

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219713Orig1s000

OTHER REVIEW(S)

Clinical Inspection Summary

Date	May 21, 2025
From	Lee Pai-Scherf, MD Michele Fedowitz, MD, Team Leader Kassa Ayalew, MD, MPH, Division Director <i>for</i> Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE, OSI
To	Ha Nguyen, Medical Officer Diana Bradford, Medical Team Leader Division of Oncology 2 (DO2), Office of Oncology Products
NDA #	NDA 219713
Applicant	Nuvation Bio Inc.
Drug	Taletrectinib
NME (Yes/No)	Yes
Therapeutic Classification	Tyrosine Kinase Inhibitor
Proposed Indication(s)	Treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC)
Consultation Request Date	December 6, 2024
Summary Goal Date	May 10, 2025 (extension to May 27, 2025)
Action Goal Date	June 11, 2025
PDUFA Date	June 23, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Studies AB-106-C203 (henceforth C203) and AB-106-G208 (henceforth G208) were submitted to the Agency in support of New Drug Application (NDA) 219713 for taletrectinib for the treatment of adult patients with locally advanced or metastatic receptor tyrosine kinase 1-positive (ROS1-positive) non-small cell lung cancer (NSCLC). Three clinical investigators, Drs. Caicun Zhou (Site # 101/# 807), Yongchang Zhang (Site # 122), and Haiyan Yang (Site # 802), as well as the Contract Research Organization (CRO), (b) (4) and the imaging CRO, (b) (4) were inspected.

Inspections of Drs. Zhou, Zhang, Yang, the CRO (b) (4) and the imaging CRO, (b) (4) did not find significant concerns regarding the study conduct, data discrepancies or integrity, Good Clinical Practice (GCP), or regulatory compliance.

Based on these inspections, Study C203 and Study G208 appear to have been conducted adequately, and the data generated by the inspected clinical investigators and the imaging

CRO and submitted by the Applicant appear acceptable in support of the proposed indication.

II. BACKGROUND

Nuvation Bio, Inc. submitted NDA 219713 seeking approval for taletrectinib for the treatment of adult patients with locally advanced or metastatic ROS1-positive NSCLC. The primary evidence of efficacy and safety supporting this indication is based on data from studies C203 and G208 for patients with fusion positive NSCLC and other solid tumors. Both studies are sponsored by AnHeart Therapeutics, LLC, a wholly owned subsidiary of Nuvation Bio, Inc.

Study C203 is a 2-stage, single-arm open-label, study of taletrectinib in subjects with locally advanced or metastatic NSCLC harboring ROS1 fusion with the objective to determine the safety, pharmacokinetics, and the recommended phase 2 dose (RP2D) of taletrectinib. At the time of the data cut-off date (June 7, 2024), Study C203 had enrolled 173 subjects, 67 were TKI pre-treated, and 106 subjects were TKI naïve across 33 centers in China.

Study G208 is a phase 2, multi-cohort, global, single-arm study designed to evaluate the safety and efficacy of taletrectinib in subjects with advanced NSCLC harboring ROS1 fusion and other solid tumors. The study enrolled 164 subjects across 5 cohorts in 74 sites throughout North America, Europe, and Asia. Fifteen subjects were enrolled in the United States across 12 sites.

In both studies, patients were required to have histologically confirmed, locally advanced or metastatic, ROS1-positive NSCLC, ECOG performance status of 0 or 1, and measurable disease per RECIST v1.1.

The primary efficacy analysis population to support the proposed indication consists of 273 evaluable subjects who were either ROS1 TKI treatment naïve or ROS1 TKI pre-treated. These subjects are defined as all ROS1-positive NSCLC participants who had at least one measurable lesion at baseline per RECIST v1.1, as determined by the Independent Review Committee (IRC), and received taletrectinib at a dose of 600 mg orally once daily in 21-day treatment cycles:

- ROS TKI treatment-naïve population (N=160): 54 subjects from Cohort 1 of Study G208 and 106 subjects from the ROS1 TKI naïve cohort of Study C203
- ROS TKI pre-treated population (N=113): 47 subjects from Cohort 2 of Study G208 and 66 subjects from the ROS1 TKI pre-treated Cohort of Study C203.

The primary efficacy endpoint to support approval was objective tumor response (ORR) assessed by IRC according to RECIST, version 1.1. The key secondary endpoint was duration of response (DoR) assessed by IRC.

All patients must sign informed consent prior to any screening evaluation. The baseline

screening procedures, including physical exam, laboratory tests, including virological examination, ECG, and ophthalmologic examination, must be performed within 28 days prior to initiation of treatment.

Tumor assessment with CT or MRI scan (chest/abdomen/pelvis) and brain MRI are to be performed at screening/baseline within 4 weeks prior to treatment initiation, followed by every 2 cycles in first the 8 cycles, then every 3 cycles for 9th to 26th cycles, and every 4 cycles thereafter until radiographic progression or discontinuation of study treatment (whichever occurs later), initiation of new anti-tumor therapy, loss to follow-up, death, withdrawal of consent, or study discontinuation, whichever occurs first. (b) (4)

(b) (4) was responsible for the central review of radiographic images from C203 and G208 studies

III. RESULTS (by site)

1. Dr. Caicun Zhou (Site # 101)

No. 507 Zhengmin Road
Yangpu District, Shanghai
China

Inspection dates: April 14 – 17, 2025

Dr. Zhou was inspected as a BIMO review-based inspection for Studies C203 and G208. This was the first inspection for this investigator.

At the time of the inspection, for study C203, the site had screened 52 subjects. Of those, 37 were enrolled (26 subjects were ROS1-TKI naïve, and 11 subjects were pre-treated with crizotinib). Of the 37 enrolled subjects, 12 subjects were on treatment, 10 were in follow-up phase for survival, 14 subjects had died, and 1 subject was lost to follow-up.

For study G208, the site had screened 2 subjects, and both were enrolled in the study. At the time of the inspection, one subject had continued on treatment and one subject had died.

Source records for all 37 subjects enrolled in study C203 and 2 subjects enrolled in G208 were reviewed. Records reviewed included, but were not limited to, informed consent, eligibility criteria and adverse event reporting, investigational product dispensing and accountability. No significant discrepancies were found when source data were compared with the data submitted to the NDA.

The inspection also verified that radiology studies to assess the primary efficacy endpoint were performed according to protocol-specified time points and all scans were submitted for central review. No issues were observed.

Additional records reviewed during the inspection included, but were not limited to,

investigator-signed agreements, financial disclosure forms, electronic records, staff training, communication with the sponsor, monitoring activities, and ethics committee approvals and correspondence. No issues were observed.

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

2. Dr. Youngchang Na Zhang (Site # 122)

No. 582 Xianjiahu
Yuelu District, Changsha City
Hunan, China

Inspection dates: March 24 – 28, 2025

Dr. Zhang was inspected as a BIMO review-based inspection for Study C203. This was the first FDA inspection for this investigator.

At the time of the inspection, the site had screened 33 subjects and enrolled 19 subjects. Of these, six subjects were still on the study drug, four subjects were in long term follow-up, and nine subjects had died.

Source records for all 19 enrolled subjects were reviewed. Records reviewed included, but were not limited to, informed consent forms, eligibility criteria, protocol adherence, concomitant medications, and adverse event reporting. No significant discrepancies were observed when compared with the data listings data sets submitted to the NDA.

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

Additional records reviewed during the inspection included, but were not limited to, Sponsor monitoring reports and correspondence, control of investigational product, study staff training, ethics committee approvals, and financial disclosure forms. No issues were observed.

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

3. Haiyan Yang (Site # 802)

283 Tongzipo Road
Yuelu District, Changsha
Hunan, China

Inspection dates: March 24 – 28, 2025

Dr. Yang was inspected as a BIMO review-based inspection for Study G208. This was the first FDA inspection for this investigator.

At the time of the inspection, the site had screened 12 subjects and enrolled eight in the study. Of these, five subjects had died due to disease progression, two subjects were still under treatment, and one was in the survival follow-up phase.

Source records for all 8 subjects enrolled at the site were reviewed and compared with the data listings submitted to the NDA. Records reviewed included, but were not limited to, informed consent forms, medical histories, inclusion/exclusion criteria, concomitant medications, laboratory reports, IP administration and patient diaries, and adverse event reporting.

The inspection verified that radiographic scans to evaluate the primary efficacy endpoint were performed as specified in the protocol and all scans were submitted for central review. Findings were consistent with the data submitted to the NDA.

Deficiencies in record keeping were noted during the inspection; however, they do not impact patient safety or data reliability.

Based on the preliminary results provided by the FDA field investigator, the data generated at Dr. Yang's site appear acceptable in support of the proposed indication in the NDA.

4. [REDACTED] (b) (4)

Inspection dates: [REDACTED] (b) (4)

This inspection assessed [REDACTED] (b) (4) oversight responsibilities for Study C203. This was the first inspection for this CRO.

[REDACTED] (b) (4) is a full-service CRO [REDACTED] (b) (4). The firm was contracted by Nuvation Bio to provide oversight for study C203, including clinical project management, site monitoring, and medical service.

Documents reviewed during inspection included verification of clinical investigator and site qualification, site monitoring processes and reports, investigational product receipt, storage, and dispensing of the IP monitoring, and review of the drug accountability at the sites, electronic records, safety and adverse event review and reporting. Monitoring files for two clinical sites (Sites #101 and #122) were reviewed in depth for compliance. No

issues were noted.

The inspection did not observe issues related to safety/adverse event handling or reporting for Study C203.

Based on the inspection, (b) (4) overall oversight of Study C203 for the areas for which they were contracted was adequate.

5. (b) (4)

Inspection dates: (b) (4)

This inspection reviewed (b) (4) responsibilities to perform an independent central imaging review for Study C203. This was the first FDA inspection for this imaging CRO.

Records reviewed included, but were not limited to, (b) (4) standard operating procedures, independent review charter, site imaging manual, training records, electronic systems, and imaging source data. The review found the processes adequate.

The inspection verified response data for 33 subjects (11 ROS1 TKI naïve and 22 ROS1 TKI pre-treated) enrolled in Study C203. Source data were compared to the efficacy line listing submitted to the NDA. No discrepancies were observed. The IDs of these subjects are as follow:

ROS1 TKI naïve	ROS1 TKI pre-treated
(b) (6)	

Based on the results of the inspection, the imaging review data generated (b) (4) (b) (4) appear acceptable in support of the proposed indication in the NDA.

{See appended electronic signature page}

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

CONCURRENCE:

Michele Fedowitz, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., Division Director, DCCE
For Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigation

CC:

Review Division /Project Manager/Raniya Al-Matari
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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/s/

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MICHELE B FEDOWITZ
05/21/2025 11:19:27 AM

KASSA AYALEW
05/22/2025 08:13:58 AM

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

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

Memorandum

Date: May 21, 2025

To: Raniya Al-Matari, Regulatory Project Manager
Division of Oncology 2 (DO2)

Barbara Scepura, Associate Director for Labeling, DO2

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

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for IBTROZI™ (taletrectinib) capsules, for oral use

NDA: 219713

Background:

In response to DO2's consult request dated November 25, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for IBTROZI™ (taletrectinib) capsules, for oral use.

PI:

OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on May 12, 2025, and our comments are provided below.

PPI:

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

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on April 15, 2025, and we do not have any comments at this time.

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

PI:

<u>Section</u>	<u>Statement from Draft</u>	<u>OPDP Comments</u>
HIGHLIGHTS OF PRESCRIBING INFORMATION	"The most frequently reported Grade 3 or 4 laboratory abnormalities (<u>≥ 5%</u>) were . . ." (underlined emphasis added)	OPDP notes that we typically see a cutoff of <u>≥ 2%</u> Grade 3 or 4 lab abnormalities listed in the Highlights for NSCLC therapies. We note that Section 6.1 of this USPI uses <u>≥ 2%</u> for the list of most common Grade 3 or 4 lab abnormalities. Is there a reason that <u>≥ 5%</u> was chosen for the highlights? When used in promotion and compared to competitors or other drugs for NSCLC, it may appear as though there are less Grade 3 or 4 lab abnormalities with this drug considering the threshold for what gets listed is higher here than for others. However, we defer to DO2 on what is appropriate.
14.1 Locally Advanced or Metastatic ROS1-Positive NSCLC	(b) (4)	We note that competitor labels for Augtyro and Rozlytrek just state "Intracranial response according to modified RECIST v1.1 was assessed by BICR." Was this subgroup analysis pre-specified and powered appropriately to measure Intracranial ORR? If not, OPDP is concerned that including this language in the label may imply that it is appropriate to draw conclusions from it, and we recommend revising to be consistent with the language in competitor labels. We defer to DO2 on whether this is appropriate.

19 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

KELLE E CARUSO
05/21/2025 11:59:11 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: May 19, 2025

To: Raniya Al-Matari, PhD
Regulatory Project Manager
Division of Oncology II (DO2)

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

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Kelle Caruso, PharmD, BCPS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): IBTROZI (taletrectinib)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 219713

Applicant: Nuvation Bio Inc.

1 INTRODUCTION

On October 23, 2024, Nuvation Bio Inc., submitted for the Agency's review an original New Drug Application (NDA) 219713 for IBTROZI (taletrectinib) capsules with a proposed indication for the treatment of locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology II (DO2) on November 26, 2024, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for IBTROZI (taletrectinib) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft IBTROZI (taletrectinib) capsules PPI received on October 23, 2024, and received by DMPP and OPDP on May 12, 2025.
- Draft IBTROZI (taletrectinib) capsules Prescribing Information (PI) received on October 23, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 12, 2025.
- Approved ROZLYTREK (entrectinib) capsules comparator labeling dated January 26, 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.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
05/19/2025 02:58:42 PM

KELLE E CARUSO
05/19/2025 03:09:01 PM

BARBARA A FULLER
05/19/2025 03:16:37 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

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

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Date of This Review:	May 12, 2025
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 219713
Product Name, Dosage Form, and Strength:	Ibuprofen (taletrectinib) capsules, 200 mg
Applicant Name:	Nuvation Bio Inc
FDA Received Date:	April 15, 2025
TTT ID #:	2024-11559-1
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 PURPOSE OF MEMORANDUM

Nuvation Bio Inc submitted revised container label and carton labeling received on April 15, 2025 for Ibtrozi. The Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Ibtrozi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Nuvation Bio Inc implemented all our recommendations and we have no additional recommendations at this time.

^a Stewart, J. Label and Labeling Review for Ibtrozi (NDA 219713). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 APR 11. TTT ID: 2024-11559.

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/s/

JANINE A STEWART
05/12/2025 10:15:35 AM

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05/12/2025 10:52:34 AM

LABEL AND LABELING REVIEW

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

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Date of This Review:	April 11, 2025
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 219713
Product Name, Dosage Form, and Strength:	Ibuprofen (taletrectinib) capsules, 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Nuvation Bio Inc
FDA Received Date:	October 23, 2024, December 12, 2024, March 7, 2025, and March 21, 2025
TTT ID #:	2024-11559
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 INTRODUCTION

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

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B

3 CONCLUSION

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

4 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Section 2 Dosage and Administration

- a. Consider adding the statement “Avoid food or drink containing grapefruit during treatment with IBTROZI” in Section (b) (4) For example:



(b) (4)

2. Section 16 How Supplied/Storage and Handling
 - a. We recommend adding the statement “and a carton of three bottles (90 tablets total) (NDC 84651-200-93).” at the end of the first paragraph. For example:



5 RECOMMENDATIONS FOR NUVATION BIO INC

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

1. In the “Recommended Dosage” statement, consider unbolding the “See prescribing information” portion for readability. For example, “Recommended Dosage: See prescribing information.”

B. Carton Labeling

1. As proposed, the net quantity statement on the principal display panel “90 capsules” is not the most accurate description of the packaging configuration. Revise the net quantity statement to the example below to more accurately describe how IBTROZI is supplied.

90 capsules

Contains three bottles of 30 capsules per bottle

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Ibtrozi received on March 21, 2025 from Nuvation Bio Inc.

Table 2. Relevant Product Information for Ibtrozi									
Initial Approval Date	N/A								
Active Ingredient	taletrectinib								
Indication	the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC)								
Dosage Form	capsules								
Strength	200 mg								
Route of Administration	oral								
Dose and Frequency	600 mg orally once daily until disease progression or unacceptable toxicity. Dosage modifications for adverse reactions: <table border="1"> <tr> <td>Dosage Reduction</td><td>Recommended Dosage</td></tr> <tr> <td>First Dosage Reduction</td><td>400 mg once daily</td></tr> <tr> <td>Second Dosage Reduction</td><td>200 mg once daily</td></tr> <tr> <td colspan="2">Permanently discontinue IBTROZI capsules in patients unable to tolerate 200 mg once daily.</td></tr> </table>	Dosage Reduction	Recommended Dosage	First Dosage Reduction	400 mg once daily	Second Dosage Reduction	200 mg once daily	Permanently discontinue IBTROZI capsules in patients unable to tolerate 200 mg once daily.	
Dosage Reduction	Recommended Dosage								
First Dosage Reduction	400 mg once daily								
Second Dosage Reduction	200 mg once daily								
Permanently discontinue IBTROZI capsules in patients unable to tolerate 200 mg once daily.									
How Supplied	Bottles of 30 capsules Carton of 3 bottles								
Storage	20°C to 25°C (68°F to 77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F).								
Container Closure	high-density polyethylene (HDPE) bottle with a (b) (4) (b) (4) cap (b) (4)								

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Ibtrozi labels and labeling submitted by Nuvation Bio Inc.

- Prescribing Information received on March 21, 2025, available from <\\CDSESUB1\EVSPROD\nda219713\0040\m1\us\114-labeling\draft\labeling\draft-pi.docx>
- Patient Package Insert received on October 23, 2024, available from <\\CDSESUB1\EVSPROD\nda219713\0002\m1\us\114-labeling\draft\labeling\draft-ppi.docx>
- Container label(s) received on March 7, 2025
- Carton labeling received on December 12, 2024

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

Container Label(s):



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

Carton Labeling:

(b) (4)



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/s/

JANINE A STEWART
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04/11/2025 01:06:48 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: April 7, 2025

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Associate Director, Cardiac Safety IRT, DCN

To: Raniya Ali Al-Matari, RPM
DO2

Subject: QT Consult to NDA 219713 (SDN 002)

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

This memo is an addendum to our previous review dated 03/17/2025 in DARRTS. We reviewed the following materials:

- Applicant's proposed label (NDA 219713 / SDN 0040; [link](#)); and
- Previous IRT review for NDA 219713 dated [03/17/2025](#) in DARRTS.

We initially provided labeling recommendations in our review dated March 17, 2025. The purpose of this review addendum is to provide you with revised labeling recommendations. While the suggested revisions only affect Section 5, this document includes all label sections pertaining to QTc for ease of reference, incorporating previously provided comments.

Our changes are highlighted ([addition](#), [deletion](#)). Each section is followed by a rationale for the changes made. We defer final labeling decisions to the Division.

2.5 Dosage Modifications for Adverse Reactions

QTc Interval Prolongation [see	Grade 2 (QTc interval 481-500 msec)	• Withhold IBTROZI until recovery to $\leq$ Grade 1 or baseline.
--------------------------------	-------------------------------------	--

Warnings and Precautions (5.3)]		• (b) (4) correct electrolytes and/or change concomitant medications. • Resume at same dose.
	Grade 3 (QTc interval ≥ 501 msec or QTc interval increase of >60 msec from baseline)	• Withhold IBTROZI until recovery to $\leq$Grade 1 or baseline. • (b) (4) correct electrolytes and/or change concomitant medications. • (b) (4)
	Grade 4 (Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)	• Permanently discontinue IBTROZI.
Reviewer's Comment: The proposal by the Applicant is acceptable		

5.3 QTc Interval Prolongation

[IBTROZI has been shown to prolong the QTc interval in a concentration-dependent manner \[see Clinical Pharmacology \(12.2\)\]](#).

(b) (4)

Significant prolongation of the QTc interval may occur when IBROTZI is inappropriately taken with food, strong CYP3A4 inhibitors, and/or drugs with a known potential to prolong QTc. Therefore, coadministration with food must be avoided and concomitant use with strong CYP3A4 inhibitors and/or drugs with a known potential to prolong QTc should be avoided [see Dosage and Administration (2.4), Drug Interactions (7.1, 7.4)].

(b) (4)

Reviewer's Comment: We do not consider it necessary to include information (b) (4). Instead, we recommend using information about onset of QTc prolongation to impact recommendations on the timing of ECG monitoring. For example, if significant QTc prolongation is expected after the first dose, then monitoring recommendations could include an ECG after the first dose. For taletrectinib, however, there is not a significant concern for QTc prolongation following the first dose due to magnitude at steady-state (~12 msec) and long terminal half-life (85 h). (b) (4)

Otherwise, we have proposed edits to improve clarity and recommend a statement concerning the potential for QTc prolongation if co-administered with a high-fat meal, strong CYP3A4 inhibitor, or another QTc prolonging drug.

6 Adverse Reactions

Table 3. Adverse Reactions

(b) (4)

Adverse Reaction ¹	IBTROZI N= (b) (4)	
	All Grades (%)	Grade 3 or 4 ^k (%)
Cardiac		
Electrocardiogram QT prolonged	19	(b) (4)

Reviewer's comment: We confirmed the Applicant's analysis. However, we want to note that the approach to rounding differs between the two columns (i.e., (b) (4) 19% and (b) (4) %). We defer to the Division concerning need for harmonization.

7.1 Effects of Other Drugs on IBTROZI

Avoid concomitant use with strong or moderate CYP3A inhibitors. Concomitant use of IBTROZI with a strong or a moderate CYP3A inhibitor (b) (4) taletrectinib exposure, which may increase the (b) (4) of adverse reactions (b) (4).

QTc prolongation.

(b) (4)

(b) (4)

^(b)
⁽⁴⁾ **Drugs That Prolong the QTc Interval**

Avoid coadministration of IBTROZI with products with a known potential to prolong QTc interval, such as antiarrhythmic drugs and other drugs that are known to prolong the QTc interval. If concomitant use cannot be avoided, monitor ECG when initiating, during concomitant use, and as clinically indicated [see Warnings and Precautions (5.3), Clinical Pharmacology (12.2)].

Reviewer's comment: We recommend inclusion of a new section ^(b) ⁽⁴⁾ to address concomitant use with other QTc prolonging drugs.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

^(b)
⁽⁴⁾

At 1.5-fold the therapeutic plasma concentration, achieved with inadvertent administration with a high fat meal, the predicted increase in $\Delta QTcF$ is XX (YY, ZZ).

Reviewer's comment: The results of our analysis and the Applicant's analysis are similar and we therefore propose including the results of the Applicant's analysis, but with rounding to one significant digit. The Applicant did not include a prediction of the increase in QTc when co-administered with food (Cmax: 714 ng/mL) and we therefore recommend requesting that the Applicant adds the predicted increase in QTc.

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 cderrcpqt@fda.hhs.gov

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/

LARS JOHANNESSEN
04/07/2025 01:43:04 PM

CHRISTINE E GARNETT
04/07/2025 01:50:14 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 219713
Submission Number	2
Submission Date	10/23/2024
Date Consult Received	12/6/2024
Drug Name	Taletrectinib
Indication	Treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC)
Therapeutic Dose	600 mg QD
Clinical Division	DO2
Protocol Review	Not previously reviewed.

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

Note: This review is a replication of our previous [review](#) dated March 4, 2025. The current version has been revised to correct minor referencing table errors. The scientific findings and conclusions remain unchanged from the original review.

This review responds to your consult dated 12/6/2024 regarding the Applicant's QT evaluation. We reviewed the following materials:

- QT evaluation report for taletrectinib ([NDA 219713/SDN 002](#));
- Cardiac safety report – see Appendix 5 in “QT evaluation report” ([NDA219713/SDN002](#));
- Applicant's draft label ([NDA219713/SDN002](#));
- Study protocol U101 ([NDA219713/SDN002](#));
- Study protocol J102 ([NDA219713/SDN002](#));
- Summary of Clinical Pharmacology Studies ([NDA219713/SDN002](#)); and
- Highlights of clinical pharmacology and cardiac safety – Appendix 2 in “QT evaluation report” ([NDA219713/SDN002](#)).

1 SUMMARY

Taletrectinib treatment was associated with concentration-dependent increase of the QTcF interval based on concentration-QTc analysis of studies DS6501-A-U101 and DS6051-A-J102 – see Table 1 for overall results. At the average maximum concentration for 600 mg QD (therapeutic dose), the predicted mean increase in the change from baseline for QTc (Δ QTc) is 13 msec. Taletrectinib is administered under fasting conditions, however, if taletrectinib is inadvertently taken with a high-fat meal the predicted mean increase in Δ QTc is 21 msec.

Both studies, DS6501-A-U101 and DS6051-A-J102, were phase 1, open label, non-randomized, multiple-ascending-dose studies in patients with cancer. Study DS6051-A-J102 was conducted in Japanese subjects with solid tumors while Study DS6501-A-U101 was conducted in North America and Europe in subjects with systemic metastases and/or unresectable solid tumors. The highest exposure in the alternative QTc assessment was provided by the 600 mg QD dose in study DS6051-A-J102, which covers high clinical exposure.

Data were analyzed using concentration-QTc analysis as the primary analysis, which suggest that talrectinib is associated with large mean increases in the QTcF interval (section 4.5). The findings of the primary analysis are further supported by the small hERG margin (~14-fold), by-time analysis (section 4.3), and categorical analysis (section 4.4).

Table 1: Summary of findings

QT assessment pathway	☐ <i>Thorough QT study</i> ☐ <i>Substitute for thorough QT study (5.1)</i> ☒ <i>Alternative QT study when a thorough QT study is not feasible (6.1)</i>				
Clinical QT study findings	- High clinical exposure scenario of talrectinib is anticipated to be when the drug product is inadvertently co-administered with high fat meal resulting in 1.5-fold increase in C_{max} (section 3.1) - The highest mean exposure in the QTc assessment was provided by 600 mg QD on day 15 in Japanese subjects with solid tumor, which covers high clinical exposure.				
	ECG parameter	Treatment	Concentration	ΔΔQTcF (msec)	90% CI (msec)
	QTcF	600 mg QD, orally without food	476 ng/mL	12.9	(10.3 to 15.6)
	QTcF	600 mg QD, orally with high fat meal	714 ng/mL	20.5	(16.3 to 24.7)
	QTcF	600 mg QD, Day 15 (Study J102)	643 ng/mL	18.2	(14.5 to 22)
In vitro findings	Integrated nonclinical risk assessment was not performed.				
In vivo findings					

2 RECOMMENDATIONS

2.1 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 0002 ([link](#)).

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

2.3 Dosage Modifications for Adverse Reactions

QTc Interval Prolongation [see Warnings and Precautions]	Grade 2 (QTc interval 481- 500 msec)	Withhold IBTROZI until recovery to $\leq$ Grade 1 or baseline. (b) (4) correct electrolytes and/or change concomitant medications. Resume at same dose.
	Grade 3 (QTc interval $\geq$ 501 msec or QTc interval increase of >60 msec from baseline)	Withhold IBTROZI until recovery to $\leq$ Grade 1 or baseline. (b) (4) correct electrolytes and/or change concomitant medications. (b) (4)
	Grade 4 (Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)	Permanently discontinue IBTROZI.

Reviewer's comment: The proposal by the Applicant is acceptable.

5.3 QTc Interval Prolongation

[IBTROZI has been shown to prolong the QTc interval in a concentration-dependent manner \[see Clinical Pharmacology \(12.2\)\].](#)

(b) (4)

Significant prolongation of the QTc interval may occur when IBROTZI is inappropriately taken with food, strong CYP3A4 inhibitors, and/or drugs with a known potential to prolong QTc. Therefore, coadministration with food must be avoided and concomitant use with strong CYP3A4 inhibitors and/or drugs with a known potential to prolong QTc should be avoided [see Dosage and Administration (2.4), Drug Interactions (7.1, 7.4)].

(b) (4)

Reviewer's comment: We agree with including information about the time to resolution of QTc prolongation because of the long half-life (terminal half-life of 85 h) for talretrectinib. However, we consider estimating time to resolution based on the PK of talretrectinib to be a better estimator since the QTc prolongation is concentration-related. Otherwise, we have proposed edits to improve clarity and recommend a statement concerning the potential for QTc prolongation if co-administered with a high-fat meal, strong CYP3A4 inhibitor, or another QTc prolonging drug.

6 Adverse Reactions

Table 3. Adverse Reactions

(b) (4)

Adverse Reaction	IBTROZI N= (b) (4)	
	All Grades (%)	Grade 3 or 4 (%)
Electrocardiogram QT prolonged	19	(b) (4)

Reviewer's comment: We confirmed the Applicant's analysis. However, we want to note that the approach to rounding differs between the two columns (i.e., (b) (4) 19% and (b) (4) %). We defer to the Division concerning need for harmonization.

7.1 Effects of Other Drugs on IBTROZI

Avoid concomitant use with strong or moderate CYP3A inhibitors. Concomitant use of IBTROZI with a strong or a moderate CYP3A inhibitor (b) (4) taletrectinib exposure, which may increase the (b) (4) of adverse reactions (b) (4)

(b) (4) **Drugs That Prolong the QTc Interval**

Avoid coadministration of IBTROZI with products with a known potential to prolong QTc interval, such as antiarrhythmic drugs and other drugs that are known to prolong the QTc interval. If concomitant use cannot be avoided, monitor ECG when initiating, during concomitant use, and as clinically indicated [see Warnings and Precautions (5.3), Clinical Pharmacology (12.2)].

Reviewer's comment: We recommend inclusion of a new section (b) (4) to address concomitant use with other QTc prolonging drugs.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)
At 1.5-fold the therapeutic plasma concentration, achieved with inadvertent administration with a high fat meal, the predicted increase in Δ QTcF is XX (YY, ZZ).

Reviewer's comment: The results of our analysis and the Applicant's analysis are similar and we therefore propose including the results of the Applicant's analysis, but with rounding to one significant digit. The Applicant did not include a prediction of the increase in QTc when co-administered with food (Cmax: 714 ng/mL) and we therefore recommend requesting that the Applicant adds the predicted increase in QTc.

3 APPLICANT'S SUBMISSION

3.1 OVERVIEW

The Applicant (Nuvation Bio, Inc.) is proposing taletrectinib (AB-106 or DS-6051b), a kinase inhibitor, for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer. The proposed therapeutic dose is 600 mg QD without food.

We have not previously been consulted on the QTc assessment for this product. Briefly, the Applicant is proposing to use concentration-response to characterize the effects on the QTc interval pursuant to the ICH E14 Q&A 6.1 approach using studies DS6501-A-U101 DS6051-A-J102. For a review of the two studies and the proposed analysis, please refer to sections 5.1 and 5.2 in the appendix.

3.1.1 Clinical Pharmacology

The clinical pharmacology of talretrectinib is summarized in the [summary of clinical pharmacology studies](#) and in the table of [highlights of clinical pharmacology](#) and cardiac safety. Briefly, talretrectinib exhibits linear kinetics in the dose range of 50 to 1200 mg taken QD. It has long absorption time (median T_{max} range between 3 – 6 hours), long half-life (terminal T_{1/2} = 80 – 100 hours) and accumulates up to 4.5-fold day 1 AUC, reaching steady state after 8 days of dosing (effective T_{1/2} ≈ 66 hours).

According to the Applicant's population PK analysis, age, sex, and race have no impact on talretrectinib PK. Similarly, no impact of mild hepatic impairment and up to moderate renal impairment was detected in the analysis. However, a DDI study determined that strong CYP3A4 inhibitor would increase talretrectinib C_{max} by 1.76-fold. A food effect study determined that high fat meal would increase the C_{max} by about 1.5.

Since the Applicant plans prohibition or dose adjustment when talretrectinib is administered in hepatic impairment or with strong CYP3A4 inhibitors, high clinical exposure scenario is anticipated when talretrectinib is inadvertently co-administered with high fat meal.

Table 2 presents the exposures at the highest test dose in the QTc assessment and coverage of the high clinical exposure scenario.

Table 2. Summary of Dose and Exposure Assessment

		Mean C _{max}
Highest therapeutic or clinical trial dosing regimen	600 mg QD without food.	*476 ng/mL (C _{max,ss})
Applicant's High clinical exposure scenario	1.5-fold increase when co-administered with high fat meal	714 ng/mL
Highest exposure in QT assessment	600 mg QD (Day 15)	643.2 ng/mL
C _{max} Ratio	643.2 / 714 = 0.9	

* Geometric mean steady state C_{max} in a global, phase 2 study in subjects with NSCLC and other solid tumors (n = 41). Although geometric mean C_{max} on Cycle 1 day 15 in a small study (study DS6051-A-J102) in Japanese subjects with solid tumors (n = 6) was 661 ng/mL, it is not considered to represent the patient population.

3.1.2 Nonclinical Safety Pharmacology Assessments

The Applicant evaluated the effects of talretrectinib on hERG current in the study report (VPT1347/2013, [link](#)). The hERG current was assessed at ambient temperature using manual patch clamp assay. The hERG IC₅₀ was 0.98 μM (using actual concentration), which corresponds to a hERG safety margin of 14-fold (high clinical C_{max} = 714 ng/mL, MW: 551.61 g/mol; PB: 94.6%) using the clinical exposure scenario (Table 2).

The effects on NaV1.5 peak was also evaluated by the Applicant (VPT1348/2013; [link](#)). The NaV1.5 peak current was assessed at room temperature using a train of 10 pulses protocol (the inter pulse frequency was 2 Hz). The protocol was used to assess the resting or tonic block (current block at the first pulse) and use-dependent block (current block by the 10th pulse). Talretrectinib inhibited the Nav1.5 peak current in a concentration-dependent manner, with IC₅₀ values of 25 μM for resting block and 0.83 μM for use-dependent block. The corresponding safety margins were 358× for resting block and 12× for use-dependent block. The positive control, flecainide (100 μM), significantly induced

a use-dependent block of the Nav1.5 peak current, indicating that talretrectinib exhibits a blocking characteristic on Nav1.5 peak current similar to flecainide at room temperature.

The in vivo QT study (VPT1662/2013, [link](#)) assessed the effects of talretrectinib on ECG parameters following single oral doses to conscious telemetrized cynomolgus monkeys (n=4). The study did not collect PK. The free Cmax of the highest dose (100 mg in the study is approximately the free Cmax of the clinical exposure scenario based on two separate in vivo studies (VPT1578-2013, [link](#) and vpt1215-2013, [link](#))¹. This is based on similar protein binding between human (94.6%) and monkeys (93.2%; vpt1218/2013, [link](#)). No changes in QTc, HR, PR, or QRS were observed at the highest dose. The lack of ECG changes in the study could be due to exposure and/or sensitivity of the study.

3.2 APPLICANT'S RESULTS

3.2.1 By-Time Analysis

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

In the by-time point analysis (Section 5.3.1 Cardiac Safety Report), talretrectinib appeared to demonstrate a modest clinically relevant effect on QTcF. This was clearest in the 800 mg daily cohort in Study DS60551-A-U101 Part I and Part Ib food effect cohort, where data were available for total of 15 subjects for steady state PK (Cycle 1 Day 15). Other cohorts/dose levels had 1-7 subjects, which is a relatively small sample size for accurately estimating the central tendency of the QTc effect. In Study DS60551-A-U101 Part I, the largest LS mean change-from baseline QTcF (Δ QTcF) for 800 mg QD (n=15) was 21.1 msec (95% CI: 15.00; 27.18 msec) at 2 hours after dosing.

Applicant also presented by-time analysis results for other intervals. Applicant used both descriptive statistics and MMRM analysis for the time points with at least three subjects.

Reviewer's comment: *Considering the small sample size, the reviewer performed non-parametric descriptive statistics analysis. The reviewer's by-time analysis results also show mean Δ QTcF greater than 10 msec in multiple time points. Please see section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

Not applicable for as this was alternative QTc assessment without placebo and positive control.

3.2.1.1.1 QT Bias Assessment

Not performed.

¹ Two studies are included because they studied different lots, and it is unclear which lot was included in the CV study. The Cmax for 100 mg/kg was similar between the two studies and an average is therefore used (472 ng/mL).

3.2.2 Categorical Analysis

No subjects in either study developed a new QTcF > 500 msec. In Study DS6051-A-U101 Part I, one subject (5.6%) at 800 mg QD experienced Δ QTcF > 60 msec. No subjects from Study DS6051-A-J102 had Δ QTcF > 60 msec. Several subjects in Study DS6051-A-U101 met tachycardic categorical outlier criteria; the clinical significance of these tachycardic outliers is unclear. No subjects developed new PR or QRS categorical outlier findings.

Reviewer's comment: *The reviewer also performed categorical analysis for all intervals. The reviewer's analysis results are similar to the Applicant's results. Please see section 4.4 for additional details. Integrated assessment of outliers is described in section 3.2.4.*

3.2.3 Exposure-Response Analysis

The Applicant conducted separate and pooled C-QTc analysis of data from studies DS6051-A-U101 and DS6051-A-J102 (See Appendix 5 for description of the designs). For pooled analysis, the Applicant conducted a statistical test of homogeneity between the 2 studies. Although mean heart rate changes >10 bpm were observed, the Applicant posits that talretrectinib did not cause clinically relevant changes in heart rate (HR), as the changes were not dose-dependent. The Applicant also posits that the changes were small and therefore unlikely to materially impact C-QTc analysis. Linear mixed effects modelling was conducted as recommended in the white paper.

C-QTc Results based on Study DS6051-A-U101

The concentration-QTc analysis for Study DS6051-A-U101 was based on 885 time-matched ECG-PK pairs. The estimated population slope of the concentration-QTc relationship was 0.031 ms per ng/mL (90% CI: 0.0217 to 0.0396; $P < 0.0001$), with a population intercept of -1.95 ms (90% CI: -3.923 to 0.027; $P = 0.1045$). The population slope of DS-6051a was significant at the 10% significance level while the population intercept was not significant.

The model predicted effects on Δ QTcF were 14.15 ms (90% CI: 10.26 to 18.04) and 26.21 ms (90% CI: 18.96 to 33.45) at the geometric mean C_{max} on Cycle 1 Day 15 of 800 mg QD (525.1 ng/mL) and 1200 mg QD (918.0 ng/mL), respectively.

An effect on Δ QTcF with 90% UCI exceeding 10 ms can be expected at DS-6051a plasma concentrations above ~315 ng/mL while an effect with 90% UCI exceeding 20 ms can be expected at plasma concentrations above ~576 ng/mL. The results of the Sponsor's analysis show an absence of significant QTc prolongation.

C-QTc Results based on Study DS6051-A-J102

The concentration-QTc analysis for Study DS6051-A-J102 was based on 133 time-matched ECG-PK pairs. The estimated population slope of the concentration-QTc relationship was 0.037 ms per ng/mL (90% CI: 0.0252 to 0.0485; $P = 0.0012$), with a population intercept of -4.84 ms (90% CI: -10.302 to 0.614; $P = 0.1400$). The population slope of DS-6051a was significant at 10% significance level while the population intercept was not significant.

The model predicted effects on Δ QTcF were 18.85 ms (90% CI: 12.90 to 24.79) and 27.79 ms (90% CI: 18.09 to 37.49) at the geometric mean C_{max} on Cycle 1 Day 15 of 600 mg QD (643.2 ng/mL) and 800 mg QD (886.2 ng/mL), respectively. An effect on

Δ QTcF with 90% UCI exceeding 10 ms can be expected at DS-6051a plasma concentrations above ~302 ng/mL while an effect with 90% UCI exceeding 20 ms can be expected at plasma concentrations above ~549 ng/mL.

C-QTc Results from Pooled data of studies DS6051-A-U101 and DS6051-A-J102

The Levene's test of homogeneity indicated that the 2 studies had equal variances.

The concentration-QTc analysis for the pooled analysis was based on 1018 time-matched ECG-PK pairs. The estimated population slope of the concentration-QTc relationship was 0.032 ms per ng/mL (90% CI: 0.0248 to 0.0388; $P < 0.0001$), with a population intercept of -2.40 ms (90% CI: -4.216 to -0.574; $P = 0.0320$). Both the population slope of DS-6051a and the population intercept were statistically significant at 10% significance level.

The model predicted effects on Δ QTcF were 15.00 ms (90% CI: 11.91 to 18.09) and 26.82 ms (90% CI: 21.30 to 32.35) at the geometric mean C_{max} on Cycle 1 Day 15 of 800 mg QD (546.6 ng/mL) and 1200 mg QD (918.0 ng/mL), respectively. An effect on Δ QTcF with 90% UCI exceeding 10 ms can be expected at DS-6051a plasma concentrations above ~331 ng/mL while an effect with 90% UCI exceeding 20 ms can be expected at plasma concentrations above ~597 ng/mL.

Reviewer's comment: *In pooling data from fed (Part 1b of U101) and fasted states (Part 1 of U101 and J102) the Applicant ignored the potential impact of food intake on QTc interval. This may introduce bias in estimating C-QTc relationship. The Applicant also excluded time-matched ECGs in cycles 2 and 3 of Study U101, thus limiting the number of evaluable time-matched ECG-PK pairs. The results of our independent analysis, which only excluded ECG/PK data during fed administration (section 4.5), are similar to the Applicant's results. It should be noted that only 1 subject received 1200 mg on Cycle 1 day 15. Therefore, the predicted Δ QTcF at this dose represent individual prediction rather than mean prediction at 1200 mg dose.*

3.2.4 Safety Analysis

The Applicant pooled safety data from Phase 1 and 2 studies in participants with solid tumors (Studies AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101) to support an integrated safety analysis. The Applicant considered three analysis populations: ROS1+NSCLC 600 mg QD, 600 mg QD (all cancer types), and overall. In subsequent sections, we will only be describing the findings for the overall analysis.

Table 3 shows the AEs included in the integrated safety analysis that belonged to the "Torsade de pointes/QT prolongation" broad SMQ. As shown, most of the AEs were related to QTc prolongation:

Three of the AEs were SAEs (cardiac arrest: 2; syncope: 1). Neither of the two participants that experienced a cardiac arrest had a reported QTc at the time of the events. No QTc prolongation was reported for the two participants that experienced an AE of ventricular tachycardia.

No participant withdrew treatment due to a QT-prolonging AEs. However, 2.8% of participants had a treatment interruption and 2.8% had a dose reduction due to QT prolonging AEs.

Reviewer's comment: *We analyzed the integrated safety analysis dataset using our customized Torsade de pointes/QTc prolongation query and identified two additional preferred terms: arrhythmia (n=2) and death (n=2). There were 86 participants with an AE belonging to the modified query and a QTc (at any time) >480 msec (QT prolongation: 84; syncope: 2). For the two participants that experienced an AE of syncope, the reported QTc prolongation did not occur near the event.*

The Applicant also performed outlier analysis using the integrated safety analysis dataset and the corresponding results are shown in Table 4.

Table 3. Integrated QT AE Safety Analysis

Grouped Term	Overall (N=412)	
	All Events	NCI CTCAE Grade ≥ 3
Torsade de pointes/QT prolongation SMQ Broad	79 (19.2%)	21 (5.1%)
<i>Electrocardiogram QT prolonged</i>	68 (16.5%)	13 (3.2%)
<i>Syncope</i>	9 (2.2%)	6 (1.5%)
<i>Cardiac arrest</i>	2 (0.5%)	2 (0.5%)
<i>Ventricular tachycardia</i>	2 (0.5%)	0

Source: QT Evaluation Report, Table 5

Table 4. Integrated Outlier analysis

Parameter	Overall (N=412)
QTcF (msec)	
>450 to ≤ 480	95 (23.1%)
>480 to ≤ 500	23 (5.6%)
>500	9 (2.2%)
Δ QTcF (msec)	
>30 to ≤ 60	158 (38.3%)
>60	45 (10.9%)

Source: QT Evaluation Report, Tables 2 and 3

Reviewer's comment: *The reported QTc outliers >500 msec were not from the two studies used for QTc assessment. All the participants with QTc >500 msec also had a Δ QTc >60.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

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

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader in a blinded manner. Compared to the ECG warehouse algorithm, we did not observe significant bias in QT measurements and the ECG acquisition and interpretation for these studies is therefore acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. To be consistent with the rest of the cohorts, we have excluded cohort 7 (fed-fasted and fasted-fed sequences) from study DS6051-A-U101. Study J102 was analyzed separately. We have included data for cycle 1 (days 1, 2, 8, and 15), cycle 2 day 1 and cycle 3 day 1. Due to small sample size, we have excluded rest of the cycles from the analysis. The reviewer evaluated the ΔQTcF effect using descriptive (nonparametric) statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for different treatment groups. The maximum ΔQTcF values by treatment are shown in Table 5. The findings show that talretrectinib has dose-dependent QTc effects, except for the lowest dose group of talretrectinib ≤ 200 mg with small sample size (i.e., $n = 3$).

Figure 1. Median and 90% CI of Δ QTcF Time-Course (Unadjusted CIs)

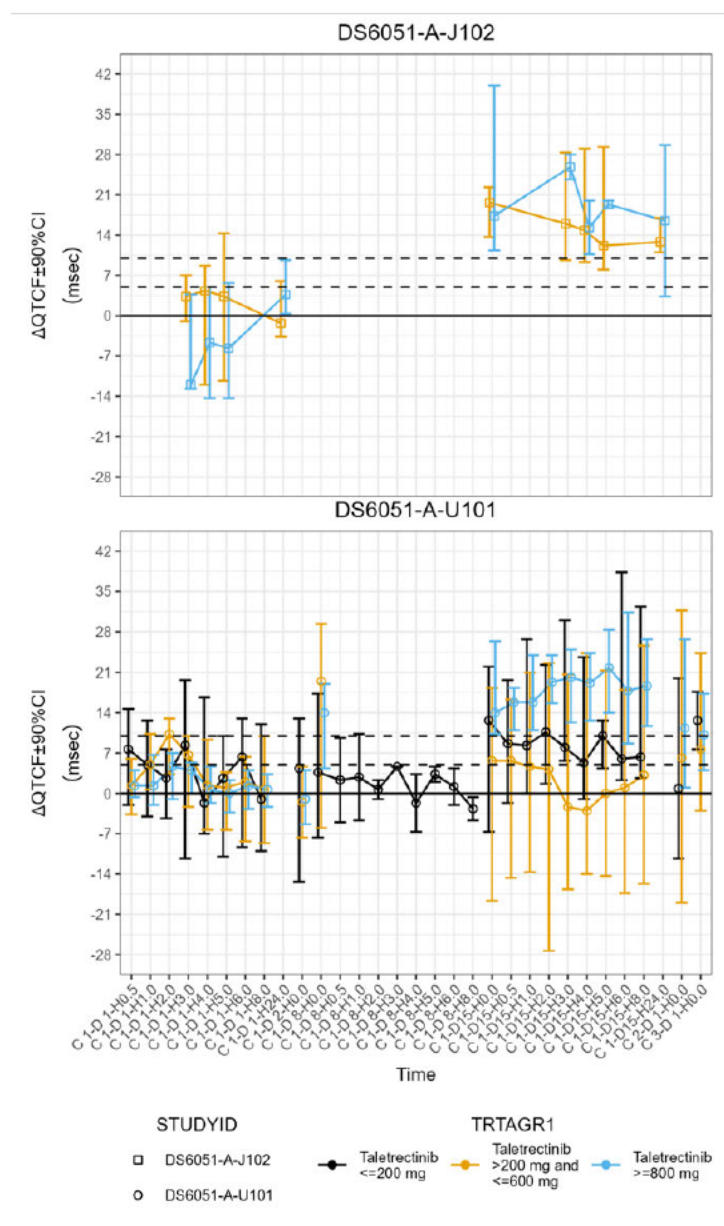


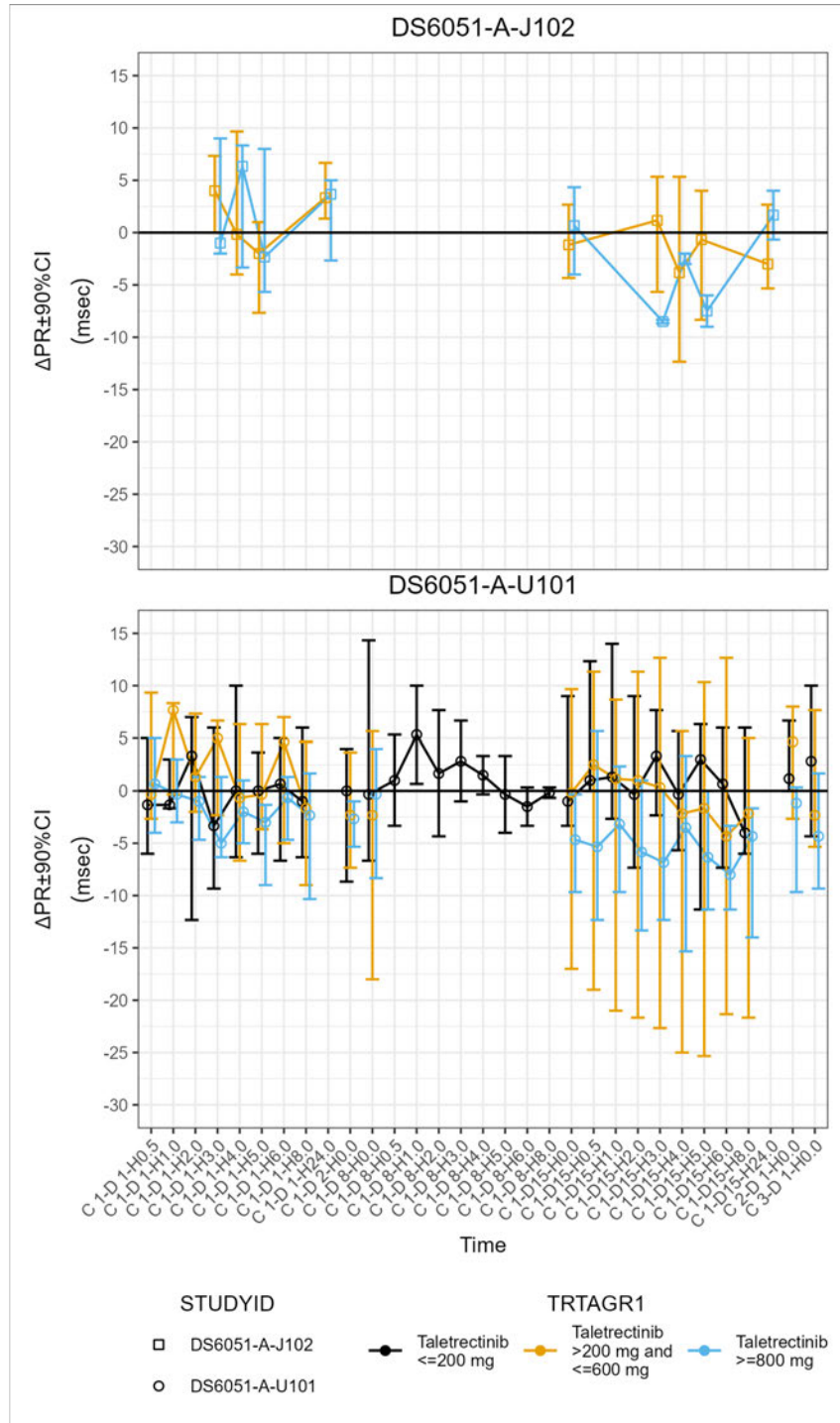
Table 5. Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Δ QTcF

TRTAGR1	Study Identifier	Period	Analysis Nominal Period Day (C)	N	Time (Hour)	Δ QTcF (msec)	90.0% CI (msec)
Taletrectinib ≤ 200 mg	DS6051-A-U101	1	15	3	6.0	6.0	(2.3 to 38.3)
Taletrectinib > 200 mg and ≤ 600 mg	DS6051-A-J102	1	15	12	5.0	12.2	(8.0 to 29.3)
Taletrectinib ≥ 800 mg	DS6051-A-U101	1	15	16	6.0	17.8	(8.7 to 31.3)

4.3.3 PR

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

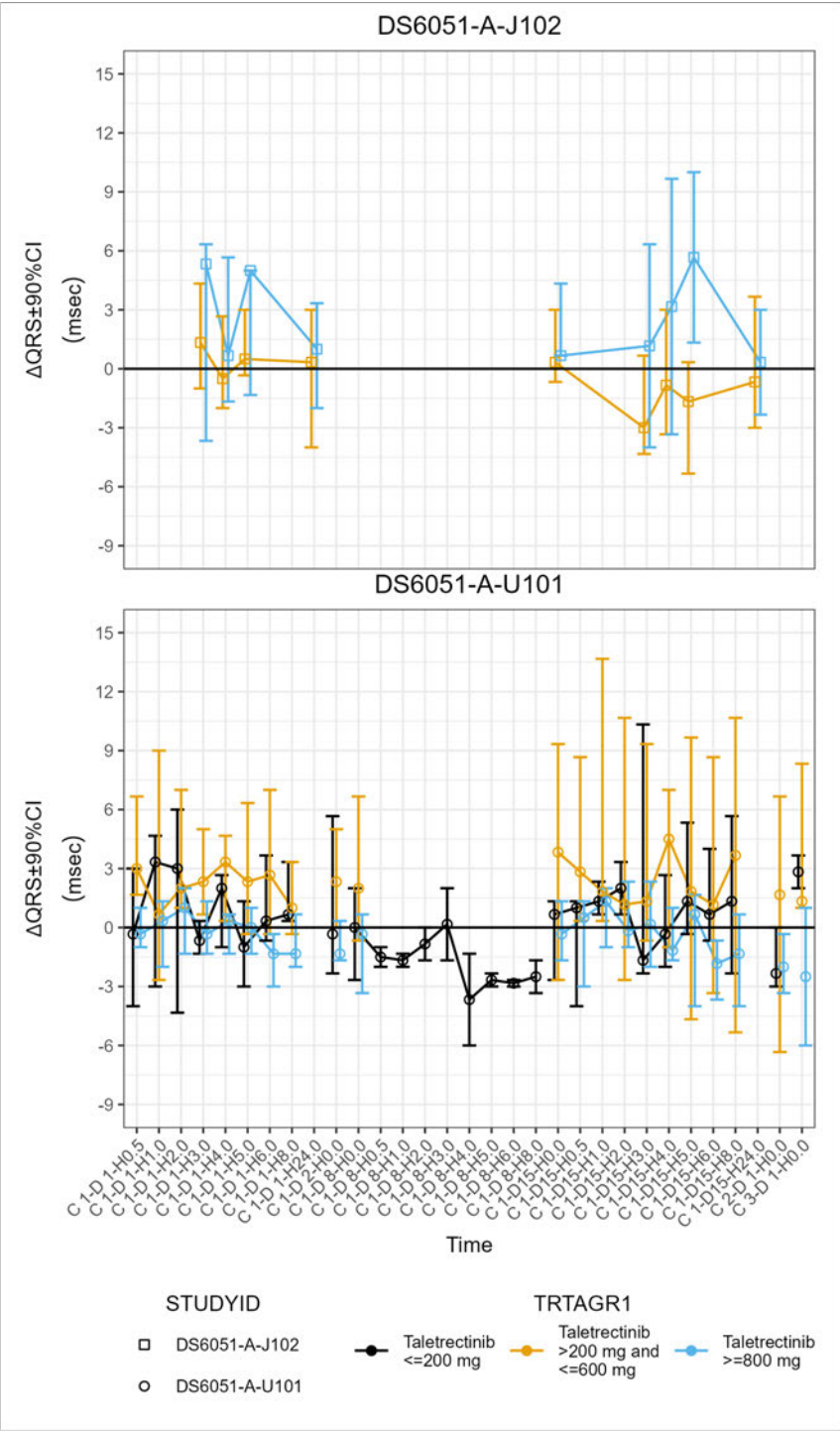
Figure 3. Median and 90% CI of Δ PR Time-Course



4.3.4 QRS

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

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, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects in any of the studies experienced QTcF values >500 msec for any dose levels of taletrectinib. Table 6 lists the categorical analysis results for Δ QTcF (<30 msec, >30 and <60, and >60 msec). One subject in taletrectinib $\geq$ 800 mg in study DS6051-A-U101 experienced Δ QTcF >60 msec.

Table 6. Categorical Analysis for Δ QTcF (Maximum)

Study Identifier	TRTAGR1	Total (N)		Value $\leq$ 30 msec		30 msec < Value $\leq$ 60 msec		Value >60 msec	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
DS6051-A-U101	Taletrectinib $\leq$ 200 mg	5	130	4 (80.0%)	127 (97.7%)	1 (20.0%)	3 (2.3%)	0 (0%)	0 (0%)
	Taletrectinib >200 mg and $\leq$ 600 mg	20	501	13 (65.0%)	489 (97.6%)	7 (35.0%)	12 (2.4%)	0 (0%)	0 (0%)
	Taletrectinib $\geq$ 800 mg	21	633	7 (33.3%)	579 (91.5%)	13 (61.9%)	52 (8.2%)	1 (4.8%)	2 (0.3%)

4.4.2 HR

Table 7 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). One subject in study DS6051-A-J102 and six subjects in study DS6051-A-U101 experienced HR >100 beats/min for different dose levels of taletrectinib.

Table 7. Categorical Analysis for HR (Maximum)

Study Identifier	TRTAGR1	Total (N)		Value $\leq$ 100 beats/min		Value >100 beats/min	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
DS6051-A-J102	Taletrectinib >200 mg and $\leq$ 600 mg	12	114	11 (91.7%)	109 (95.6%)	1 (8.3%)	5 (4.4%)
	Taletrectinib $\geq$ 800 mg	3	26	3 (100.0%)	26 (100.0%)	0 (0%)	0 (0%)
DS6051-A-U101	Taletrectinib $\leq$ 200 mg	5	130	5 (100.0%)	130 (100.0%)	0 (0%)	0 (0%)
	Taletrectinib >200 mg and $\leq$ 600 mg	20	501	17 (85.0%)	495 (98.8%)	3 (15.0%)	6 (1.2%)
	Taletrectinib $\geq$ 800 mg	21	633	18 (85.7%)	622 (98.3%)	3 (14.3%)	11 (1.7%)

4.4.3 PR

None of the subjects in both studies experienced PR >220 msec; with and without 25% increase over baseline for any dose levels of talrectinib.

4.4.4 QRS

None of the subjects in both studies experienced QRS >120 msec; with 25% increase over baseline for any dose levels of talrectinib.

4.5 EXPOSURE-RESPONSE ANALYSIS

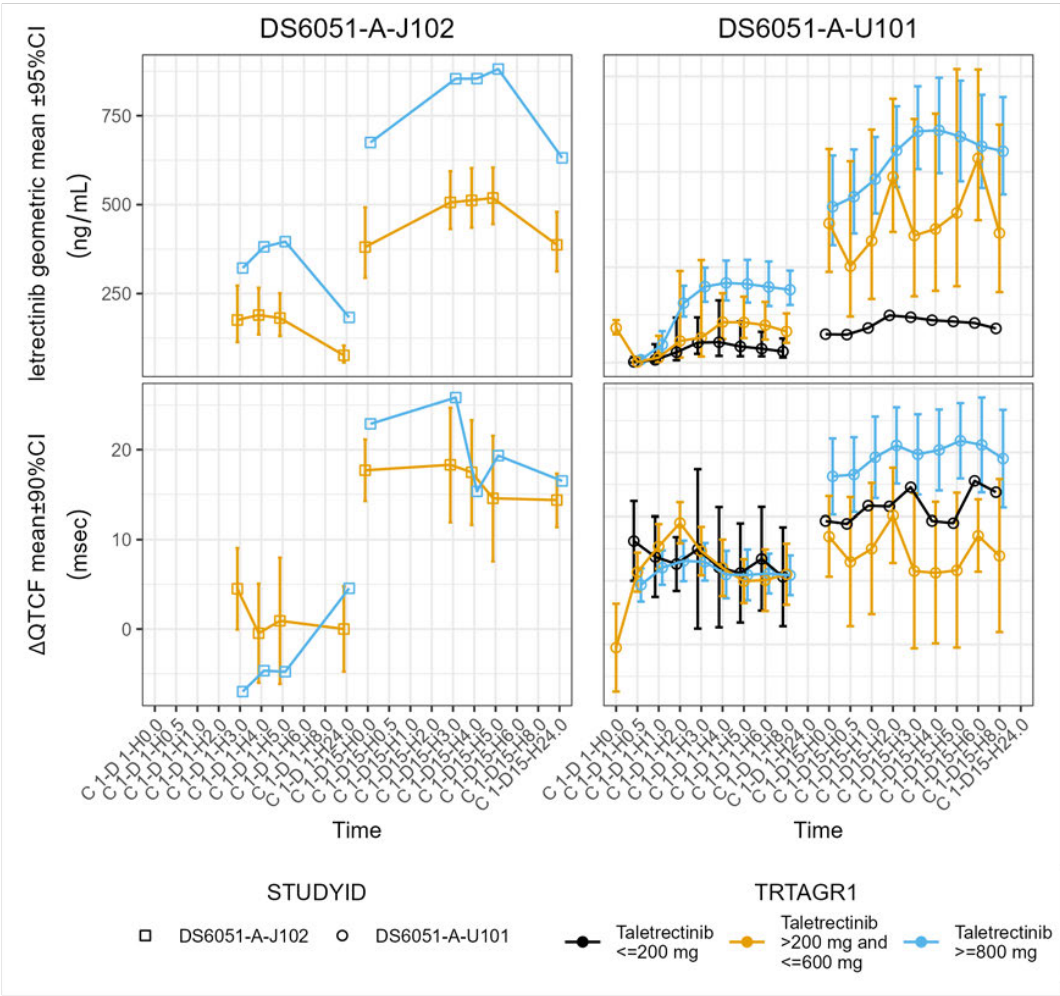
Exposure-response analysis was conducted using subjects taking talrectinib in fasted condition and with baseline and at a least one post-baseline ECG, with time-matched PK. ECG/PK data during fed administration were excluded from concentration-QTc analysis.

4.5.1 QTc

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

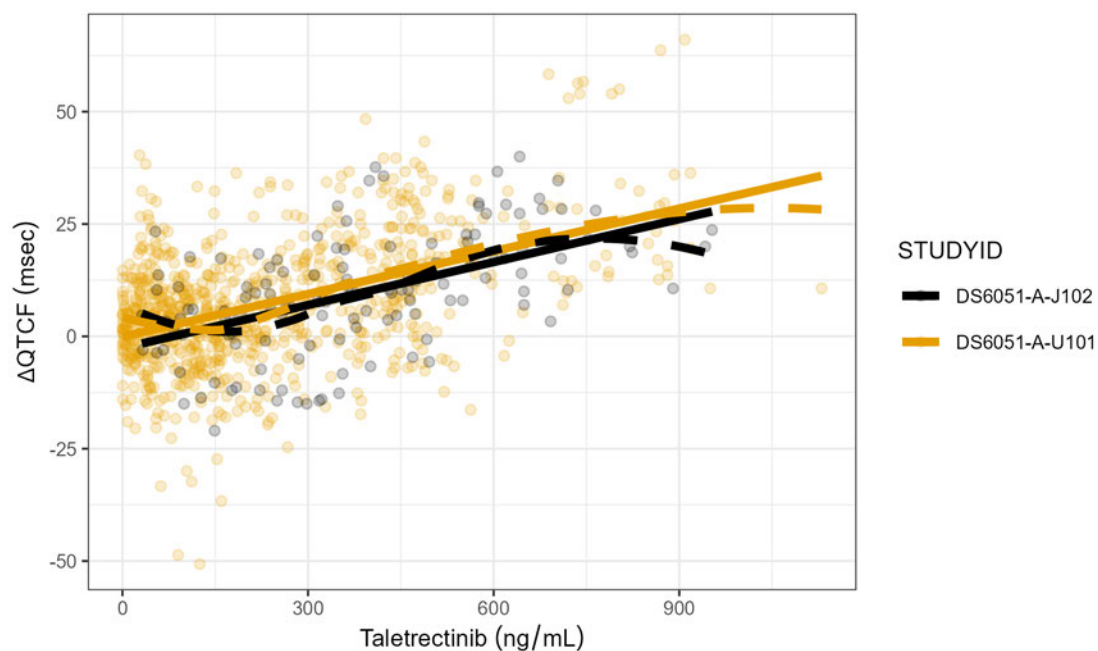
Figure 2 shows the time-course of Δ HR, with an absence of significant Δ HR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and Δ QTcF, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and Δ QTcF and supports the use of a linear model. As can be seen in Figure 6, the slopes of the C-QTs relationships appears similar between study DS6051-A-J102 and study DS6051-A-U101, and thus support pooled analysis. Pooled analysis is also supported by similar ECG collection schedules, doses evaluated, dosing conditions, and study populations.

Figure 5. Time-Course of Drug Concentration (Top) and QTcF (Bottom)²



² Δ QTcF shown were obtained via descriptive statistics and might differ from Figure 1

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



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 8.

Figure 7. Goodness-of-Fit Plot for QTcF

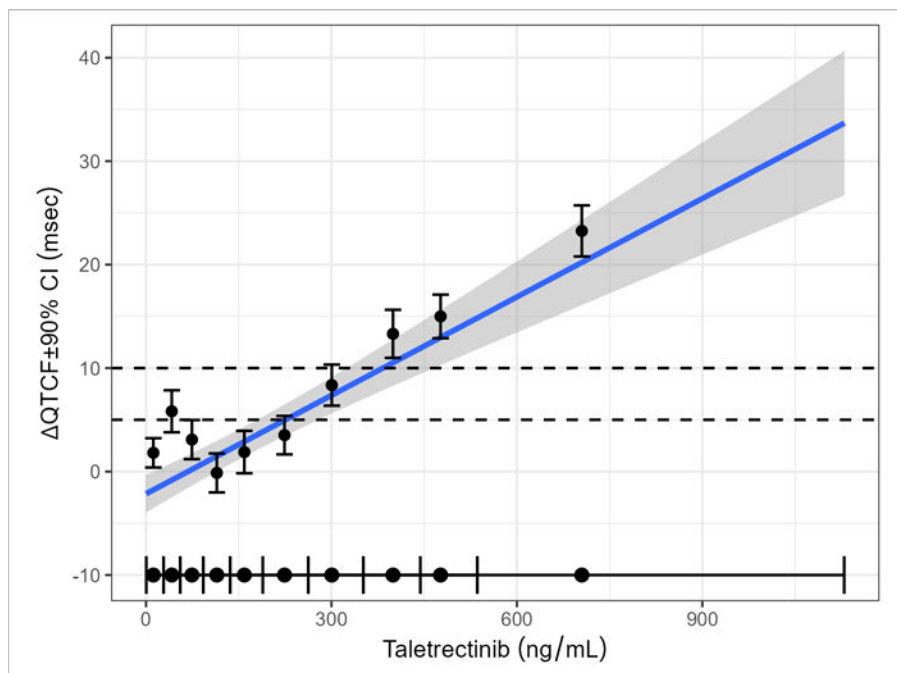


Table 8. Predictions From Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day	Taletrectinib (ng/mL)	Δ QTcF (msec)	90.0% CI (msec)
Taletrectinib 600 mg QD (highest exposure in QTc assessment) [n=6]	15	643.2	18.2	(14.5 to 22.0)
600 mg QD without food in patients with NSCLC and solid tumors	-	476.0	12.9	(10.3 to 15.6)
600 mg QD with High fat meal	-	714.0	20.5	(16.3 to 24.7)
Taletrectinib 800 mg QD [n=17]	15	537.4	14.9	(11.9 to 17.9)
Taletrectinib 1200 mg QD [n=1]	15	918	27.0	(21.4 to 32.5)

4.5.1.1 Assay Sensitivity

Not applicable as this was an alternative QTc assessment without placebo nor positive control.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 EVALUATION OF THE APPLICANT'S CLINICAL QT STUDIES

1. QT Studies					
Study	ECG Quality	Treatments		Sample Size	ECG & PK Assessments
		Arms	Dose Coverage		
Protocol Number: DS6501-A-U101 Population: Patients Design: Other	Digital: Yes Central Read? Yes Blinded? Yes Replicates? Yes	Highest Dose: 1200 mg Placebo: No Positive Control: No	High clinical	Part 1: 35 ($\geq$ 800 mg QD: 21) Part 1b: 11 (400 mg fed/fasted) (800 mg fasted only).	Baseline: Pre-dose baseline Timing: See below
Protocol Number: DS6051-A-J102 Population: Patients Design: Other	Digital: Yes Central Read? Yes Blinded? Yes Replicates? Yes	Highest Dose: 800 mg Placebo: No Positive Control: No	Therapeutic	15	Baseline: Pre-dose baseline Timing: See below

Reviewer's comments: Study DS6051-A-U101 was an open-label, multiple dose study with 3 parts: a Dose Escalation Part I, a food effect Part Ib, and a Dose expansion Part II. The Applicant's cardiodynamic analysis is based on ECG and PK data from Part I and Part Ib (including both fasted and fed portions) of Study. The dose escalation part was conducted in 6 cohorts at 50 mg QD (Cohort 1, n=1), 100 mg QD (Cohort 2, n=1), 200 mg QD (Cohort 3, n=3), 400 mg QD (Cohort 4, n=3), 800 mg QD (Cohort 5 and 5b, n=11), and 1200 mg QD (Cohort 6, n=3) by mouth once daily in 21-day cycles. The food effect was examined in Cohort 7 (n=11) with a single oral dose of 400 mg on Day -7 and Day -1, taken with or without food.

Study DS6051-A-J102 was a Phase 1, open-label, multiple-dose study in Japanese subjects with advanced solid tumors. Doses tested in this study were 400 mg (n=6), 600 mg (n=6), or 800 mg (n=3) in 21-day cycles, taken without food. Data from cycle 1 for all 3 dose levels were used for cardiodynamic analysis.

ECG and PK collection schedule:

- DS6501-A-U101 (Part I): Actual schedule varies by cohort.
 - o ECG/PK: C1D1 and C1D15: Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, and 8 h.
 - o ECG only: C1D8 and C2D8: Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, and 8 h. Pre-dose on C1D2, C2-70D1, C2D15, C3D15
- DS6501-A-U101 (Part Ib): Actual schedule varies by cohort.
 - o ECG/PK: C1 D-7, D-1, and D15: Pre-dose, 2, 6 h. Pre-dose on C1D8, C2-6D1
- DS6501-A-J102:
 - o ECG/PK: C1D1 and C1D15: Pre-dose, 3, 4, 5, and 24 h. Pre-dose on C2D1.
 - o ECG only: C4D1 and every 2 subsequent cycles – timing of collection is unclear.

5.2 EVALUATION OF THE APPLICANT'S CLINICAL QT ANALYSIS PLAN

1. Analysis plan	
1.1 Study Objectives Related to QT	
What QTc effect size is the analysis trying to exclude?	20 ms
1.2 Data Pooling	
Data pooling?	Yes
Did Applicant propose an assessment for heterogeneity?	Yes
Is the data pooling appropriate?	No
<i>Reviewer's comments: Studies were analyzed independently and pooled. In the pooled analysis, the Applicant included subjects in Part 1b taking taletrectinib with food. This is not appropriate as food may interfere with assessment of the QTc effects of drugs.</i>	
1.3 QT Correction Method	
Is an HR increase or decrease greater than 10 beats/min?	No
Primary method for QT correction	QTcF
<i>Reviewer's comments: A 10 msec mean increase in QTc interval cannot be excluded as this is an alternative QTc assessment without placebo and positive control.</i>	
1.4 Assay Sensitivity	
Assay sensitivity methods proposed by Applicant	☐ Moxifloxacin ☐ Exposure-margin ☐ QT bias assessment ☐ Other ☒ Not applicable (objective is large mean effects)
1.5 By-Time Analysis	
1.5.1 Investigational Drug	
Primary analysis	No
Did the Applicant use IUT or descriptive statistics?	Both

For IUT: Does the Applicant use MMRM to analyze longitudinal values that consider the correlation across time-points, or use ANCOVA by-time-point without considering correlation?	MMRM
For IUT: Is the MMRM model specified correctly with regard to covariance structure, covariates, or if ANCOVA, is the model specified correctly with regard to covariates?	Yes
<i>The by-time point analysis was performed for Parts I and Ib of Study DS6051-A-U101 separately, and for Study DS6051-A-J102 separately. To support the by-time point statistical modeling described below, descriptive statistics (e.g., number of subjects, mean, SD, median, maximum, and minimum) were used to summarize the absolute values of the ECG variables and the corresponding change-from- baseline values by cohort at each time point. The by-time point analysis for QTcF interval on DS-6051b was based on a mixed model for repeated measures (MMRM) with $\Delta QTcF$ interval as the dependent variable, time (i.e., postbaseline time point with at least 3 subjects within treatment: categorical), treatment (Cohort 1 to Cohort X of DS-6051b; note that Cohort 5, Cohort 5b, and Cohort 8 in Study DS6051-A-U101 were all on 800 mg QD; Cohort 5b and Cohort 8 were just adding more subjects for the 800 mg QD dose tested in Cohort 5 and therefore, Cohorts 5, 5b, and 8 were pooled together as a single cohort) and time-by-treatment interaction as fixed effects, and baseline QTcF as a covariate. An unstructured covariance matrix was specified for the repeated measures at post-baseline time points within subjects.</i> Reviewer's comments: We evaluated the single delta effect of all intervals using non-parametric descriptive statistics.	
1.5.2 Positive Control	
Primary analysis	N/A
Did the Applicant adjust for multiplicity?	N/A
1.6.1 Investigational Drug	
Primary analysis	Yes
What is the dependent variable in the Applicant's model?	Single delta
White paper model?	Yes
Which concentration covariate(s) are included in the model?	Parent
Which methods did the Applicant use for predicting the QT effect?	☒ Model-based confidence intervals ☐ Bootstrap-derived confidence intervals

1.6.2 Positive Control			
Primary analysis		N/A	
Same model as investigational drug		N/A	
1.7 Categorical Analysis			
QTcF / ΔQTcF?	Yes	QRS?	Yes
PR?	Yes	HR?	Yes

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/

ELIFORD N KITABI
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03/17/2025 07:17:09 AM

Interdisciplinary Review Team for Cardiac Safety Studies
QT Study Review

Submission	NDA 219713
Submission Number	2
Submission Date	10/23/2024
Date Consult Received	12/6/2024
Drug Name	Taletrectinib
Indication	Treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC)
Therapeutic Dose	600 mg QD
Clinical Division	DO2
Protocol Review	Not previously reviewed.

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

This review responds to your consult dated 12/6/2024 regarding the Applicant's QT evaluation. We reviewed the following materials:

- QT evaluation report for taletrectinib ([NDA 219713/SDN 002](#));
- Cardiac safety report – see Appendix 5 in “QT evaluation report” ([NDA219713/SDN002](#));
- Applicant's draft label ([NDA219713/SDN002](#));
- Study protocol U101 ([NDA219713/SDN002](#));
- Study protocol J102 ([NDA219713/SDN002](#));
- Summary of Clinical Pharmacology Studies ([NDA219713/SDN002](#)); and
- Highlights of clinical pharmacology and cardiac safety – Appendix 2 in “QT evaluation report” ([NDA219713/SDN002](#)).

1 SUMMARY

Taletrectinib treatment was associated with concentration-dependent increase of the QTcF interval based on concentration-QTc analysis of studies DS6501-A-U101 and DS6051-A-J102 – see Table 1 for overall results. At the average maximum concentration for 600 mg QD (therapeutic dose), the predicted mean increase in the change from baseline for QTc (Δ QTc) is 13 msec. Taletrectinib is administered under fasting conditions, however, if taletrectinib is inadvertently taken with a high-fat meal the predicted mean increase in Δ QTc is 21 msec.

Both studies, DS6501-A-U101 and DS6051-A-J102, were phase 1, open label, non-randomized, multiple-ascending-dose studies in patients with cancer. Study DS6051-A-J102 was conducted in Japanese subjects with solid tumors while Study DS6501-A-U101

was conducted in North America and Europe in subjects with systemic metastases and/or unresectable solid tumors. The highest exposure in the alternative QTc assessment was provided by the 600 mg QD dose in study DS6051-A-J102, which covers high clinical exposure.

Data were analyzed using concentration-QTc analysis as the primary analysis, which suggest that talrectinib is associated with large mean increases in the QTcF interval (section 4.5). The findings of the primary analysis are further supported by the small hERG margin (~14-fold), by-time analysis (section 4.3), and categorical analysis (section 4.4).

Table 1: Summary of findings

QT assessment pathway	☐ Thorough QT study ☐ Substitute for thorough QT study (5.1) ☒ Alternative QT study when a thorough QT study is not feasible (6.1)																								
Clinical QT study findings	- High clinical exposure scenario of taletrectinib is anticipated to be when the drug product is inadvertently co-administered with high fat meal resulting in 1.5-fold increase in Cmax (section 3.1) - The highest mean exposure in the QTc assessment was provided by 600 mg QD on day 15 in Japanese subjects with solid tumor, which covers high clinical exposure. <table><tr><th>ECG parameter</th><th>Treatment</th><th>Concentration</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr><tr><td>QTcF</td><td>600 mg QD, orally without food</td><td>476 ng/mL</td><td>12.9</td><td>(10.3 to 15.6)</td></tr><tr><td>QTcF</td><td>600 mg QD, orally with high fat meal</td><td>714 ng/mL</td><td>20.5</td><td>(16.3 to 24.7)</td></tr><tr><td>QTcF</td><td>600 mg QD, Day 15 (Study J102)</td><td>643 ng/mL</td><td>18.2</td><td>(14.5 to 22)</td></tr></table>					ECG parameter	Treatment	Concentration	ΔΔQTcF (msec)	90% CI (msec)	QTcF	600 mg QD, orally without food	476 ng/mL	12.9	(10.3 to 15.6)	QTcF	600 mg QD, orally with high fat meal	714 ng/mL	20.5	(16.3 to 24.7)	QTcF	600 mg QD, Day 15 (Study J102)	643 ng/mL	18.2	(14.5 to 22)
ECG parameter	Treatment	Concentration	ΔΔQTcF (msec)	90% CI (msec)																					
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QTcF	600 mg QD, orally with high fat meal	714 ng/mL	20.5	(16.3 to 24.7)																					
QTcF	600 mg QD, Day 15 (Study J102)	643 ng/mL	18.2	(14.5 to 22)																					
In vitro findings	Integrated nonclinical risk assessment was not performed.																								
In vivo findings																									

2 RECOMMENDATIONS

2.1 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 0002 ([link](#)).

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

2.3 Dosage Modifications for Adverse Reactions

QTc Interval Prolongation [see Warnings and Precautions]	Grade 2 (QTc interval 481- 500 msec)	Withhold IBTROZI until recovery to $\leq$ Grade 1 or baseline. (b) (4) correct electrolytes and/or change concomitant medications. Resume at same dose.
	Grade 3 (QTc interval ≥ 501 msec or QTc interval increase of >60 msec from baseline)	Withhold IBTROZI until recovery to $\leq$ Grade 1 or baseline. (b) (4) correct electrolytes and/or change concomitant medications. (b) (4)
	Grade 4 (Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)	Permanently discontinue IBTROZI.

Reviewer's comment: The proposal by the Applicant is acceptable.

5.3 QTc Interval Prolongation

[IBTROZI has been shown to prolong the QTc interval in a concentration-dependent manner \[see Clinical Pharmacology \(12.2\)\].](#)

(b) (4)

Significant prolongation of the QTc interval may occur when IBROTZI is inappropriately taken with food, strong CYP3A4 inhibitors, and/or drugs with a known potential to prolong QTc. Therefore, coadministration with food must be avoided and concomitant use with strong CYP3A4 inhibitors and/or drugs with a known potential to prolong QTc should be avoided [see Dosage and Administration (2.4), Drug Interactions (7.1, 7.4)].

(b) (4)

Reviewer's comment: We agree with including information about the time to resolution of QTc prolongation because of the long half-life (terminal half-life of 85 h) for talretrectinib. However, we consider estimating time to resolution based on the PK of talretrectinib to be a better estimator since the QTc prolongation is concentration-related. Otherwise, we have proposed edits to improve clarity and recommend a statement concerning the potential for QTc prolongation if co-administered with a high-fat meal, strong CYP3A4 inhibitor, or another QTc prolonging drug.

6 Adverse Reactions

Table 3. Adverse Reactions

(b) (4)

Adverse Reaction	IBTROZI N= (b) (4)	
	All Grades (%)	Grade 3 or 4 (%)
Electrocardiogram QT prolonged	19	(b) (4)

Reviewer's comment: We confirmed the Applicant's analysis. However, we want to note that the approach to rounding differs between the two columns (i.e., (b) (4) 19% and (b) (4) %). We defer to the Division concerning need for harmonization.

7.1 Effects of Other Drugs on IBTROZI

Avoid concomitant use with strong or moderate CYP3A inhibitors. Concomitant use of IBTROZI with a strong or a moderate CYP3A inhibitor (b) (4) talretrectinib exposure, which may increase the (b) (4) of adverse reactions (b) (4).

(b) (4)
<u>(b) (4) Drugs That Prolong the QTc Interval</u> <u>Avoid coadministration of IBTROZI with products with a known potential to prolong QTc interval, such as antiarrhythmic drugs and other drugs that are known to prolong the QTc interval. If concomitant use cannot be avoided, monitor ECG when initiating, during concomitant use, and as clinically indicated [see Warnings and Precautions (5.3), Clinical Pharmacology (12.2)].</u>
<i>Reviewer's comment:</i> We recommend inclusion of a new section (b) (4) to address concomitant use with other QTc prolonging drugs.

12.2 Pharmacodynamics <u>Cardiac Electrophysiology</u> (b) (4) <u>At 1.5-fold the therapeutic plasma concentration, achieved with inadvertent administration with a high fat meal, the predicted increase in ΔQTcF is XX (YY, ZZ).</u> <i>Reviewer's comment:</i> The results of our analysis and the Applicant's analysis are similar and we therefore propose including the results of the Applicant's analysis, but with rounding to one significant digit. The Applicant did not include a prediction of the increase in QTc when co-administered with food (C_{max}: 714 ng/mL) and we therefore recommend requesting that the Applicant adds the predicted increase in QTc.

3 APPLICANT'S SUBMISSION

3.1 OVERVIEW

The Applicant (Nuvation Bio, Inc.) is proposing talrectinib (AB-106 or DS-6051b), a kinase inhibitor, for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer. The proposed therapeutic dose is 600 mg QD without food.

We have not previously been consulted on the QTc assessment for this product. Briefly, the Applicant is proposing to use concentration-response to characterize the effects on the QTc interval pursuant to the ICH E14 Q&A 6.1 approach using studies DS6501-A-U101 DS6051-A-J102. For a review of the two studies and the proposed analysis, please refer to sections 5.1 and 5.2 in the appendix.

3.1.1 Clinical Pharmacology

The clinical pharmacology of talretrectinib is summarized in the [summary of clinical pharmacology studies](#) and in the table of [highlights of clinical pharmacology](#) and cardiac safety. Briefly, talretrectinib exhibits linear kinetics in the dose range of 50 to 1200 mg taken QD. It has long absorption time (median T_{max} range between 3 – 6 hours), long half-life (terminal T_{1/2} = 80 – 100 hours) and accumulates up to 4.5-fold day 1 AUC, reaching steady state after 8 days of dosing (effective T_{1/2} ≈ 66 hours).

According to the Applicant's population PK analysis, age, sex, and race have no impact on talretrectinib PK. Similarly, no impact of mild hepatic impairment and up to moderate renal impairment was detected in the analysis. However, a DDI study determined that strong CYP3A4 inhibitor would increase talretrectinib C_{max} by 1.76-fold. A food effect study determined that high fat meal would increase the C_{max} by about 1.5.

Since the Applicant plans prohibition or dose adjustment when talretrectinib is administered in hepatic impairment or with strong CYP3A4 inhibitors, high clinical exposure scenario is anticipated when talretrectinib is inadvertently co-administered with high fat meal.

Table 2 presents the exposures at the highest test dose in the QTc assessment and coverage of the high clinical exposure scenario.

Table 2. Summary of Dose and Exposure Assessment

		Mean C _{max}
Highest therapeutic or clinical trial dosing regimen	600 mg QD without food.	*476 ng/mL (C _{max,ss})
Applicant's High clinical exposure scenario	1.5-fold increase when co-administered with high fat meal	714 ng/mL
Highest exposure in QT assessment	600 mg QD (Day 15)	643.2 ng/mL
C _{max} Ratio	643.2 / 714 = 0.9	

* Geometric mean steady state C_{max} in a global, phase 2 study in subjects with NSCLC and other solid tumors (n = 41). Although geometric mean C_{max} on Cycle 1 day 15 in a small study (study DS6051-A-J102) in Japanese subjects with solid tumors (n = 6) was 661 ng/mL, it is not considered to represent the patient population.

3.1.2 Nonclinical Safety Pharmacology Assessments

The Applicant evaluated the effects of talretrectinib on hERG current in the study report (VPT1347/2013, [link](#)). The hERG current was assessed at ambient temperature using manual patch clamp assay. The hERG IC₅₀ was 0.98 μM (using actual concentration), which corresponds to a hERG safety margin of 14-fold (high clinical C_{max} = 714 ng/mL, MW: 551.61 g/mol; PB: 94.6%) using the clinical exposure scenario (Table 2).

The effects on NaV1.5 peak was also evaluated by the Applicant (VPT1348/2013; [link](#)). The NaV1.5 peak current was assessed at room temperature using a train of 10 pulses protocol (the inter pulse frequency was 2 Hz). The protocol was used to assess the resting or tonic block (current block at the first pulse) and use-dependent block (current block by the 10th pulse). Talretrectinib inhibited the Nav1.5 peak current in a concentration-dependent manner, with IC₅₀ values of 25 μM for resting block and 0.83 μM for use-dependent block. The corresponding safety margins were 358× for resting block and 12× for use-dependent block. The positive control, flecainide (100 μM), significantly induced

a use-dependent block of the Nav1.5 peak current, indicating that talretrectinib exhibits a blocking characteristic on Nav1.5 peak current similar to flecainide at room temperature.

The in vivo QT study (VPT1662/2013, [link](#)) assessed the effects of talretrectinib on ECG parameters following single oral doses to conscious telemetrized cynomolgus monkeys (n=4). The study did not collect PK. The free Cmax of the highest dose (100 mg in the study is approximately the free Cmax of the clinical exposure scenario based on two separate in vivo studies (VPT1578-2013, [link](#) and vpt1215-2013, [link](#))¹. This is based on similar protein binding between human (94.6%) and monkeys (93.2%; vpt1218/2013, [link](#)). No changes in QTc, HR, PR, or QRS were observed at the highest dose. The lack of ECG changes in the study could be due to exposure and/or sensitivity of the study.

3.2 APPLICANT'S RESULTS

3.2.1 By-Time Analysis

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

In the by-time point analysis (Section 5.3.1 Cardiac Safety Report), talretrectinib appeared to demonstrate a modest clinically relevant effect on QTcF. This was clearest in the 800 mg daily cohort in Study DS60551-A-U101 Part I and Part Ib food effect cohort, where data were available for total of 15 subjects for steady state PK (Cycle 1 Day 15). Other cohorts/dose levels had 1-7 subjects, which is a relatively small sample size for accurately estimating the central tendency of the QTc effect. In Study DS60551-A-U101 Part I, the largest LS mean change-from baseline QTcF (Δ QTcF) for 800 mg QD (n=15) was 21.1 msec (95% CI: 15.00; 27.18 msec) at 2 hours after dosing.

Applicant also presented by-time analysis results for other intervals. Applicant used both descriptive statistics and MMRM analysis for the time points with at least three subjects.

Reviewer's comment: *Considering the small sample size, the reviewer performed non-parametric descriptive statistics analysis. The reviewer's by-time analysis results also show mean Δ QTcF greater than 10 msec in multiple time points. Please see section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

Not applicable for as this was alternative QTc assessment without placebo and positive control.

3.2.1.1.1 QT Bias Assessment

Not performed.

¹ Two studies are included because they studied different lots, and it is unclear which lot was included in the CV study. The Cmax for 100 mg/kg was similar between the two studies and an average is therefore used (472 ng/mL).

3.2.2 Categorical Analysis

No subjects in either study developed a new QTcF > 500 msec. In Study DS6051-A-U101 Part I, one subject (5.6%) at 800 mg QD experienced Δ QTcF > 60 msec. No subjects from Study DS6051-A-J102 had Δ QTcF > 60 msec. Several subjects in Study DS6051-A-U101 met tachycardic categorical outlier criteria; the clinical significance of these tachycardic outliers is unclear. No subjects developed new PR or QRS categorical outlier findings.

Reviewer's comment: *The reviewer also performed categorical analysis for all intervals. The reviewer's analysis results are similar to the Applicant's results. Please see section 4.4 for additional details. Integrated assessment of outliers is described in section 3.2.4.*

3.2.3 Exposure-Response Analysis

The Applicant conducted separate and pooled C-QTc analysis of data from studies DS6051-A-U101 and DS6051-A-J102 (See Appendix 5 for description of the designs). For pooled analysis, the Applicant conducted a statistical test of homogeneity between the 2 studies. Although mean heart rate changes >10 bpm were observed, the Applicant posits that talretrectinib did not cause clinically relevant changes in heart rate (HR), as the changes were not dose-dependent. The Applicant also posits that the changes were small and therefore unlikely to materially impact C-QTc analysis. Linear mixed effects modelling was conducted as recommended in the white paper.

C-QTc Results based on Study DS6051-A-U101

The concentration-QTc analysis for Study DS6051-A-U101 was based on 885 time-matched ECG-PK pairs. The estimated population slope of the concentration-QTc relationship was 0.031 ms per ng/mL (90% CI: 0.0217 to 0.0396; $P < 0.0001$), with a population intercept of -1.95 ms (90% CI: -3.923 to 0.027; $P = 0.1045$). The population slope of DS-6051a was significant at the 10% significance level while the population intercept was not significant.

The model predicted effects on Δ QTcF were 14.15 ms (90% CI: 10.26 to 18.04) and 26.21 ms (90% CI: 18.96 to 33.45) at the geometric mean C_{max} on Cycle 1 Day 15 of 800 mg QD (525.1 ng/mL) and 1200 mg QD (918.0 ng/mL), respectively.

An effect on Δ QTcF with 90% UCI exceeding 10 ms can be expected at DS-6051a plasma concentrations above ~315 ng/mL while an effect with 90% UCI exceeding 20 ms can be expected at plasma concentrations above ~576 ng/mL. The results of the Sponsor's analysis show an absence of significant QTc prolongation.

C-QTc Results based on Study DS6051-A-J102

The concentration-QTc analysis for Study DS6051-A-J102 was based on 133 time-matched ECG-PK pairs. The estimated population slope of the concentration-QTc relationship was 0.037 ms per ng/mL (90% CI: 0.0252 to 0.0485; $P = 0.0012$), with a population intercept of -4.84 ms (90% CI: -10.302 to 0.614; $P = 0.1400$). The population slope of DS-6051a was significant at 10% significance level while the population intercept was not significant.

The model predicted effects on Δ QTcF were 18.85 ms (90% CI: 12.90 to 24.79) and 27.79 ms (90% CI: 18.09 to 37.49) at the geometric mean C_{max} on Cycle 1 Day 15 of 600 mg QD (643.2 ng/mL) and 800 mg QD (886.2 ng/mL), respectively. An effect on

Δ QTcF with 90% UCI exceeding 10 ms can be expected at DS-6051a plasma concentrations above ~302 ng/mL while an effect with 90% UCI exceeding 20 ms can be expected at plasma concentrations above ~549 ng/mL.

C-QTc Results from Pooled data of studies DS6051-A-U101 and DS6051-A-J102

The Levene's test of homogeneity indicated that the 2 studies had equal variances.

The concentration-QTc analysis for the pooled analysis was based on 1018 time-matched ECG-PK pairs. The estimated population slope of the concentration-QTc relationship was 0.032 ms per ng/mL (90% CI: 0.0248 to 0.0388; $P < 0.0001$), with a population intercept of -2.40 ms (90% CI: -4.216 to -0.574; $P = 0.0320$). Both the population slope of DS-6051a and the population intercept were statistically significant at 10% significance level.

The model predicted effects on Δ QTcF were 15.00 ms (90% CI: 11.91 to 18.09) and 26.82 ms (90% CI: 21.30 to 32.35) at the geometric mean C_{max} on Cycle 1 Day 15 of 800 mg QD (546.6 ng/mL) and 1200 mg QD (918.0 ng/mL), respectively. An effect on Δ QTcF with 90% UCI exceeding 10 ms can be expected at DS-6051a plasma concentrations above ~331 ng/mL while an effect with 90% UCI exceeding 20 ms can be expected at plasma concentrations above ~597 ng/mL.

Reviewer's comment: *In pooling data from fed (Part 1b of U101) and fasted states (Part 1 of U101 and J102) the Applicant ignored the potential impact of food intake on QTc interval. This may introduce bias in estimating C-QTc relationship. The Applicant also excluded time-matched ECGs in cycles 2 and 3 of Study U101, thus limiting the number of evaluable time-matched ECG-PK pairs. The results of our independent analysis, which only excluded ECG/PK data during fed administration (section 4.5), are similar to the Applicant's results. It should be noted that only 1 subject received 1200 mg on Cycle 1 day 15. Therefore, the predicted Δ QTcF at this dose represent individual prediction rather than mean prediction at 1200 mg dose.*

3.2.4 Safety Analysis

The Applicant pooled safety data from Phase 1 and 2 studies in participants with solid tumors (Studies AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101) to support an integrated safety analysis. The Applicant considered three analysis populations: ROS1+NSCLC 600 mg QD, 600 mg QD (all cancer types), and overall. In subsequent sections, we will only be describing the findings for the overall analysis.

Table 3 shows the AEs included in the integrated safety analysis that belonged to the "Torsade de pointes/QT prolongation" broad SMQ. As shown, most of the AEs were related to QTc prolongation:

Three of the AEs were SAEs (cardiac arrest: 2; syncope: 1). Neither of the two participants that experienced a cardiac arrest had a reported QTc at the time of the events. No QTc prolongation was reported for the two participants that experienced an AE of ventricular tachycardia.

No participant withdrew treatment due to a QT-prolonging AEs. However, 2.8% of participants had a treatment interruption and 2.8% had a dose reduction due to QT prolonging AEs.

Reviewer's comment: We analyzed the integrated safety analysis dataset using our customized Torsade de pointes/QTc prolongation query and identified two additional preferred terms: arrhythmia (n=2) and death (n=2). There were 86 participants with an AE belonging to the modified query and a QTc (at any time) >480 msec (QT prolongation: 84; syncope: 2). For the two participants that experienced an AE of syncope, the reported QTc prolongation did not occur near the event.

The Applicant also performed outlier analysis using the integrated safety analysis dataset and the corresponding results are shown in Table 4.

Table 3. Integrated QT AE Safety Analysis

Grouped Term	Overall (N=412)	
	All Events	NCI CTCAE Grade ≥ 3
Torsade de pointes/QT prolongation SMQ Broad	79 (19.2%)	21 (5.1%)
<i>Electrocardiogram QT prolonged</i>	68 (16.5%)	13 (3.2%)
<i>Syncope</i>	9 (2.2%)	6 (1.5%)
<i>Cardiac arrest</i>	2 (0.5%)	2 (0.5%)
<i>Ventricular tachycardia</i>	2 (0.5%)	0

Source: QT Evaluation Report, Table 5

Table 4. Integrated Outlier analysis

Parameter	Overall (N=412)
QTcF (msec)	
>450 to ≤ 480	95 (23.1%)
>480 to ≤ 500	23 (5.6%)
>500	9 (2.2%)
Δ QTcF (msec)	
>30 to ≤ 60	158 (38.3%)
>60	45 (10.9%)

Source: QT Evaluation Report, Tables 2 and 3

Reviewer's comment: The reported QTc outliers >500 msec were not from the two studies used for QTc assessment. All the participants with QTc >500 msec also had a Δ QTc >60.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

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

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader in a blinded manner. Compared to the ECG warehouse

algorithm, we did not observe significant bias in QT measurements and the ECG acquisition and interpretation for these studies is therefore acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. To be consistent with the rest of the cohorts, we have excluded cohort 7 (fed-fasted and fasted-fed sequences) from study DS6051-A-U101. Study J102 was analyzed separately. We have included data for cycle 1 (days 1, 2, 8, and 15), cycle 2 day 1 and cycle 3 day 1. Due to small sample size, we have excluded rest of the cycles from the analysis. The reviewer evaluated the $\Delta QTcF$ effect using descriptive (nonparametric) statistics.

4.3.1 QTc

Figure 1 displays the time profile of $\Delta QTcF$ for different treatment groups. The maximum $\Delta QTcF$ values by treatment are shown in Table 4. The findings show that talretrectinib has dose-dependent QTc effects, except for the lowest dose group of talretrectinib ≤ 200 mg with small sample size (i.e., $n = 3$).

Figure 1. Median and 90% CI of Δ QTcF Time-Course (Unadjusted CIs)

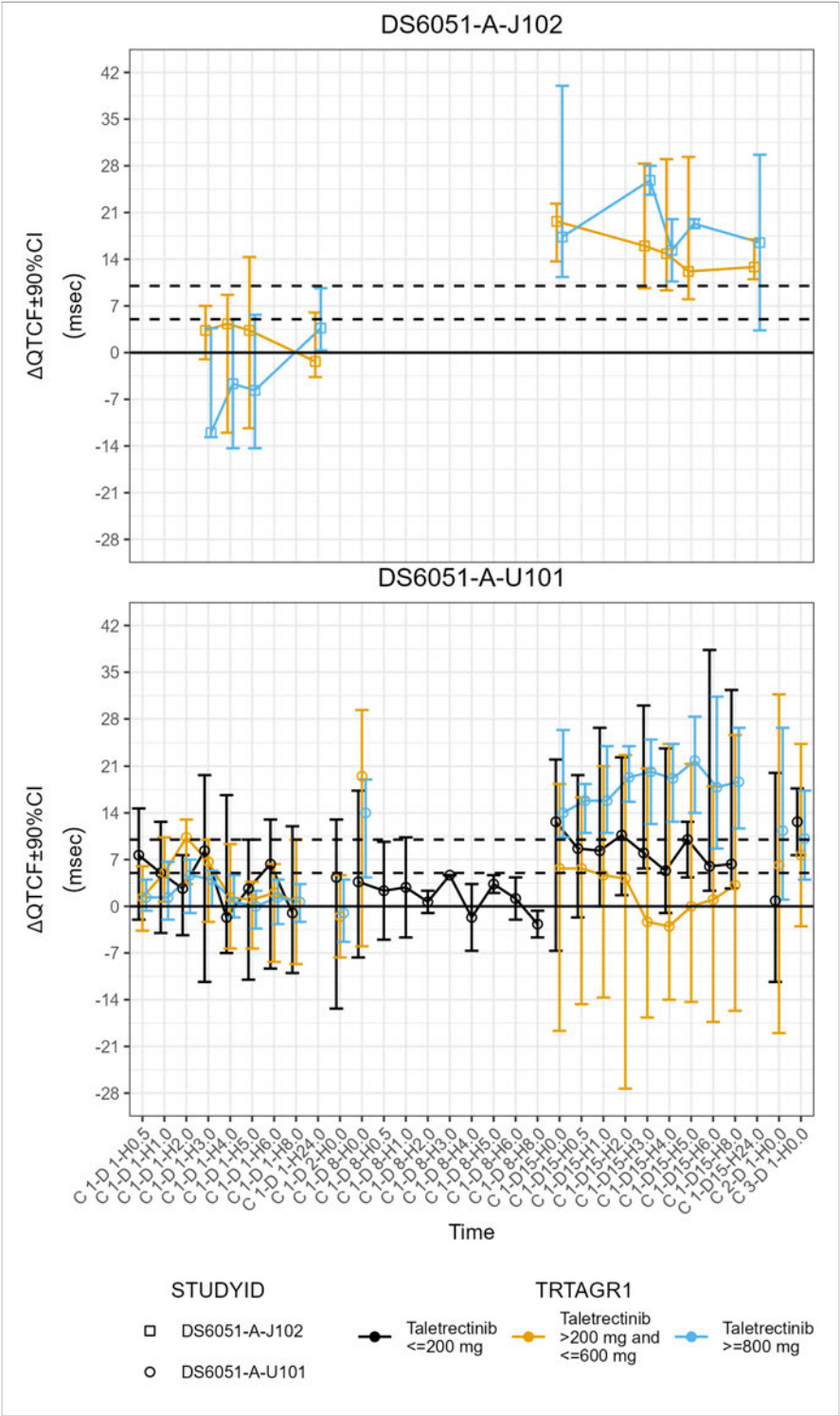


Table 5. Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for $\Delta QTCF$

TRTAGR1	Study Identifier	Period	Analysis Nominal Period Day (C)	N	Time (Hour)	$\Delta QTCF$ (msec)	90.0% CI (msec)
Taletrectinib ≤ 200 mg	DS6051-A-U101	1	15	3	6.0	6.0	(2.3 to 38.3)
Taletrectinib > 200 mg and ≤ 600 mg	DS6051-A-J102	1	15	12	5.0	12.2	(8.0 to 29.3)
Taletrectinib ≥ 800 mg	DS6051-A-U101	1	15	16	6.0	17.8	(8.7 to 31.3)

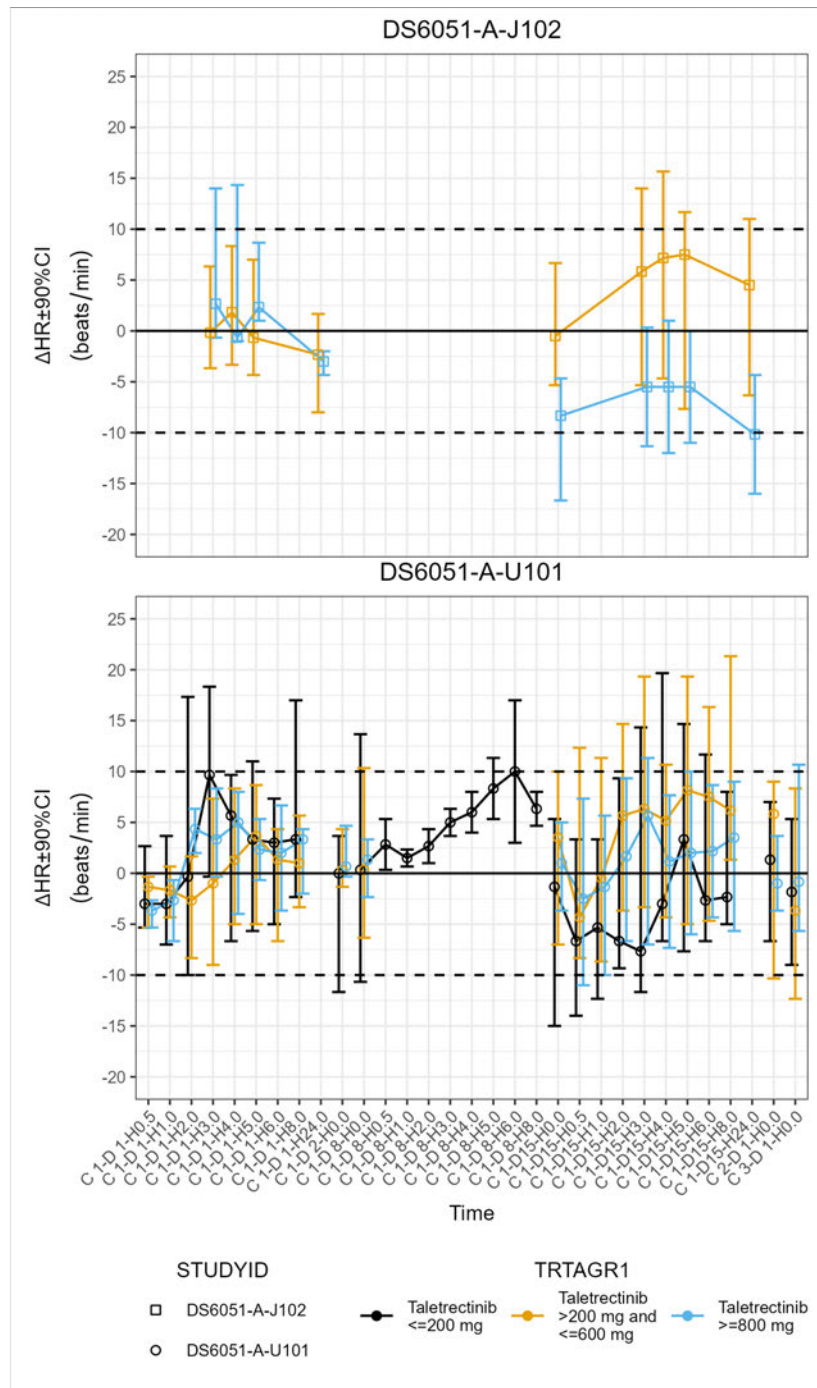
4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for different treatment groups. The maximum ΔHR values by treatment are shown in Table 6.

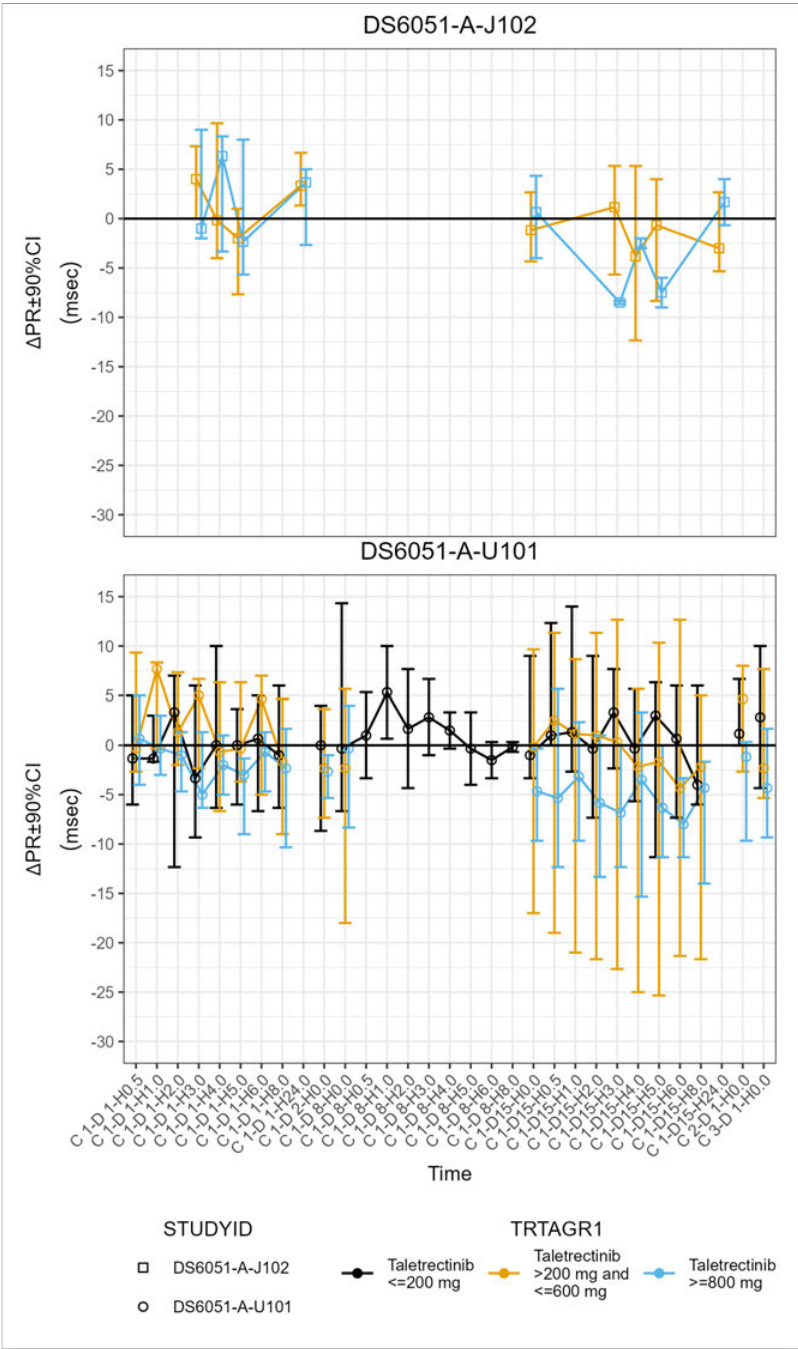
Figure 2. Median and 90% CI of Δ HR Time-Course



4.3.3 PR

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

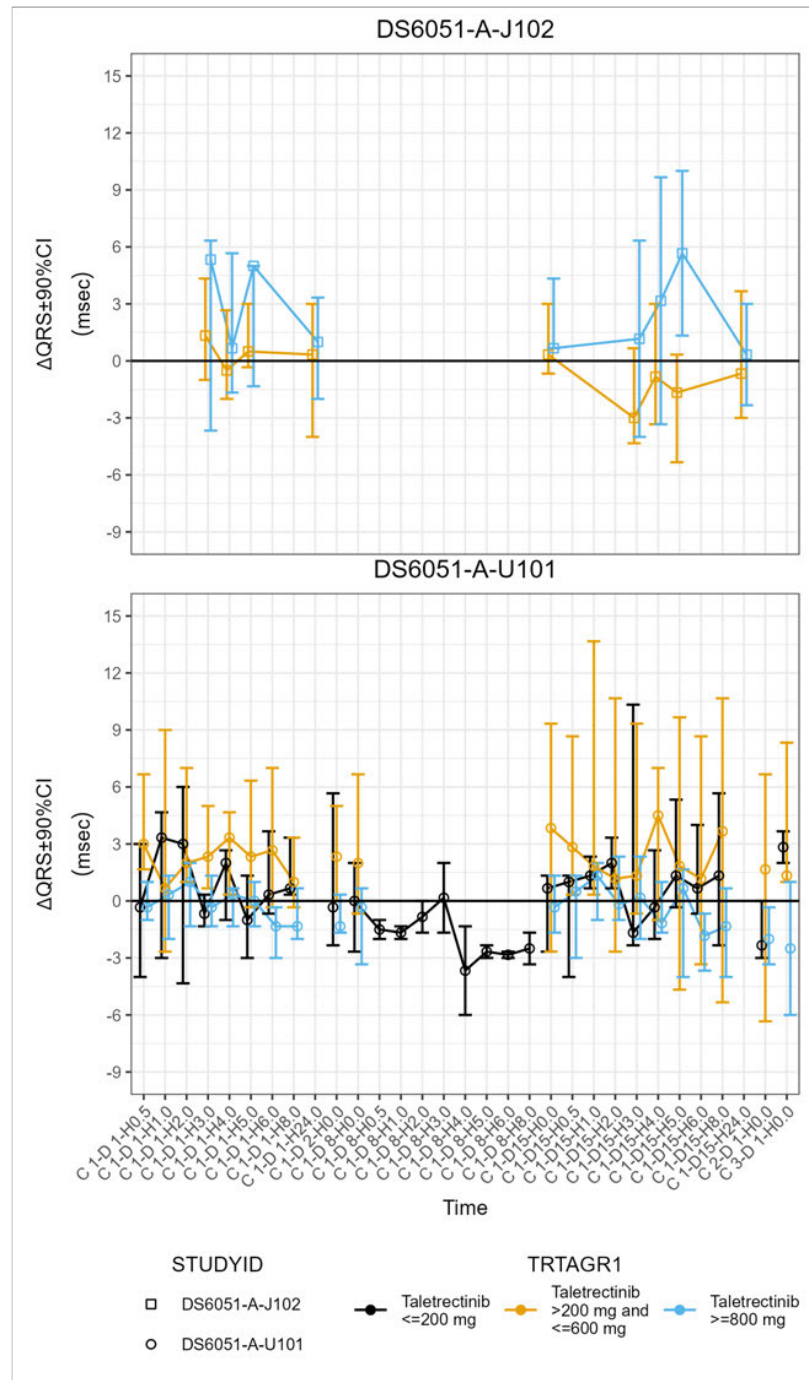
Figure 3. Median and 90% CI of Δ PR Time-Course



4.3.4 QRS

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

Figure 4. Median and 90% CI of 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, which includes both scheduled and unscheduled ECGs. In the

following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects in any of the studies experienced QTcF values >500 msec for any dose levels of taletrectinib. Table 10 lists the categorical analysis results for Δ QTcF (<30 msec, >30 and <60, and >60 msec). One subject in taletrectinib $\geq$ 800 mg in study DS6051-A-U101 experienced Δ QTcF >60 msec.

Table 6. Categorical Analysis for Δ QTcF (Maximum)

Study Identifier	TRTAGR1	Total (N)		Value $\leq$ 30 msec		30 msec < Value $\leq$ 60 msec		Value >60 msec	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
DS6051-A-U101	Taletrectinib $\leq$ 200 mg	5	130	4 (80.0%)	127 (97.7%)	1 (20.0%)	3 (2.3%)	0 (0%)	0 (0%)
	Taletrectinib >200 mg and $\leq$ 600 mg	20	501	13 (65.0%)	489 (97.6%)	7 (35.0%)	12 (2.4%)	0 (0%)	0 (0%)
	Taletrectinib $\geq$ 800 mg	21	633	7 (33.3%)	579 (91.5%)	13 (61.9%)	52 (8.2%)	1 (4.8%)	2 (0.3%)

4.4.2 HR

Table 11 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). One subject in study DS6051-A-J102 and six subjects in study DS6051-A-U101 experienced HR >100 beats/min for different dose levels of taletrectinib.

Table 7. Categorical Analysis for HR (Maximum)

Study Identifier	TRTAGR1	Total (N)		Value $\leq$ 100 beats/min		Value >100 beats/min	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
DS6051-A-J102	Taletrectinib >200 mg and $\leq$ 600 mg	12	114	11 (91.7%)	109 (95.6%)	1 (8.3%)	5 (4.4%)
	Taletrectinib $\geq$ 800 mg	3	26	3 (100.0%)	26 (100.0%)	0 (0%)	0 (0%)
DS6051-A-U101	Taletrectinib $\leq$ 200 mg	5	130	5 (100.0%)	130 (100.0%)	0 (0%)	0 (0%)
	Taletrectinib >200 mg and $\leq$ 600 mg	20	501	17 (85.0%)	495 (98.8%)	3 (15.0%)	6 (1.2%)
	Taletrectinib $\geq$ 800 mg	21	633	18 (85.7%)	622 (98.3%)	3 (14.3%)	11 (1.7%)

4.4.3 PR

None of the subjects in both studies experienced PR >220 msec; with and without 25% increase over baseline for any dose levels of taletrectinib.

4.4.4 QRS

None of the subjects in both studies experienced QRS >120 msec; with 25% increase over baseline for any dose levels of talrectinib.

4.5 EXPOSURE-RESPONSE ANALYSIS

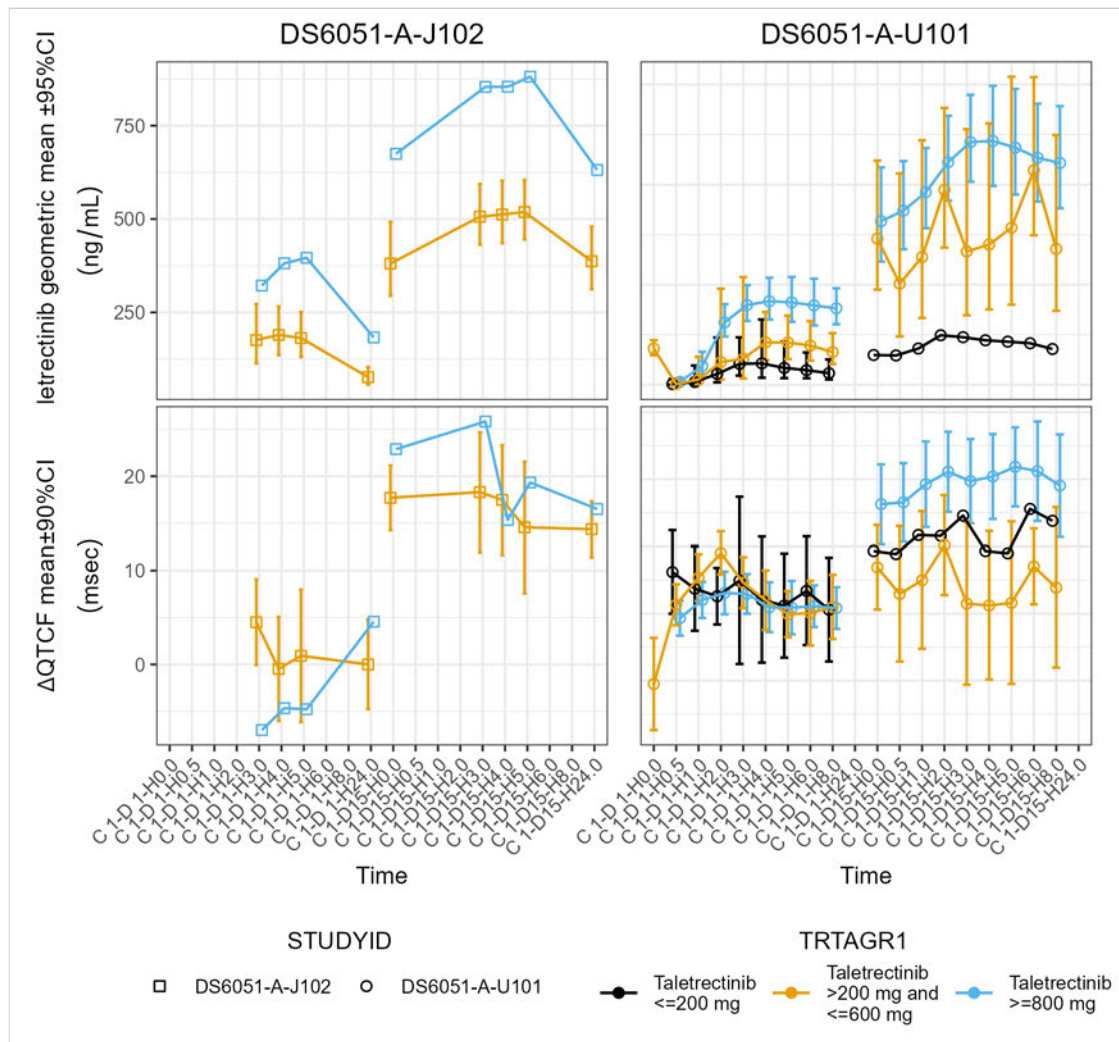
Exposure-response analysis was conducted using subjects taking talrectinib in fasted condition and with baseline and at a least one post-baseline ECG, with time-matched PK. ECG/PK data during fed administration were excluded from concentration-QTc analysis.

4.5.1 QTc

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

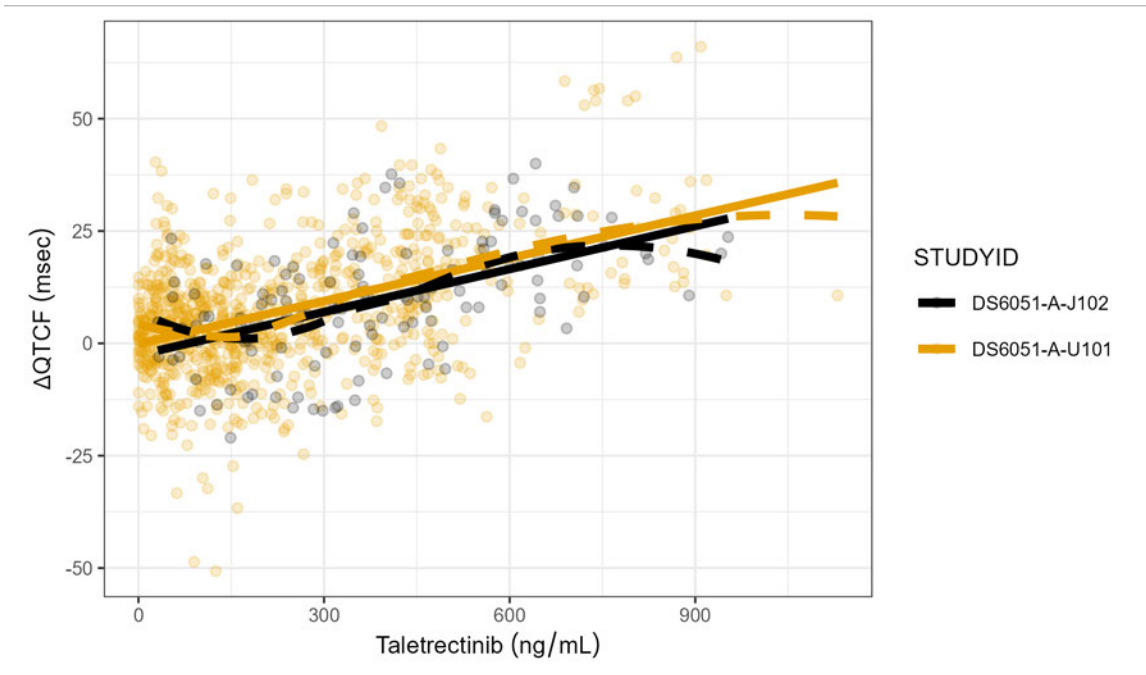
Figure 2 shows the time-course of Δ HR, with an absence of significant Δ HR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and Δ QTcF, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and Δ QTcF and supports the use of a linear model. As can be seen in Figure 6, the slopes of the C-QTs relationships appears similar between study DS6051-A-J102 and study DS6051-A-U101, and thus support pooled analysis. Pooled analysis is also supported by similar ECG collection schedules, doses evaluated, dosing conditions, and study populations.

Figure 5. Time-Course of Drug Concentration (Top) and QTcF (Bottom)²



² $\Delta QTcF$ shown were obtained via descriptive statistics and might differ from Figure 1

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



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 8.

Figure 7. Goodness-of-Fit Plot for QTcF

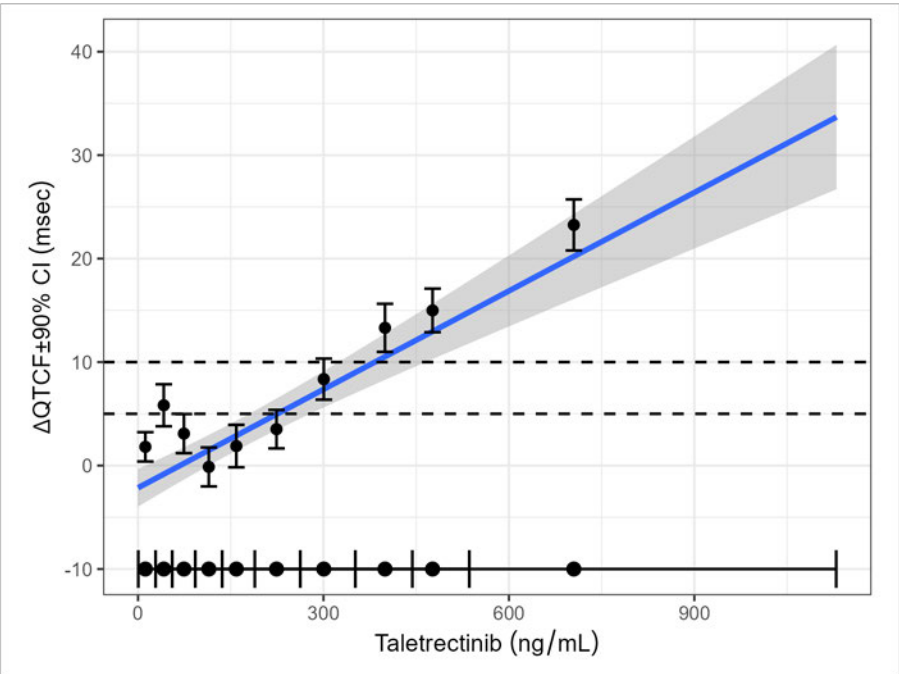


Table 8. Predictions From Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day	Taletrectinib (ng/mL)	Δ QTcF (msec)	90.0% CI (msec)
Taletrectinib 600 mg QD (highest exposure in QTc assessment) [n=6]	15	643.2	18.2	(14.5 to 22.0)
600 mg QD without food in patients with NSCLC and solid tumors	-	476.0	12.9	(10.3 to 15.6)
600 mg QD with High fat meal	-	714.0	20.5	(16.3 to 24.7)
Taletrectinib 800 mg QD [n=17]	15	537.4	14.9	(11.9 to 17.9)
Taletrectinib 1200 mg QD [n=1]	15	918	27.0	(21.4 to 32.5)

4.5.1.1 Assay Sensitivity

Not applicable as this was an alternative QTc assessment without placebo nor positive control.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 EVALUATION OF THE APPLICANT'S CLINICAL QT STUDIES

1. QT Studies					
Study	ECG Quality	Treatments		Sample Size	ECG & PK Assessments
		Arms	Dose Coverage		
Protocol Number: DS6501-A-U101 Population: Patients Design: Other	Digital: Yes Central Read? Yes Blinded? Yes Replicates? Yes	Highest Dose: 1200 mg Placebo: No Positive Control: No	High clinical	Part 1: 35 (≥ 800 mg QD: 21) Part 1b: 11 (400 mg fed/fasted) (800 mg fasted only).	Baseline: Pre-dose baseline Timing: See below
Protocol Number: DS6051-A-J102 Population: Patients Design:	Digital: Choose an item. Central Read? Yes Blinded? Yes Replicates? Yes	Highest Dose: 800 mg Placebo: No Positive Control: No	Therapeutic	15	Baseline: Pre-dose baseline Timing: See below

Other					
Reviewer's comments: Study DS6051-A-U101 was an open-label, multiple dose study with 3 parts: a Dose Escalation Part I, a food effect Part Ib, and a Dose expansion Part II. The Applicant's cardiodynamic analysis is based on ECG and PK data from Part I and Part Ib (including both fasted and fed portions) of Study. The dose escalation part was conducted in 6 cohorts at 50 mg QD (Cohort 1, n=1), 100 mg QD (Cohort 2, n=1), 200 mg QD (Cohort 3, n=3), 400 mg QD (Cohort 4, n=3), 800 mg QD (Cohort 5 and 5b, n=11), and 1200 mg QD (Cohort 6, n=3) by mouth once daily in 21-day cycles. The food effect was examined in Cohort 7 (n=11) with a single oral dose of 400 mg on Day -7 and Day -1, taken with or without food. Study DS6051-A-J102 was a Phase 1, open-label, multiple-dose study in Japanese subjects with advanced solid tumors. Doses tested in this study were 400 mg (n=6), 600 mg (n=6), or 800 mg (n=3) in 21-day cycles, taken without food. Data from cycle 1 for all 3 dose levels were used for cardiodynamic analysis. ECG and PK collection schedule: - DS6501-A-U101 (Part I): Actual schedule varies by cohort. - o ECG/PK: C1D1 and C1D15: Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, and 8 h. - o ECG only: C1D8 and C2D8: Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, and 8 h. Pre-dose on C1D2, C2-70D1, C2D15, C3D15 - DS6501-A-U101 (Part Ib): Actual schedule varies by cohort. - o ECG/PK: C1 D-7, D-1, and D15: Pre-dose, 2, 6 h. Pre-dose on C1D8, C2-6D1 - DS6501-A-J102: - o ECG/PK: C1D1 and C1D15: Pre-dose, 3, 4, 5, and 24 h. Pre-dose on C2D1. - o ECG only: C4D1 and every 2 subsequent cycles – timing of collection is unclear.					

5.2 EVALUATION OF THE APPLICANT'S CLINICAL QT ANALYSIS PLAN

1. Analysis plan
1.1 Study Objectives Related to QT

What QTc effect size is the analysis trying to exclude?	20 ms
1.2 Data Pooling	
Data pooling?	Yes
Did Applicant propose an assessment for heterogeneity?	Yes
Is the data pooling appropriate?	No
<i>Reviewer's comments: Studies were analyzed independently and pooled. In the pooled analysis, the Applicant included subjects in Part 1b taking taletrectinib with food. This is not appropriate as food may interfere with assessment of the QTc effects of drugs.</i>	
1.3 QT Correction Method	
Is an HR increase or decrease greater than 10 beats/min?	No
Primary method for QT correction	QTcF
<i>Reviewer's comments: A 10 msec mean increase in QTc interval cannot be excluded as this is an alternative QTc assessment without placebo and positive control.</i>	
1.4 Assay Sensitivity	
Assay sensitivity methods proposed by Applicant	☐ Moxifloxacin ☐ Exposure-margin ☐ QT bias assessment ☐ Other ☒ Not applicable (objective is large mean effects)
1.5 By-Time Analysis	
1.5.1 Investigational Drug	
Primary analysis	No
Did the Applicant use IUT or descriptive statistics?	Both
For IUT: Does the Applicant use MMRM to analyze longitudinal values that consider the correlation across time-points, or use ANCOVA by-time-point without considering correlation?	MMRM

For IUT: Is the MMRM model specified correctly with regard to covariance structure, covariates, or if ANCOVA, is the model specified correctly with regard to covariates?	Yes
<i>The by-time point analysis was performed for Parts I and Ib of Study DS6051-A-U101 separately, and for Study DS6051-A-J102 separately. To support the by-time point statistical modeling described below, descriptive statistics (e.g., number of subjects, mean, SD, median, maximum, and minimum) were used to summarize the absolute values of the ECG variables and the corresponding change-from- baseline values by cohort at each time point. The by-time point analysis for QTcF interval on DS-6051b was based on a mixed model for repeated measures (MMRM) with ΔQTcF interval as the dependent variable, time (i.e., postbaseline time point with at least 3 subjects within treatment: categorical), treatment (Cohort 1 to Cohort X of DS-6051b; note that Cohort 5, Cohort 5b, and Cohort 8 in Study DS6051-A-U101 were all on 800 mg QD; Cohort 5b and Cohort 8 were just adding more subjects for the 800 mg QD dose tested in Cohorts 5 and therefore, Cohorts 5, 5b, and 8 were pooled together as a single cohort) and time-by-treatment interaction as fixed effects, and baseline QTcF as a covariate. An unstructured covariance matrix was specified for the repeated measures at post-baseline time points within subjects.</i> Reviewer's comments: We evaluated the single delta effect of all intervals using non-parametric descriptive statistics.	
1.5.2 Positive Control	
Primary analysis	N/A
Did the Applicant adjust for multiplicity?	N/A
1.6.1 Investigational Drug	
Primary analysis	Yes
What is the dependent variable in the Applicant's model?	Single delta
White paper model?	Yes
Which concentration covariate(s) are included in the model?	Parent
Which methods did the Applicant use for predicting the QT effect?	☒ Model-based confidence intervals ☐ Bootstrap-derived confidence intervals
1.6.2 Positive Control	
Primary analysis	N/A

Same model as investigational drug		N/A	
1.7 Categorical Analysis			
QTcF / ΔQTcF?	Yes	QRS?	Yes
PR?	Yes	HR?	Yes

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