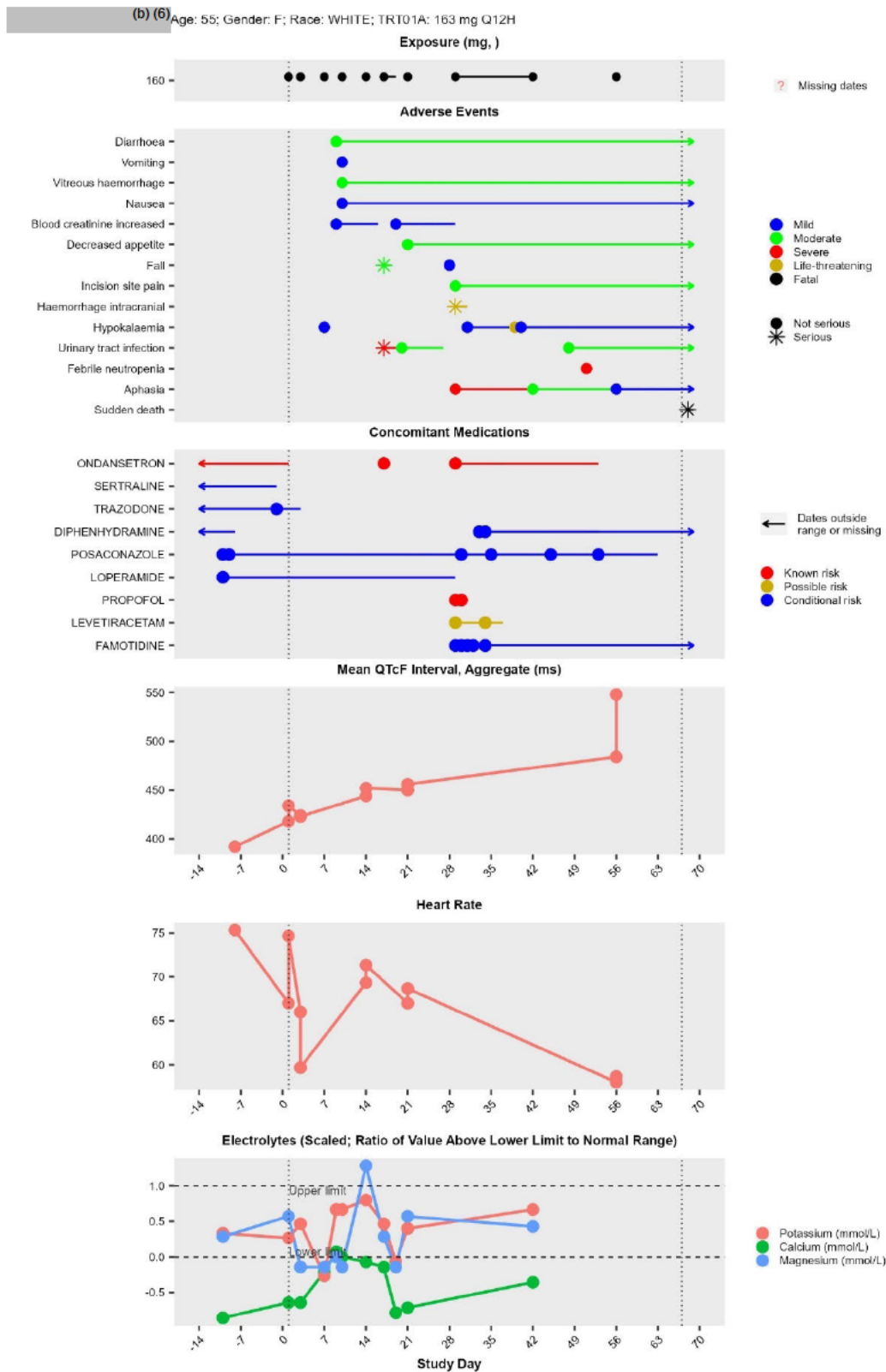
neutrophil ($1.48 \times 10^9/\text{L}$, RR: $1.8\text{--}7.5 \times 10^9/\text{L}$), and low hemoglobin (71 g/L, RR: 120-160 g/L). The subject's most recent disease response assessment prior to the event was on Day 42 that showed no response with 20% marrow blasts. On Day 29, the subject was found by her daughter down on the floor. The subject was breathing and responsive but was unable to speak and was subsequently taken to the hospital. The subject was diagnosed with a serious adverse event of *Grade 4 haemorrhage intracranial*. The subject underwent craniectomy and was treated with levetiracetam for seizure prophylaxis and mannitol for the intracranial hemorrhage. On Day 31, the event was resolved. On Day 67, the subject had a visit for lab tests (values not reported) and transfusion. The subject received 1 unit of platelets. It was reported the subject had an uneventful evening and overnight. On Day 68, 1 day after the most recent dose of the study drug, the subject was found not breathing by her daughter. The cause of death was unknown.

On Day 56, the subject's ECG showed normal sinus rhythm with QTc prolongation (QTcF 548 msec, baseline 418 msec) at 2 hour post-dose. Calcium was below normal on Day 42 (see Figure 7). The subject was on ondansetron from Day 29 to 53.

The subject had thrombocytopenia prior start of study treatment, which increased the risk of serious bleeding. Given this and the subject's recent intracranial hemorrhage, the sponsor adjudicated the event to be sudden death, likely secondary to progressive AML.

Figure 7. Graphic Patient Profile for Subject

(b) (6)



Syncope: Subject (b) (6) is a 65-year-old white female. On Day 15, 4 days after the most recent dose of the study drug, while in bathroom the subject felt a fluttering sensation leading to a syncopal episode resulting in fall on the floor with a head strike and forehead laceration. The code team responded, the event passed, and the subject reported feeling like herself again. The subject was sent to the emergency department (ED) where a transthoracic ECHO incidentally showed a new wall motion abnormality of unclear chronicity. The subject had ongoing history of hypertrophic cardiomyopathy and had recently received diuresis for lower extremity edema likely compromising the cardiac output. The study drug was temporarily interrupted from Day 15 to Day 18 and resumed at the same dose on Day 19. On Day 20, the Grade 3 syncope event was resolved and the subject was discharged.

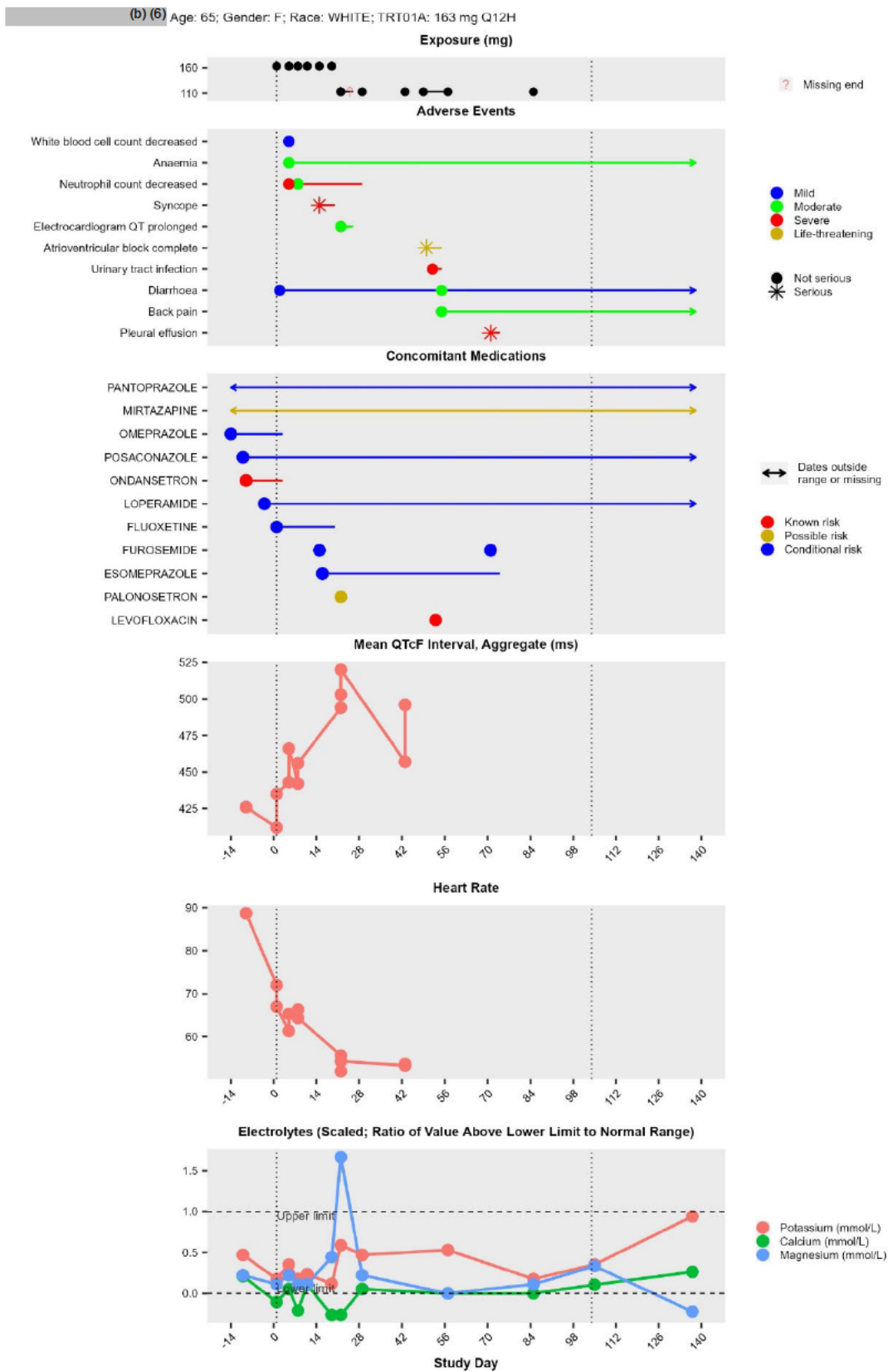
On Day 22, 2 days after the most recent dose of the study drug, pre-dose ECG showed **QTc prolongation** (QTcF 494 msec, baseline 428 msec). Lab tests showed increased magnesium, decreased calcium and normal potassium (Figure 8). Repeat pre-dose ECG showed average QTcF of 455 msec. The subject was dosed at the next lower level (113 mg). *The 2-hour and 4-hour post-dose ECG showed QTc prolongation (mean QTcF 503 and 520 msec, respectively).* Treatment with the study drug was interrupted due to these events. On Day 26, ECG showed normal sinus rhythm with QTcF of 475 msec. The Grade 2 and Grade 3 electrocardiogram QT prolonged was resolved. *The investigator and the sponsor assessed the QTc prolongation to be related to study drug.*

On Day 49, an ECHO showed left ventricular ejection fraction of 55 (baseline 70; unit and reference range not reported). On Day 50, 7 days after the most recent dose of the study drug, the subject presented to a local hospital reported with an episode of syncope with head strike. Syncope was preceded by a sensation of light headedness. The subject was found to be bradycardic with heart rate ranged in the 20s with complete heart block. A temporary pacing wire placement via right internal jugular vein was performed. The subject was hospitalized with a SAE of Grade 4 **atrioventricular block complete**. The pre-syncopal symptom of light headedness was reproducible with interruption of paced rhythm. Treatment with the study drug was temporarily interrupted due to this event and due to the known risk of QTc prolongation. Posaconazole was stopped due to the concern for drug-related adverse effect.

The etiology of complete heart block was unclear but was considered as possibly related to the progression of 30-year history of hypertrophic cardiomyopathy, adverse effect from protocol therapy, or ischemia given presumed microvascular septal disease on cardiac MRI. The subject also reported a 20-year history of episodes of pre-syncopal lightheadedness that might reflect prior intermittent episodes of complete heart block.

Figure 8. Graphic Patient Profile for Subject

(b) (6)



Syncope: Subject (b) (6) is a 57-year-old white male. On Day 11, 1 day after the most recent dose, the subject experienced a Grade 4 syncope which resulted in hospitalization and was life threatening. The subject's relevant medical history included ventricular dilatation. On Day -3, the subject was admitted for management of AML. He was doing normal during admission. On Day 11, the subject went for his usual walk inside the hospital when he felt lightheaded and dizzy. He ate a banana but felt nauseous and passed out. Code blue was called but the subject did not sustain a fall as he was sitting in a chair at that time. The subject regained consciousness within 15 to 20 seconds and had a vomiting episode. He denied chest pain, shortness of breath and palpitations. As he was transferred via wheelchair, the subject had another episode of syncope and thus, was brought to the intensive care unit (ICU) for evaluation. At arrival, his vital signs showed heart rate 60-70, blood pressure 100/50 and oxygen saturation 95 percent at room air. Cardiology suspected vasovagal syncope unlikely arrhythmia as he had nausea and vomiting. The subject had been having poor appetite the last few days and was dehydrated. The subject has been complaining on nausea and been on Compazine (prochlorperazine) 10 mg as needed (prn) and poor appetite was probably due to these specific notations. ECG showed normal sinus rhythm and heart rate in the 60s. Bedside transthoracic echocardiogram (TTE) was performed and showed normal left ventricular ejection fraction (LVEF) at 55 percent. An unspecified imaging showed no intracranial hemorrhage or acute intracranial abnormality. On Day 12, the subject was feeling normal and was transferred to leukemia floor after a day of observation with no acute event. The study drug was continued without interruption.

The subject's QTcF values were all below 450 msec.

The investigator and the sponsor assessed the Grade 4 syncope not related to the study drug. The subject had left ventricular dilatation which could be contributory. The subject also had poor appetite, dehydrated, lightheaded and dizzy when the event occurred.

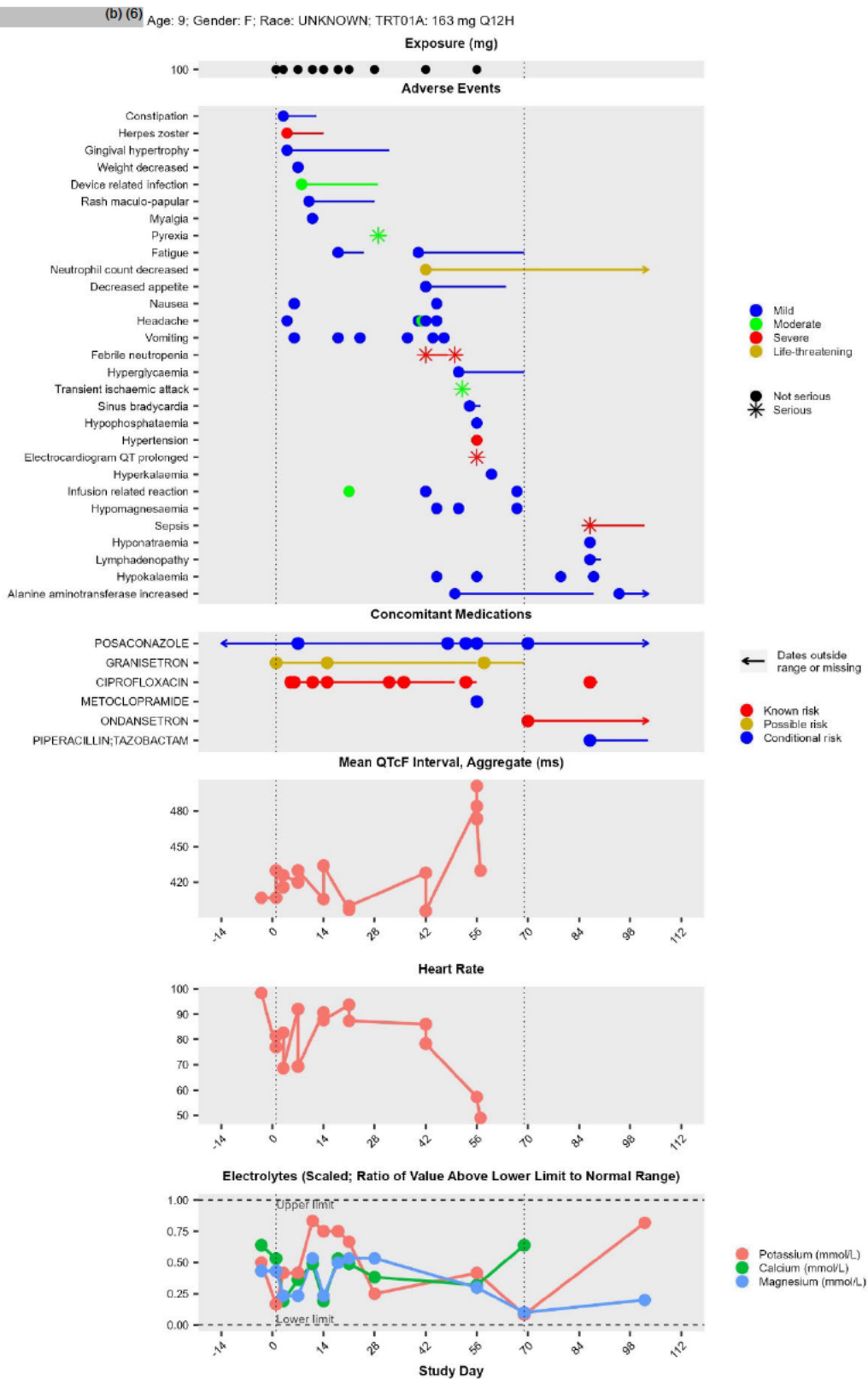
Electrocardiogram QT prolonged: Subject (b) (6) is a 9-year-old female. The subject had two episodes of SAEs of febrile neutropenia on Day 42 (temperature 38.7°C; WBC count $0.3 \times 10^9/L$, RR: $4.5-13.5 \times 10^9/L$; neutrophil count $0.06 \times 10^9/L$, RR not reported) and Day 50 (temperature 40°C; WBC count $0.3 \times 10^9/L$; neutrophil count not reported), which were resolved on Day 42 and Day 52 respectively.

On Day 56, at 6-minute post-dose, HR was 58 bpm (RR: 70-110 bpm) and BP was 100/61 mmHg. At 45-minute post-dose, ECG showed QTcF prolonged at 486 msec (baseline 407 msec) with no arrhythmia. The subject was diagnosed with a serious adverse event of Grade 3 electrocardiogram QT prolonged (seriousness criteria: medically significant and requiring inpatient hospitalization). Electrolytes were within reference range. Magnesium supplementation was increased. Drugs which can induce QTc-prolongation including ciprofloxacin and granisetron were stopped and posaconazole dose was reduced. No action was taken with the study drug. QTcF was increased to 508 msec at 4 hours post-dose and reduced to 471 msec at 7 hours post-dose. HR was lower than normal at 46/57/56 bpm at 3/4/5 hours post-dose and BP was higher than normal at 140/90 and 127/76 mmHg at 3 and 4 hours post-dose. On Day 57, QTcF was 433 msec and the SAE of electrocardiogram QT prolonged was considered resolved.

The investigator and the sponsor assessed the event of Electrocardiogram QT prolonged as related to study drug.

Figure 9. Graphic Patient Profile for Subject

(b) (6)



QTc prolongation was managed per protocol with dose interruption and dose reduction (Grade 3). Four subjects (4%) reported a TEAE of QTc prolongation leading to dose reduction and 11 subjects (12%) reported a TEAE of QTc prolongation leading to dose interruption.

ECG data showed that 10 subjects (11%) had QTcF > 500 msec and 16 subjects (17%) had change from baseline > 60 msec. All the subjects with QTcF > 500 msec had change from baseline > 60 msec as well. Fifty-seven subjects (61%) had mean HR > 100 bpm.

The reviewer has also examined the safety population (safety population 2) (b) (6) which included 149 patients with relapsed or refractory acute leukemia treated with revumenib at the recommended dosage in study SNDX-5613-0700 (Phase 1 Arm A 267 mg BID without strong CYP3A4 inhibitors, Arm B 163 mg BID with strong CYP3A4 inhibitors, and Phase 2 all cohorts 163 mg BID with strong CYP3A4 inhibitors). In total, 36 subjects (24%) had QTcF > 500 msec (18 subjects, 12%, 17 of whom had ΔQTcF > 60 msec) or change from baseline QTcF > 60 msec (35 subjects, 23%). The percentage was similar to that of safety population 1. Of these subjects, 73% had their first event (QTcF > 500 msec or change from baseline > 60 msec) in the first 4 weeks. Of the scheduled visits, 70% subjects had their first event between 1-4 hours post-dose (n = 21) and 50% subjects had their first event at 2-hour post-dose (n = 15).

Customized query of QT prolongation/TdP showed 59 subjects out of 149 (40%) with events (Table 11), higher than safety population 1 (31%). Eleven subjects (7%) had SAEs (PTs: syncope [2], death, sudden death [2], cardio-respiratory arrest, cardiac arrest, and electrocardiogram QT prolonged [4]) and five were fatal (3%, death, sudden death [2], cardio-respiratory arrest, and cardiac arrest). Three led to drug discontinuation (2%, sudden death [2] and cardiac arrest). No ventricular arrhythmias were reported. Overall the safety profile of QT prolongation/TdP appears similar to the safety population 1.

Out of 149 subjects, 12 subjects (8%) reported AEs of tachycardia (narrow FMQ tachycardia, PTs: sinus tachycardia, heart rate increased, tachycardia, ventricular tachycardia). One was an SAE (0.7%, PT: sinus tachycardia) and no event led to drug discontinuation. One ventricular tachycardia was of Grade 3.

Table 12. Customized Query of QT prolongation/TdP, Safety Population at Recommended Dose¹

Preferred Term	Number of Subjects (%)
Electrocardiogram QT prolonged	52 (26.8)
Seizure	2 (1.0)
Cardiac arrest	1 (0.5)
Syncope	4 (2.1)
Death	1 (0.5)
Cardio-respiratory arrest	1 (0.5)
Ventricular tachycardia	1 (0.5)
Sudden death	2 (1.0)

¹ Included 149 subjects from Phase 1 Arm A 267 mg BID without strong CYP3A4 inhibitors, Arm B 163 mg BID with strong CYP3A4 inhibitors, and Phase 2 all cohorts 163 mg BID with strong CYP3A4 inhibitors

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/s/

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JUSTIN S COLLAZO
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ELIFORD N KITABI
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MICHAEL Y LI
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CHRISTINE E GARNETT
04/23/2024 08:19:57 AM

Consult Memorandum

Date:	April 12, 2024
To:	Rachel McMullen, Pharm. D., RPM, CDER/OND/ORO/DROOD, Donna Przepiorka, Lead Reviewer, CDER/OND/OD/DHMI
From:	Christopher Trindade, M.D., Lead Reviewer, CDRH/OPEQ/OHT7/DMGP/MGB2
Through:	Karen Bijwaard, M.S., Senior Policy Advisor, CDRH/OPEQ/OHT7/DMGP Donna Roscoe, Ph.D., Acting Director, CDRH/OPEQ/OHT7/DMGP, and Reena Philip, Ph.D., Associate Director OCE
ICC Number:	NDA 218944 (b) (4) ICCR# 00973681 (b) (4)
Subject:	NDA 218994 (b) (4): "A Phase 1/2, Open-label, Dose-Escalation and Dose-Expansion Cohort Study of SNDX-5613 in Patients with Relapsed/Refractory Leukemias, Including Those Harboring an <i>MLL/KMT2A</i> Gene Rearrangement or Nucleophosmin 1 (<i>NPM1</i>) Mutation (version 17, dated, 11/18/2023)"
Dug Name:	Revumenib (SNDX-5613)
Drug Sponsor:	Syndax
Biomarker(s):	KMT2A
Device Name:	(b) (4)
Device Sponsor:	(b) (4)

I. BACKGROUND and PURPOSE.

Revumenib is an unapproved KMT2A FDA drug being developed for the treatment of patients with relapsed or refractory (R/R) acute leukemia. The interaction of menin with the epigenetic regulator *KMT2A* in acute leukemia with *KMT2A* rearrangement (*KMT2Ar*) or mutant *NPM1* (*mNPM1*, *NPM1c*) leads to upregulation of leukemogenic genetic programs. Revumenib targets the *KMT2A*-menin interaction downregulates aberrant expression of *HOX* and *MEIS1* and reverses leukemogenesis that has activity against translocations and partial tandem duplications (PTD). PTD has a worse prognosis than translocations. The resistance mutations known thus far after prolonged monotherapy exposure to revumenib are M327, G331, T349, and S160 in the menin protein (1-3).

The workflow for most hematology/cytogenetics labs is first karyotyping with Giemsa staining to create G banding of each chromosome. This is done to show rearrangements (translocations), deletions, additions, and complex karyotypes. Some labs may skip karyotyping or if this proves unsuccessful the next step is fluorescence *in situ* hybridization (FISH), and finally to figure out partial tandem duplication (which revumenib has some activity against); the cytogenetic's lab would use genome optical mapping such as the Cytoarray Scan™ (4).

CDRH was requested to consult on two questions.

1. Breakthrough Therapy-designated drug is approved prior to completion of the review of the PMA for the companion diagnostic, it would be prudent to have some degree of confidence about whether the assay used for eligibility confirmation is appropriate for that use. **Please comment on the adequacy of the central laboratory assay for identification of *KMT2Ar* in patients with acute leukemias.** If the response to FDA comment 5(d)(iv) is not adequate, please provide us with a list of the minimal information you will need, and we will send that in an information request to the applicant.

2. Is the KMT2Ar the assay (b) (4) would identify that would not be pathogenic or likely pathogenic variants?

This consult was received on February 21st, 2024 with a due date of June 12th, 2024.

II. DRUG DESCRIPTION and PROPOSED INDICATION

Revumenib - is not FDA approved and is a first in class menin inhibitor that is meant for patients that weigh (b) (4) kg.

III. DEVICE USE IN THE TRIAL

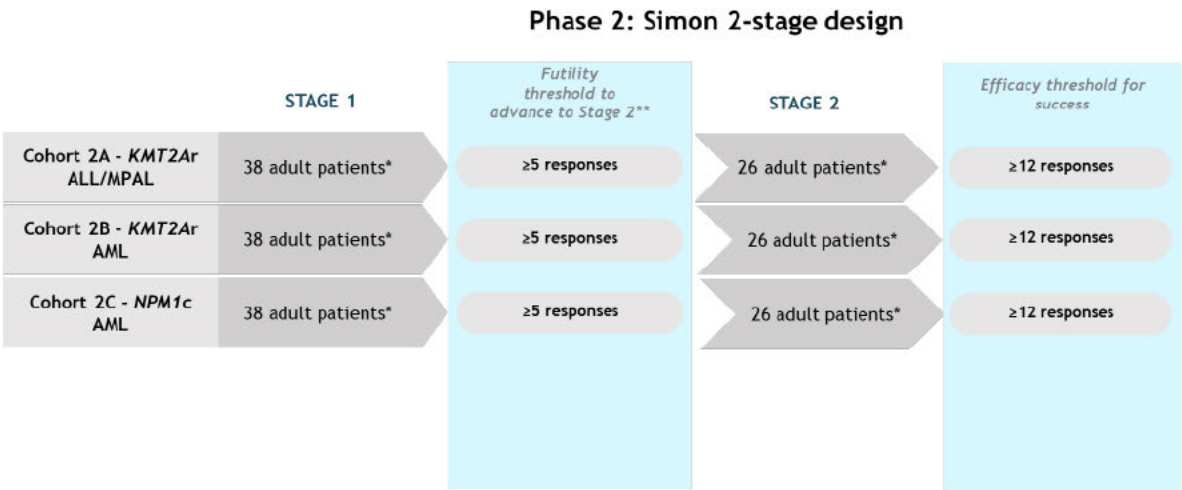
Study SNDX-5613-0700 is a Phase 1/2, open-label, dose-escalation and expansion study of SNDX-5613, which is a menin inhibitor. Patients aged ≥30 days and weighing ≥35 kg if intended to receive SNDX-5613 in combination with cobicistat, with R/R acute leukemia are planned to be enrolled. This Phase 1/2 study was opened in September 2019 and at the time of this amendment, Phase 1 Arms A-F are closed to enrollment. The Phase 2 portion initiated with the identification of a recommended Phase 2 dose (RP2D) for patients receiving a strong cytochrome P450 (CYP)3A4 inhibitor azole. At the time of this amendment, Phase 2 Cohorts 2A and 2B are closed to enrollment. Phase 2 Cohort 2C is currently enrolling.

1.2. Study Schema

1.2.1. Phase 1

		Escalation Study Design	Regimen	Starting Dose
Arm A	With or without moderate CYP3A4 inhibitor	Rolling 6	q12h	113 mg
Arm B	With a strong CYP3A4 inhibitor (azole)	Rolling 6	q12h	113 mg
Arm C	With a strong CYP3A4 inhibitor (cobicistat)	Rolling 6	q12h	113 mg
Arm D	With a moderate CYP3A4 inhibitor (fluconazole)	Rolling 6	q12h	163 mg
Arm E	Without a CYP3A4 inhibitor	Rolling 6	TID	163mg
Arm F	With a moderate CYP3A4 inhibitor (isavuconazole)	Rolling 6	q12h	226 mg

Abbreviations: q12h = every 12 hours; TID = 3 times per day
Note: Phase 1 Arms A-F are closed to enrollment. Phase 1 Arm G patients will not undergo dose escalation and will receive SNDX-5613 163 mg q12h with a strong CYP3A4i or 276 mg q12h without a strong CYP3A4i. Patients <40 kg will receive BSA-based dosing (Section 3.1.2).



*Up to an additional 20 pediatric patients may be enrolled (N=84) in each cohort.
**An interim analysis for efficacy will also be conducted as per [Section 9.5](#).

IV. QUESTIONS TO THE SPONSOR

CDER QUESTION

- d. Identify the FDA-cleared assay used for central confirmatory testing for a KMT2Ar. If the assay was not FDA-cleared, please provide the following information:
- i. A statement of intended use.
 - ii. The specific test method (including instruments, reagents, and specimen handling).
 - iii. Confirmation that the lab has a process in place for reagent control.
 - iv. A brief discussion of how the test method was validated analytically for each specimen type.
 - v. A statement of the performance obtained for accuracy and analytical sensitivity.

Sponsor Response to Clinical Information Request #5d:

(b) (4)

(b) (4)

CDRH RESPONSE to CDER:

Syndax appears to have answered the questions presented to them except “iv” does not appear to provide a brief discussion of the studies, but only list the studies. Because there is no description of the samples used, the study design, and the results other than accuracy (for which a statement of performance with no information about how accuracy was determined, the number of samples, the range of results is not discernable), CDRH is not able to comment on whether the test is adequately analytically validated. Below is the assay validation that is requested for analytical validation of FISH assays. For the CTA, A through D would be appropriate.

(b) (4)

(b) (4)

CDER QUESTION

2) Please see the applicant's response to FDA comment 4(a) regarding KMT2Ar resistant to revumenib. Are there any KMT2Ar that the assay would identify that would not be pathogenic or likely pathogenic variants?

Sponsor Response to Clinical Information Request #4a:

(b) (4)

CDRH RESPONSE to CDER:

Please note break apart FISH can't identify a pathogenic variant. Other molecular techniques such as NGS, to identify pathogenic variants can be used.

(b) (4)

(b) (4)

however, the company did not obtain this information.

V. References

1. Issa, G. C., Aldoss, I., DiPersio, J., Cuglievan, B., Stone, R., Arellano, M., ... & Stein, E. M. (2023). The menin inhibitor revumenib in KMT2A-rearranged or NPM1-mutant leukaemia. *Nature*, 615(7954), 920-924.
2. Barajas, J. M., Rasouli, M., Umeda, M., Hiltenbrand, R., Abdelhamed, S., Mohnani, R., ... & Klco, J. M. (2024). Acute myeloid leukemias with UBTF tandem duplications are sensitive to Menin inhibitors. *Blood*, 143(7), 619-630.

3. Di Fazio, P. (2023). Targeting menin: a promising therapeutic strategy for susceptible acute leukemia subtypes. *Signal Transduction and Targeted Therapy*, 8(1), 384.
4. Perner, F., Stein, E. M., Wenge, D. V., Singh, S., Kim, J., Apazidis, A., ... & Cai, S. F. (2023). MEN1 mutations mediate clinical resistance to menin inhibition. *Nature*, 615(7954), 913-919.
5. Subject Matter Experts: [REDACTED] (b) (4)

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/s/

RACHEL S MCMULLEN
04/24/2024 03:23:17 PM