CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219972Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 13, 2025
To:	Raniya Al-Matari, Ph.D. 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)** Adesola Adejuwon, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	HYRNUO (sevabertinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 219972
Applicant:	Bayer HealthCare Pharmaceuticals Inc.

1 INTRODUCTION

On March 28, 2025, Bayer Healthcare Pharmaceuticals Inc. submitted for the Agency's review an original New Drug Application (NDA) 219972 for HYRNUO (sevabertinib) tablets, for oral use. The Applicant is seeking an accelerated approval

(b) (4)

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 May 1, 2025, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for HYRNUO (sevabertinib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft HYRNUO (sevabertinib) tablets, for oral use PPI received on March 28, 2025, and received by DMPP and OPDP on November 10, 2025.
- Draft HYRNUO (sevabertinib) tablets, for oral use Prescribing Information (PI) received on March 28, 2025, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 10, 2025.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

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

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)

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

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

Memorandum

Date: November 12, 2025

To: Raniya Ali Al-Matari, Ph.D., Regulatory Health Project Manager, Division of Oncology 2 (DO2)

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

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

Subject: OPDP Labeling Comments for HYRNUO® (sevabertinib) tablets, for oral use

NDA: 219972

Background:
In response to DO2's consult request dated March 28, 2025, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for HYRNUO® (sevabertinib) tablets, for oral use (Hyrnuo).

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on November 10, 2025, and our comments are provided below.

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

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on November 4, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Adesola (Sola) Adejuwon at 240 402 5773 or Adesola.Adejuwon@fda.hhs.gov.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

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

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

Date of This Review:	November 12, 2025
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 219972
Product Name, Dosage Form, and Strength:	Hyrnuo (sevabertinib) tablets, 10 mg
Applicant Name:	Bayer HealthCare Pharmaceuticals Inc.
FDA Received Date:	November 4, 2025
TTT ID #:	2025-13912-3
DMEPA 2 Safety Evaluator:	Adeola Oluwatimilehin, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 PURPOSE OF MEMORANDUM

Bayer HealthCare Pharmaceuticals Inc. submitted revised container label and carton labeling received on November 4, 2025 for Hyrnuo. The Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Hyrnuo (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

Bayer HealthCare Pharmaceuticals Inc. implemented all of our recommendations[b] and we have no additional recommendations at this time.

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[a] Oluwatimilehin, A. Review of Revised Label and Labeling for Hyrnuo (NDA 219972). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 OCT 02. TTT ID: 2025-13912-2.

[b] NDA 219972. Sevabertinib (BAY 2927088). Response to FDA Information Request. Whippany (NJ): Bayer HealthCare Pharmaceuticals Inc. 2025 OCT 10. Available from: \\CDSESUB1\EVSPROD\nda219972\0056\m1\us\111-information-amendment\response-to-fda-information-request-dated-10oct2025.pdf.

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Consult Memorandum

Date:	November 4, 2025
To:	Raniya Al-Matari., CDER/OND/ORO/DROOD Kevin Breen, M.D., CDER/OND/OOD/DOII Diana Bradford, M.D., Team Lead, CDER/OND/OOD/DOII Nicole Drezner, M.D., Deputy Division Director, CDER/OND/OOD/DOII
From:	Soumen Roy, Ph.D., Scientific Reviewer, CDRH/OHT7/DMGP/MPCB
Through:	Rama Kamesh Bikkavilli, Ph.D., Acting Branch Chief, CDRH/OHT7/DMGP/MPCB Shyam Kalavar, MPH, CT(ASCP), Branch Chief, CDRH/OHT7/DMGP/MPCB Soma Ghosh, Ph.D., Acting Division Director, CDRH/OHT7/DMGP
ICC Number:	ICCR# 01093576 | NDA219972
Subject:	CDER consult request for NDA 219972
Drug Name:	Sevabertinib (HYRNUO)
Drug Sponsor:	Bayer HealthCare Pharmaceuticals, Inc.
Biomarker(s):	ERBB2/HER2 activating mutations (single nucleotide variants and exon 20 insertions) in the tyrosine kinase domain
Device Name:	The Oncomine™ Dx Target Test
Device Sponsor:	Thermo Fisher Scientific
Related Submissions:	P160045/S050

I. BACKGROUND and PURPOSE

CDER is currently reviewing NDA 219972 from Bayer HealthCare Pharmaceuticals, Inc. that seeks approval for HYRNUO™ (sevabertinib) for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumors have activating ERBB2/HER2 mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy. CDRH received a supplemental premarket approval (sPMA) application for the detection of ERBB2/HER2 activating mutations (SNVs and exon 20 insertions) in patients with NSCLC who may benefit from treatment with sevabertinib. The tissue-based Oncomine™ Dx Target Test (P160045/S050) was submitted by Thermo Fisher Scientific on April 22, 2025, seeking contemporaneous approval as a companion diagnostic (CDx) device for sevabertinib. The device is expected to be co-approved with the drug.

During the course of NDA and sPMA review, the CDRH reviewers provided feedback to drug labeling and attended relevant CDER meetings. The following section is a summary of the sPMA review for CDER's consideration.

II. PROPOSED DRUG INTENDED USE

HYRNUO (Sevabertinib) is indicated for the treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors have HER2 (ERBB2) tyrosine kinase domain activating mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1)], and who have received a prior systemic therapy.

This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DOR) [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

III. CDx for the PROPOSED DRUG INTENDED USE

Biomarker(s) Detected: ERBB2/HER2 activating mutations (single nucleotide variants and exon 20 insertions) in the tyrosine kinase domain

Technology: The Oncomine™ Dx Target Test. Next-generation sequencing (NGS) using amplicon-based targeted sequencing

The device is expected to be co-approved with the drug.

IV. P160045/S050 ONCOMINE DX TARGET TEST (ODxTT) REVIEW SUMMARY

Life Technologies Corporation, a subsidiary of Thermo Fisher Scientific (TFS or sponsor), submitted this 180-Day PMA supplement (P160045/S050) on April 22, 2025 to expand the companion diagnostic (CDx) indications for the Oncomine Dx Target Test (ODxT Test) to identify ERBB2/HER2 activating mutations (SNVs and exon 20 insertions) in formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples from patients with non-small cell lung cancer (NSCLC) who may benefit from treatment with Sevabertinib (HYRNUO). The sPMA was submitted for contemporaneous review with NDA 219972.

The Bayer sevabertinib Study 21607 enrolled NSCLC patients with ERBB2/HER2 activating mutations as determined by prospective local testing using tissue or plasma samples. The majority of the efficacy population (Primary Analysis Set - Group D and Group E) used to support the current NDA application were enrolled based on tissue-based assays. The local tests included various technologies including NGS and PCR tests. Upon completion of the study, the ODxTT was used to retrospectively test all available clinical tissue samples. Since ODxTT was not the clinical trial assay, a bridging study was needed to demonstrate the clinical effectiveness of the device to aid in the selection of NSCLC patients with ERBB2/HER2 activating mutations for sevabertinib therapy.

The efficacy population included 122 patients with advanced NSCLC with HER2 (ERBB2) tyrosine kinase domain activating mutations based on prospective local testing. Of those, tumor tissue samples from 67.2% (82/122) of patients were retrospectively tested using Oncomine™ Dx Target Test (Life Technologies Corporation). While 92.7% (76/82) of samples were positive for HER2 (ERBB2) activating mutations, 0% (0/82) did not have HER2 (ERBB2) activating mutations identified, and 7.3% (6/82) were unevaluable.

The Objective Response Rate (ORR) observed in the CTA-positive population was 71.4% (95% CI: 59.4% - 81.6%). The CDx-positive and CTA-positive population demonstrated an ORR of 76.2% (95% CI: 60.5% - 87.9%). The lower limit of the 95% CI of 59.4% for the CTA-positive population establishes statistically significant sevabertinib efficacy and satisfies the prespecified efficacy acceptance criterion of >30%.

Concordance analysis between clinical trial assays (CTA) and the companion diagnostic demonstrated excellent agreement with Positive Percent Agreement (PPA) of 100.0% (95% CI: 95.2% - 100.0%),

Negative Percent Agreement (NPA) of 100.0% (95% CI: 97.0% - 100.0%), and Overall Percent Agreement (OPA) of 100.0% (95% CI: 98.1% - 100.0%).The improved concordance was achieved through inclusion of four novel HER2 variants in a custom hotspot file that were validated through plasmid testing.

In conclusion, CDRH considers the supplemental PMA for ODxTT approvable as a companion diagnostic device for sevabertinib to select NSCLC patients with ERBB2/HER2 activating mutations.

REVIEWER NOTE: The sponsor initially proposed a broad indication (b) (4) (b) (4), with a primary efficacy population of 81 patients from Group D and a supporting population of 55 patients from Group E. CDER narrowed the indication to HER2 tyrosine kinase domain (TKD) activating mutations only, based on superior efficacy in TKD patients (ORR 74.4%) compared to non-TKD mutations (ORR 25.0%) in the March 2025 data cutoff. CDER cited insufficient clinical data for non-TKD mutations as the rationale for this limitation.

CDRH considers the supplemental PMA for Oncomine™ Dx Target Test approvable as a companion diagnostic device for HYRNUO™ (sevabertinib) to select NSCLC patients with ERBB2/HER2 TKD activating mutations. However, since CDERs action date is on November 19/2025, CDRH closed this submission with an ADEF (approvable pending approval of the drug by CDER) decision for the Thermo Fisher Oncomine™ Dx Target Test, P160045/S050, (companion diagnostic for sevabertinib NDA 219972) to meet CDRH's MDUFA timeline. The Approval Order will be issued upon CDER's approval of the sevabertinib NDA to ensure contemporaneous availability of both the drug and CDx device.

Drug label review

CDRH reviewed sections 1, 2 and 14 of the Sevabertinib (HYRNUO) drug label and have the following comments for the edits included by CDER:

Section 1:
CDER is considering the following intended use:

HYRNUO is indicated for the treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors have HER2 (ERBB2) tyrosine kinase domain activating mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1)], and who have received a prior systemic therapy.

This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DOR) [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

CDRH aligns with CDER regarding narrowing down the indication to only TKD mutations.

Section 2.1:
CDER is considering the following text for patient selection:

Select patients for treatment of advanced NSCLC with HYRNUO based on the presence of HER2 (ERBB2) tyrosine kinase domain activating mutations in tumor specimens [see Clinical Studies (14)].

Information on FDA-approved tests is available at http://www.fda.gov/CompanionDiagnostics.

Section 14:
CDRH added the sentences with blue font (below):

HER2 (ERBB2) activating mutations were determined in tumor tissue or plasma by local laboratories prior to enrollment. The efficacy population included 122 patients with advanced NSCLC with HER2 (ERBB2) tyrosine kinase domain activating mutations based on prospective local testing. Of those, tumor tissue samples from 67.2% (82/122) of patients were retrospectively tested using Oncomine™ Dx Target Test (Life Technologies Corporation). While 92.7%% (76/82) of samples were positive for HER2 (ERBB2) activating mutations, 0% (0/82) did not have HER2 (ERBB2) activating mutations identified, and 7.3% (6/82) were unevaluable. . Patients with treated, stable and asymptomatic brain metastases were eligible. Patients with symptomatic CNS metastases, clinically significant cardiac disease, and history of steroid dependent interstitial lung disease (ILD)/pneumonitis were excluded.

This consult review is limited to the information provided in NDA 219972. If there are any questions regarding this review, please contact Soumen Roy by phone 301-837-7262 and email at Soumen.Roy@fda.hhs.gov

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/s/

RANIYA A AL-MATARI
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Clinical Inspection Summary

Date	October 21, 2025
From	Lee Pai-Scherf, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE, OSI
To	Kevin Breen, Physician Diana Bradford, Physician, Team Leader Nicole Drezner, Physician, Deputy Director Division of Oncology 2 (DO2), Office of Oncology Products
NDA #	219972
Applicant	Bayer Healthcare Pharmaceuticals, Inc.
Drug	Sevabertinib (BAY 2927088)
NME (Yes/No)	Yes
Therapeutic Classification	HER2 tyrosine kinase inhibitor
Proposed Indication(s)	For the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, and who have received prior systemic therapy
Consultation Request Date	April 29, 2025
Summary Goal Date	October 31, 2025
Action Goal Date	November 19, 2025
PDUFA Date	November 28, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study 21607 were submitted to the Agency in support of New Drug Application (NDA) 219972 for sevabertinib (BAY 2927088) for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations and who have received prior systemic therapy. Three clinical investigators, Dr. Ticiana Leal (Site #14003), Dr. Tae Min Kim (Site #56002), and Dr. Herbert Ho Fung Loong (Site #65001), as well as the General Clinical Imaging Services (GCIS) at Bayer Healthcare Pharmaceuticals, Inc were inspected. The following findings were observed during the inspections.

Protocol Deviation at Site #56002: As previously communicated to the Division, the inspection of Dr. Tae Min Kim identified one protocol deviation involving subject (b) (6) (sevabertinib), who should not have been enrolled according to protocol inclusion criterion 5.1.1 due to mixed histology (sarcomatoid carcinoma with squamous cell and spindle cell components) documented in the pathology report. The subject achieved a partial response (PR) per blinded independent central review (BICR) and

experienced non-serious drug-related adverse events that have resolved. The protocol deviation did not impact the subject safety, and OSI defers to the review division regarding inclusion of this subject's data in the primary efficacy analysis.

Data Discrepancy at Bayer Clinical Imaging Services: The inspection of Bayer's Clinical Imaging Services identified a data discrepancy for subject (b) (6), where the tumor Assessment 1 scan date was incorrectly listed as (b) (6) instead of the actual date (b) (6) in the original NDA submission. This error resulted from an incorrect procedure date in one scan image out of 1,301 total images. Bayer had already submitted the corrected data to FDA on 6/27/2025 as part of an efficacy update, though the error and rationale were not described. At OSI's request, the sponsor provided a detailed explanation of the data error and the rationale for the Best Overall Response (BOR) change. The timeline correction changed the subject's BOR from Progressive Disease (PD) to Stable Disease (SD) because the corrected Assessment 1 date occurred before both the PD assessment and new anti-cancer therapy initiation, allowing the PR assessment to be included in BOR derivation per RECIST v1.1 criteria. Since the PR was not confirmed by a subsequent PR or CR but met minimum duration requirements for SD (≥6 weeks from first treatment according to Statistical Analysis Plan v2.0), the BOR was reclassified as SD per RECIST v1.1. OSI acknowledges the error was corrected and agrees with Bayer's rationale for the BOR change. *See Results, Bayer Healthcare Pharmaceuticals, Inc. for full details.*

Except for the observations noted above, the inspections did not identify significant concerns regarding study conduct, data discrepancies, Good Clinical Practice (GCP), or regulatory compliance. The data generated by these clinical investigators appear acceptable in support of the proposed indication.

II. BACKGROUND

Bayer Healthcare Pharmaceuticals Inc. submitted NDA 219972 seeking approval for BAY 2927088 (b) (4) (b) (4) (b) (4). The primary evidence of efficacy and safety supporting this indication is based on data from Study 21607, a first-in-human study of BAY 2927088 in participants with advanced NSCLC.

Study 21607 is an open-label, multicenter, single-arm phase 1/2 first-in-human study evaluating sevabertinib in NSCLC patients with EGFR (ex20ins), HER2 activating mutations, or EGFR driver mutations with secondary mutations.

The study consists of three parts: 1) Dose-escalation/backfill (DE/BF) to determine maximum tolerated dose (MTD), safety, tolerability, and pharmacokinetics (PK); 2) Dose Expansion across 7 NSCLC groups (A-G) to characterize safety/tolerability/PK at the recommended dose; and 3) Extension (Phase 2) to evaluate efficacy at the recommended phase 2 dose (RP2D) of 20mg twice daily (BID).

Total enrollment included 375 patients across 75 centers in 14 countries, including 30 subjects at 7 U.S. centers. The primary efficacy population to support the proposed indication consists of 81 subjects with HER2-mutated NSCLC, prior systemic therapy, and HER2-targeting therapy naïve enrolled in Group D of the study. The supportive population includes 55 subjects with HER2-mutated NSCLC with prior HER2-targeted ADC progression (Group E).

The primary objectives include determining safety, tolerability, PK, MTD, RP2D, and efficacy. The primary efficacy endpoint to support the proposed indication is ORR by BICR per RECIST v1.1. Key secondary endpoints are duration of response (DoR) per BICR, ORR and DoR and progression-free survival (PFS) by investigator assessment, and overall survival (OS).

Written informed consent and baseline procedures (history/physical, labs, hepatitis B and C serology, ECG, ECHO/MUGA, ophthalmological exam, tumor mutation status, PD-L1 expression) must be completed within 28 days of C1D1. Tumor imaging includes baseline CT/MRI of chest/abdomen/pelvis and brain MRI, followed by imaging every 6 weeks for 36 weeks, then every 9 weeks. Dose Expansion subjects require central imaging submission within 7 working days.

Follow-up procedures include end-of-treatment visit, safety follow-up, and survival contact every 3 months for 24 months post-treatment.

III. RESULT

1. **Dr. Ticiana Leal (Site # 14003)**
   Winship Cancer Institute, Emory University
   1365 Clifton Road Ne
   Atlanta, GA 30322

   Inspection dates: August 4 – 7, 2025

   Dr. Leal underwent a BIMO review-based inspection for Study 21607. This was the first inspection for this investigator.

   At the time of the inspection, the site had screened 13 subjects and enrolled 6 subjects with three subjects in the follow-up phase.

   Source records for all subjects were reviewed and compared with data submitted to the NDA. The review encompassed both Electronic Medical Records (EMR), and paper files for each subject, including informed consent forms, inclusion/exclusion criteria, protocol-required procedures, concomitant medications, adverse events, investigational product (IP) accountability, adverse events and progress notes. No significant discrepancies were

observed between source records and the data listings submitted to the NDA.

The inspection verified that radiographic scans were performed as specified in the protocol. All scans were submitted for central review, consistent with the data submitted to the NDA.

Additional records reviewed included financial disclosure forms, Institutional Review Board (IRB) approvals and communications, study staff training records, delegation of authority and responsibility logs, staff qualification records, and site training documentation. No issues were noted with these documents.

Based on the inspection results, the data generated by Dr. Leal's appear acceptable in support of the proposed indication in the NDA.

2. Dr. Tae Min Kim (Site # 56002)
Seoul National University Hospital 101
Daehak-Ro, Jongno-Gu
Seoul Teugbyeolsi 03080
South Korea

Inspection dates: August 25 - 29, 2025

Dr. Kim underwent a BIMO review-based inspection for Study 21607. The site was last inspected in December 2023, with findings of underreporting of non-serious adverse events.

At the time of this inspection, the site had screened and enrolled 19 subjects in the 21607 study.

Paper and electronic source records for all 19 subjects enrolled at the site were reviewed and included informed consent forms, medical progress notes, eligibility criteria, pathology report, genetic testing reports, adverse events, selected laboratory reports, and investigational drug administration records were reviewed. Records were compared with eCRF entries and data listing tables submitted to the NDA.

One protocol violation was observed and previously communicated by OSI to the review division via email on 8/27/2025.

- Subject (b) (6) (sevabertinib) should not have been enrolled according to protocol inclusion criterion 5.1.1, which states "Documented histologically or cytologically confirmed locally advanced NSCLC not suitable for definitive therapy or recurrent or metastatic NSCLC at screening (small cell or mixed histologies are excluded)." The subject's pathology report from lobectomy documented mixed histology with "sarcomatoid carcinoma, pleomorphic

carcinoma (squamous cell component 80%, spindle cell carcinoma component 20%)." Therefore, this subject should have been excluded from the study.

However, this 62-year-old male subject was enrolled in Study 21607 Group D. He received his first dose of sevabertinib on (b) (6) and achieved a best overall response of PR per BICR. During treatment, he experienced drug-related non-serious adverse events including diarrhea, rash, palmar-plantar erythrodysesthesia syndrome, and paronychia, all of which have resolved. At the data cut-off date (10/14/2024), the subject's treatment was ongoing. The subject experienced disease progression on (b) (6) during the follow-up phase, was discontinued from the study, and died on (b) (6) due to disease progression.

Reviewer's comment: Given the histology report of sarcomatoid carcinoma with mixed histology, subject (b) (6) should not have been enrolled in the investigational trial with sevabertinib. Dr. Kim stated that he judged the subject as having NSCLC sarcomatoid carcinoma rather than mixed histologies. Additionally, it was understood by Dr. Kim that "mixed histology" referred to small cell cancer and because the subject had no evidence of small cell carcinoma or its mixed histology, the subject was enrolled.

Based on available information, the above protocol violation did not impact the subject's safety. OSI defers to the review division to determine whether to include data from this subject in the primary efficacy analysis.

The inspection also verified that imaging scans to assess efficacy endpoints of ORR and DOR were performed according to protocol-specified time points, and all scans at the site were submitted for central review. No discrepancies were observed.

Additional records reviewed but not limited to Ethics Committee (EC) approvals, sponsor and monitor correspondence, financial disclosure forms, study staff training records, and electronic case report forms (eCRFs). No issues were noted with these documents.

3. Dr. Herbert Ho Fung Loong (Site # 65001)
Prince of Wales Hospital
30-32 Ngan Shing Street
Sha Tin, New Territories
Hong Kong, China

Inspection dates: August 18 – 22, 2025

Dr. Loong underwent a BIMO review-based inspection for Study 21607. This was the first inspection for this investigator.

At the time of the inspection, the site had screened 17 subjects and enrolled 12 subjects in the 21607 study.

Source records for all 12 enrolled subjects were reviewed and compared with data

submitted to the NDA. Paper records reviewed included medical progress notes, pathology reports, discharge reports, laboratory results, eligibility criteria, safety assessments, and radiology reports. No significant discrepancies were found between source records and the submitted data.

Imaging scans to assess efficacy endpoints of ORR and DOR were performed according to protocol-specified time points. All scans were submitted for central review, and no discrepancies were observed.

Additional records reviewed included Ethics Committee (EC) approvals, sponsor and monitor correspondence, financial disclosure forms, study staff training records, and electronic case report forms (eCRFs). No issues were noted with these documents.

Based on the inspection results, the data generated by Dr. Loong appear to be acceptable in support of the NDA.

4. **Bayer Healthcare Pharmaceuticals, Inc (General Clinical Imaging Services)**
   100 Bayer Blvd
   Whippany, New Jersey

   Inspection dates: August 11 – 15, 2025

   This inspection reviewed Bayer's responsibilities to perform an independent central imaging review for Study 21607. The firm was last inspected in December 2024 without significant findings.

   Records reviewed included, but were not limited to, Bayer's imaging procedures, data collection and handling, adherence to the Imaging Review Charter, staff training, selection of readers, reader financial disclosure, blinding, and quality assurance of queries posted by the imaging team to sites.

   The inspection verified tumor response data for twenty one subjects from Group D and ten subjects from Group E who were reported as having achieved an objective tumor response in the NDA. The IDs of these subjects are as follows:

Subject ID
Group D
(b) (6)
Group E
(b) (6)

*A data discrepancy concerning scan date was identified for this subject.

Subject (b) (6)* was a 29-year-old female with stage IVB disease enrolled in Study 21607, Group D on (b) (6). She received of study treatment from (b) (6) to (b) (6). Treatment was discontinued on (b) (6) due to serious hepatic toxicity. The subject died of respiratory failure on (b) (6), approximately one year after her last dose.

The data discrepancy was identified for this subject's tumor Assessment 1, where the scan date was incorrectly listed as (b) (6) instead of the actual date (b) (6). The issue arose from an incorrect procedure date in one scan image (out of 1,301 total images) and was discovered during a retrospective quality assurance review to ensure RECIST data conformity.

This error was identified in March 2025, after the initial CSR data cutoff date (10/14/2024). The subject had a follow-up scan (Assessment 2) on (b) (6) that was assessed as PD per BICR. At the time of the inspection, Bayer informed the inspector that the error and the corrected information had not been submitted to the FDA and Bayer was asked to submit an NDA amendment.

Radiographic Images for Subject (b) (6)

Assessment	Actual Date of Scan	Date of Scan in CSR (cutoff date 10/14/2024)	Date of Scan in CSR Addendum (cutoff date 3/28/2025)	BICR Read
Baseline	(b) (6)			-
Assessment 1				PR
Assessment 2				PD
BOR* per BICR				**PD (CSR) → SD (CSR addendum)**

*BOR = best overall response

Reviewer's Comment: *In their response received on 8/20/2025, Bayer indicated that the corrected scan date for subject (b) (6) had in fact already been submitted to the agency on 6/27/2025 (Seq 0016) as part of an efficacy update with the 90-day safety*

update. Although the error and the rationale for changing the BOR from PD to SD for subject (b) (6) *were not described in that submission.*

In their subsequent responses to OSI dated 8/20/2025 and 10/17/2025, Bayer explained that the BOR change from PD to SD for subject (b) (6) *was solely due to timeline correction and did not involve changes to the individual BICR assessment. With the original incorrect date* (b) (6)*, the PR assessment was excluded from BOR derivation because it occurred after both the PD date and new anti-cancer therapy start date. After correction to* (b) (6)*, the PR assessment was included in BOR derivation since it occurred before the PD assessment* (b) (6) *and before the subject's new therapy initiation* (b) (6)*. Since the PR was not confirmed by a subsequent PR or CR but met minimum duration requirements for SD (≥6 weeks from first treatment according to Statistical Analysis Plan v2.0), the BOR was reclassified as SD per RECIST v1.1 in the CSR addendum with a cutoff date of 03/28/2025.*

OSI acknowledges that the error was corrected in the CSR Addendum previously submitted to the Agency and agree with Bayer's rationale for changing subject (b) (6) (b) (6) *BOR from PD to SD.*

No other discrepancies were observed during the inspection. The data generated at Bayer appear acceptable to support the NDA.

{See appended electronic signature page}

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

CONCURRENCE:

{*See appended electronic signature page}*

Michele Fedowitz, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {*See appended electronic signature page}*

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

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

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/s/

LEE HONG PAI SCHERF
10/21/2025 01:47:28 PM

MICHELE B FEDOWITZ
10/21/2025 01:53:38 PM

JENN W SELLERS
10/21/2025 02:24:19 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)

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

Date of This Review:	October 2, 2025
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 219972
Product Name, Dosage Form, and Strength:	Hyrnuo (sevabertinib) tablets, 10 mg
Applicant Name:	Bayer HealthCare Pharmaceuticals Inc.
FDA Received Date:	September 25, 2025
TTT ID #:	2025-13912-2
DMEPA 2 Safety Evaluator:	Adeola Oluwatimilehin, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 PURPOSE OF MEMORANDUM

Bayer HealthCare Pharmaceuticals Inc. submitted revised container label and carton labeling received on September 25, 2025 for Hyrnuo. The Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Hyrnuo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The container label and carton labeling are unacceptable from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Bayer HealthCare Pharmaceuticals Inc. in Section 3.

3 RECOMMENDATIONS FOR BAYER HEALTHCARE PHARMACEUTICALS INC.

A. General Comment (Container Label and Carton Labeling)

1. As currently presented, the placement of the graphic  directly in front of the proprietary name may lead to the misinterpretation of the propriety name as "OHYRUNO". We recommend moving the graphic away from the proprietary name.

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

[a] Oluwatimilehin, A. Label and Labeling Review for Hyrnuo (NDA 219972). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 SEP 04. TTT ID: 2025-13912-1.

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/s/

ADEOLA O OLUWATIMILEHIN
10/02/2025 09:55:36 AM

TINGTING GAO
10/02/2025 11:20:53 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

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

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

Date of This Review:	September 4, 2025
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 219972
Product Name, Dosage Form, and Strength:	Hyrnuo (sevabertinib) tablets, 10 mg
Applicant Name:	Bayer HealthCare Pharmaceuticals Inc.
FDA Received Date:	September 3, 2025
TTT ID #:	2025-13912-1
DMEPA 2 Safety Evaluator:	Adeola Oluwatimilehin, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 PURPOSE OF MEMORANDUM

Bayer HealthCare Pharmaceuticals Inc. submitted revised container label and carton labeling received on September 3, 2025 for Hyrnuo. The Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Hyrnuo (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 DISCUSSION

Bayer HealthCare Pharmaceuticals Inc. implemented all of our previous recommendations. Bayer also stated that the container is a square bottle with four flat sides, and confirmed that the linear barcode will be oriented on the container label such that it is not distorted or obstructed by container curvature.[b]

However, the container label and carton labeling can be improved from a medication error perspective.

3 CONCLUSION

The container label and carton labeling are unacceptable from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Bayer HealthCare Pharmaceuticals Inc. in Section 4.

4 RECOMMENDATIONS FOR BAYER HEALTHCARE PHARMACEUTICALS INC.

A. General Comments (Container Label and Carton Labeling)

1. As currently presented, the graphic (b) (4) positioned directly before the proprietary name competes with the legibility and may lead to the misinterpretation of the propriety name. Specifically, the graphic may be misinterpreted as the letter "O" and may lead to misinterpretation of the proprietary name as "OHYRUNO". We recommend relocating the graphic away from the proprietary name. Consider changing the color of the graphic (b) (4) (b) (4)

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

[a] Oluwatimilehin, A. Label and Labeling Review for Hyrnuo (NDA 219972). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 JUL 21. TTT ID: 2025-13912.

[b] NDA 219972. Sevabertinib (BAY 2927088). Response to FDA Information Request. Whippany (NJ): Bayer HealthCare Pharmaceuticals Inc. 2025 Sept 3. Available from: \\CDSESUB1\EVSPROD\nda219972\0036\m1\us\111-information-amendment\response-to-fda-ir-19aug2025.pdf.

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ADEOLA O OLUWATIMILEHIN
09/04/2025 10:23:24 AM

TINGTING GAO
09/04/2025 10:40:54 AM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 219972
Submission Number	0004
Submission Date	3/28/2025
Date Consult Received	5/2/2025
Drug Name	Sevabertinib (BAY 2927088)
Indication	Treatment of advanced non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy
Therapeutic Dose	20 mg BID
Clinical Division	DO2
Protocol Review	Link

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

This review responds to your consultation request dated 05/02/2025, regarding the Applicant's QT evaluation. We reviewed the following materials:

- Previous IRT review dated 02/12/2024 in DARRTS;
- Cardiac Safety Report for CPMX50213 (NDA 219972 / SN 0001; link);
- Interim Clinical Study Report for Study 21607 (NDA 219972 / SN 0001; link);
- Summary of Clinical Safety (NDA 219972 / SN 0001; link);
- Datasets for CPMX50213 (NDA 219972 / SN 0001; link); and
- Highlights of clinical pharmacology and cardiac safety (IND 155685/ SN 0090; link).

1 SUMMARY

Based on data from Study 21607, sevabertinib does not demonstrate mean QTcF interval prolongation ≥20 msec (Table 1). In the absence of a positive control and a placebo group, there is reluctance to conclude a lack of an effect of sevabertinib on the QTc interval.

Study 21607, a non-randomized, open-label, single-arm, multicenter Phase 1 first-in-human trial, was conducted to determine the maximum tolerated dose (MTD) or maximum administered dose as well as to determine the recommended Phase 2 dose (RP2D) of sevabertinib in participants with advanced NSCLC. The highest dose provided 2.2-fold therapeutic exposure.

Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that sevabertinib is associated with ≥20 msec mean increase in the QTcF interval (section 4.5). The findings of the primary analysis are further supported by the lack of dose-dependent QTc prolongation in the by-time analysis.

Table 1: Summary of findings

<table>
<tr><td>QT assessment pathway</td><td>☐ Thorough QT study
☐ Substitute for thorough QT study (5.1)
☒ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• High clinical exposure scenario is expected with moderate CYP3A4 inhibition or in severe hepatic impairment. The increase in exposure in these scenarios has not been characterized (section 3.1)
• The highest dose in QTc assessment (60 mg) covers the anticipated therapeutic sevabertinib Cmax by 2.2-fold. As the QTc assessment is conducted in the target patient population, the QTc effects of the recommended therapeutic dosing regimen in this population is considered sufficiently characterized.
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Concentration (ug/L)</th><th>ΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>ΔQTcF</td><td>20 mg BID with a light meal</td><td>900</td><td>1.5</td><td>(0.4 to 2.6)</td></tr>
<tr><td>ΔQTcF</td><td>60 mg QD</td><td>2020</td><td>3.9</td><td>(2.0 to 5.8)</td></tr>
</table></td></tr>
<tr><td>In vitro findings</td><td rowspan="2">Integrated nonclinical risk assessment was not performed.</td></tr>
<tr><td>In vivo findings</td></tr>
</table>

2 RECOMMENDATIONS

2.1 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 1 (link). Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

(b) (4)

Reviewer's comment: *We propose to use labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance (link).*

3 APPLICANT'S SUBMISSION

3.1 OVERVIEW

Sevabertinib (BAY 2927088) is an oral, reversible TKI that potently and selectively inhibits EGFR and HER2 driver mutations. Sevabertinib is being developed for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy. The maximum proposed clinical dosing regimen is 20 mg BID.

We previously reviewed the QT assessment plan for this study report when submitted under IND 155685 (02/12/2024 in DARRTS). IRT agreed with the proposed evaluation plan to exclude large mean increase in QTc (≥20 msec) according to the recommendations in ICH E14 Q&A 6.1 without relying on an integrated nonclinical risk assessment. IRT requested additional details regarding the study used for the concentration-QTc analysis.

The current submission includes a cardiac safety report and concentration-QTc analysis CPMX50213 based on study 21607. A concentration-QTc analysis of results from this study were reviewed previously by IRT (02/12/2024 in DARRTS). The current submission provides additional details requested by IRT.

Study 21607 was an open label, first-in-human study of sevabertinib in participants with advanced NSCLC harboring an EGFR and/or HER2 mutation. The study drug was administered in 21-day cycles with continual daily oral administration and no treatment pause between cycles. The concentration-QTc analysis includes 1975 paired QT/QTc and concentration observations from 234 patients from Cycle 1. These were collected on day 1 and day 15 at pre-dose and 1, 2, 4, 6, and 24 h post dose and day 8 pre-dose. For the bioavailability group, additional measurements were included from day -4 at 1, 2, 4, 6, and 24 h post dose.

Study drug was administered in a liquid formulation (L) and tablet formulation (T). Dose groups are shown in Figure 1.

Figure 1. Applicant Table: Participants (data points) per dose group included in the PKS/QTS data set

Visit	10 mg (L/QD)	20 mg (L/QD)	40 mg (L/QD)	40 mg (T/QD)	60 mg (T/QD)	10 mg (T/BID)	20 mg (T/BID)	30 mg (T/BID)	40 mg (T/BID)
C1	3 (28)	6 (65)	9* (109)	14 (160)	4** (71)	33 (250)	150 (1144)	10 (100)	5 (48)

*4 of 9 participants were in the bioavailability group (D-4 as baseline)
**all 4 participants were in the bioavailability group (D-4 as baseline)
Source: Cardiac Safety Report for CPMX50213 (link), page 15

Abbreviations: L, liquid; T, tablet

Since there are multiple dose levels in this study, the treatments have been pooled into three treatment groups namely subtherapeutic, therapeutic, and supratherapeutic.

Subtherapeutic treatment group included:

- Sevabertinib 10 mg QD LSF (n = 3)
- Sevabertinib 10 mg BID TAB (n = 33)
- Sevabertinib 20 mg QD LSF (n = 6)

Therapeutic treatment group included:

- Sevabertinib 20 mg BID TAB (n = 150)
- Sevabertinib 40 mg QD LSF (n = 9)

  Page 21 of cpmx50213-study-report.pdf shows that the 20 mg TAB/BID and 40 mg LSF/QD have very similar exposures.

Supratherapeutic treatment group included:

- Sevabertinib 30 mg BID TAB (n = 10)
- Sevabertinib 40 mg BID TAB (n = 5)
- Sevabertinib 40 mg QD TAB (n = 14)
- Sevabertinib 60 mg QD TAB (n = 4).

3.1.1 Clinical Pharmacology

See highlights of clinical pharmacology and cardiac safety. Briefly, sevabertinib is rapidly absorbed after oral administration with food and reaches peak concentration at median Tmax of 2-hours (range: 0.5–8.2 hours). Food decreases sevabertinib exposure (e.g., administration with high fat meal results in 39% lower Cmax than when administered with light, low-fat meal). When administered with light meal in subjects with NSCLC, sevabertinib tablets 20 mg BID provided geometric Cmax (CV%) of 902 ng/mL (45%).

Sevabertinib is mainly eliminated through CYP3A4 mediated metabolism (terminal $T_{1/2}$ = 5-6 hours, and effective $T_{1/2}$ = 8.9 hours). Its major metabolite, M1, account for 38.5% of total systemic drug exposure and has mean $T_{1/2}$ of 10 hours. Sevabertinib PK is dose-proportional but time dependent. Single dose $T_{1/2}$ seems to be shorter (4-6 hours) than $T_{1/2}$ after multiple doses (6 – 8 hours). Sevabertinib and its metabolites are mainly eliminated through feces, with only 11% eliminated through renal excretion.

Evaluation of the impact of intrinsic and extrinsic factors on the PK of sevabertinib has revealed the following:

- Itraconazole, a strong CYP3A4 inhibitor increased sevabertinib Cmax and AUC by 1.6 and 2.3 respectively. The Applicant proposes to reduce the dose of sevabertinib by half, when co-administered with strong CYP3A4 inhibitors.

The impact of moderate CYP3A4 inhibitors is not known. No dose adjustment has been recommended when co-administering with such drugs.

- Renal impairment is not anticipated to have clinically meaningful effect on exposure to sevabertinib and M1.
- Age, sex, and race were found to have no impact on PK of sevabertinib in a population PK analysis.
- The impact of moderate and severe hepatic impairment on the PK of sevabertinib has not been characterized. Although higher exposure is anticipated in hepatic impairment, this population is not contraindicated.

Based on the available data, the anticipated high clinical exposure scenario is moderate CYP3A4 inhibitors or severe hepatic impairment. But the extent of increase in Cmax in such scenario is not yet known.

Based on DDI studies with itraconazole and carbamazepine, after single doses of 10 mg and 40 mg sevabertinib, M1 Cmax were 44.1 ng/mL and 172 ng/mL, respectively. These Cmax values were 23% and 25% of the corresponding Cmax values of sevabertinib. The respective Tmax values of M1 were about 7 and 4 hours, for the single 10 mg and 40 mg dose. Therefore, Cmax of M1 at the recommended therapeutic dose is estimated to be 25% of therapeutic Cmax of sevabertinib. Sevabertinib Cmax after a single 20 mg dose is around 718 ng/mL (Pooled Dose expansion and dose escalation study), and the corresponding M1 Cmax is estimated to be 179.5 ng/mL. Given the half-life of 10 hours, accumulation factor is 1.8 after 20 mg BID, and therefore steady state Cmax is about 318 ng/mL. Co-administration with carbamazepine increased M1 Cmax by 1.4-fold. Therefore, Cmax of M1 at high clinical exposure scenario and the highest dose in the QTc assessment is anticipated to be around 445 ng/mL and 505 ng/mL, respectively.

Table 2. Summary of Dose and Exposure Assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	20 mg BID, oral tablets, taken with light meal.	Sevabertinib: 902 ng/mL ($C_{max,ss}$) M1: 225.5 ng/mL
Applicant's High clinical exposure scenario	Sevabertinib: co-administration with moderate CYP3A4 inhibitors or severe hepatic impairment. M1: 1.4-fold increase in Cmax with co-administration with strong CYP3A4 inducers.	Sevabertinib: unknown M1: 445 ng/mL
Highest dose in QT assessment	60 mg oral tablets	Sevabertinib: 2020 ng/mL M1: 505 ng/mL*
C_{max} Ratio	Sevabertinib: 2020 / 900 = 2.2 for clinical exposure. M1: 505/445 = 1.13 for high clinical scenario for M1.	

*25% of 2020 ng/mL.

3.1.2 Nonclinical Safety Pharmacology Assessments

Please see previous review dated 02/12/2024. Briefly, the hERG safety margin for sevabertinib is expected to be 27. For M1, based on the derived high clinical Cmax of

445 ng/mL (MW = 482.9, %bound = 98.15%), the hERG safety margin is likely to be 182.

In conscious instrumented telemetry male Beagle dogs, following single oral doses of up to 15 mg/kg of sevabertinib, no test item related and dose-dependent effects on heart rate, arterial blood pressure, left ventricular pressure, ECG intervals (PQ, QRS), and body temperature were observed. Up to the high dose, the QT/QTca interval in the ECG was on average not affected; individual animals, however, displayed slightly prolonged (up to ~8 ms) QTca intervals at about 1.5 to 4 h post-treatment.

3.2 APPLICANT'S RESULTS

3.2.1 By-Time Analysis

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

The Applicant listed the descriptive statistics of mean change-from-baseline (ΔQTcF, ΔHR, ΔQRS, and ΔPR) by all post dose time points, separately for each treatment group.

Sevabertinib showed minimal impact on heart rate with decreases of less than 5 beats/min, which were likely due to procedural variations in ECG recording rather than drug effects.

The overall mean changes from baseline in QTcF were less than 20 msec for all treatment groups.

A statistically significant increase in ΔPR with increasing concentration was found, this increase, which can be partly attributed to the small decrease in heart rate over time, was considered small and not of clinical relevance.

No consistent trend was observed across dose and time for QRS prolongation.

Reviewer's comment: *Given the sparse time points, the reviewer evaluated the ΔQTcF effect using descriptive statistics. To improve clarity, the figures only present Day 1 and Day 15 data from Cycle 1 and the time points with subject number <10 were excluded from the by-time analysis. The trend shown in by-time analysis from reviewer's analysis is similar to the trend shown in the Applicant's by-time analysis. Please see Section 4.3 for details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.2 Categorical Analysis

Twenty-two participants experienced an increase in HR > 100 beats/min and ≥25% over baseline.

Three participants had ΔQTc > 60 msec at a few time points. For two participants a decrease in HR of 31 and 19 beats/min was reported at the same time point possibly explaining the QTc findings.

Nine participants showed a ΔPR > 25% with PR > 200 msec at selected time points. For 8 out of 9 participants the PR prolongation was observed at a single time point and for the 9th participant at 2 time points.

Three participants showed large QRS duration changes resulting in a QRS duration > 110 msec. These were due to intermittent "Right Bundle Branch Blocks" that occurred however, sporadically and only at selected time points. Thus, a consistent drug effect on QRS was not observed.

Reviewer's comment: *Reviewer's categorical analysis has different cutoff values for PR and QRS. Reviewer's analysis results are similar to the Applicant's analysis results. Please see Section 4.4 for details.*

3.2.3 Exposure-Response Analysis

The Applicant used the model recommended in the white paper when a study does not have a placebo control (i.e., $\Delta QT_{\{cik\}} = (\Theta_0 + \eta_{\{0,i\}}) + (\Theta_2 + \eta_{\{2,i\}})C_{\{ik\}} + \Theta_4(QT_{\{ci0\}} - QT_{\{c0\}})$). As the drug had no influence on HR, the Applicant used the Fredericia formula for deriving HR corrected QT interval (i.e., QTcF). The results of the Applicant's analysis show an absence of significant QTc prolongation. No hysteresis was observed. The model estimated intercept and slope were 0.1899 msec (p-value = 0.7752) and 0.1858 msec/µg/L (p-value = 0.0055).

At the Cmax after nominal dosing of 20 mg BID (874 µg/L) the upper limit of the 90% confidence interval of predicted ΔQTcF is well below threshold of regulatory concern of 20 ms for oncology drugs. This threshold was also not reached at the highest observed concentration of 3519.0 µg/L, which was 4 times the geometric mean Cmax after 20 mg BID.

In addition to the above modelling, the Applicant conducted sensitivity analysis by evaluating the [redacted] effect in their concentration-QT analysis. The [redacted] and CONC*[redacted] interaction terms were included in the sensitivity analysis. Female had significantly higher intercept, but the interaction term was not significant.

Reviewer's comment: *The Applicant's findings from the C-QTc analysis are consistent with the findings of the reviewer as they both indicate that sevabertinib QTc effects exclude ≥ 20 msec mean increase in QTc interval (See Section 4.5).*

3.2.4 Safety Analysis

The safety database for study 21607 includes 357 patients treated for a median of 5 months.

In study 21607, one subject in the 20 mg BID group experienced grade 3 arrhythmia on day 168. Confounding factors included intermittent pneumonia and diarrhea, anemia and hypokalemia as well as concomitant treatment for these conditions, in addition to pre-existing coronary artery disease (page 52 at link).

One subject in the 20 mg BID group experienced fatal cardio-respiratory arrest on day 45. Confounding factors included underlying advanced lung cancer, emphysema, coronary artery calcification, sinus tachycardia, and left anterior fascicular block, renal

failure, pneumonia exacerbation, and concomitant medications (e.g. moxifloxacin, benzylpenicillin, insulin; page 31 at link).

Four subjects experienced seizure, all grade 3. For three of these subjects, these events led to dose interruption or delay. For two subjects, these events occurred during a 30 mg BID treatment period, otherwise these subjects were treated with 20 mg BID. Additional information about these events was not available.

Outlier analysis of QTc, QRS, PRS, and heart rate did not show a dose-dependent pattern of clinically significant changes.

Reviewer's comment: *The adverse events of clinical importance per the ICH E14 guidelines did not have a clear causal relationship to sevabertinib.*

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

Both digital ECG waveforms and non-digital ECG waveforms (i.e., scanned or digitized ECGs) were submitted for review. Digitized ECG waveforms were semi-automatically read. Most ECGs (92%) were digital, and the non-digital ECGs were evenly distributed. No further sensitivity analysis was performed.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

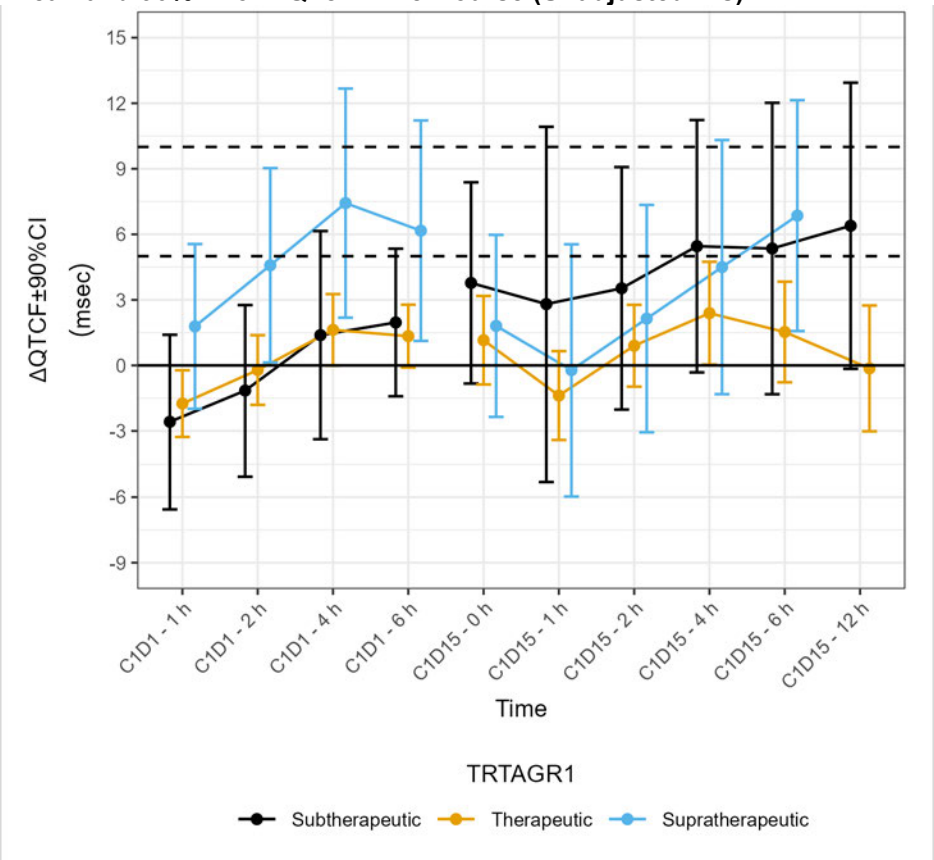
The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. The timepoints with subject number less than 10 were excluded from the by-time analysis. To improve clarity, the figures only present Day 1 and Day 15 from Cycle 1.

The statistical reviewer evaluated the ΔQTcF effect using descriptive statistics.

4.3.1 QTc

Figure 2 displays the time profile of ΔQTcF for different treatment groups on Day 1 and Day 15 of Cycle 1. No dose dependent increase in ΔQTcF was observed.

Figure 2. Mean and 90% CI of ΔQTcF Time-Course (Unadjusted CIs)



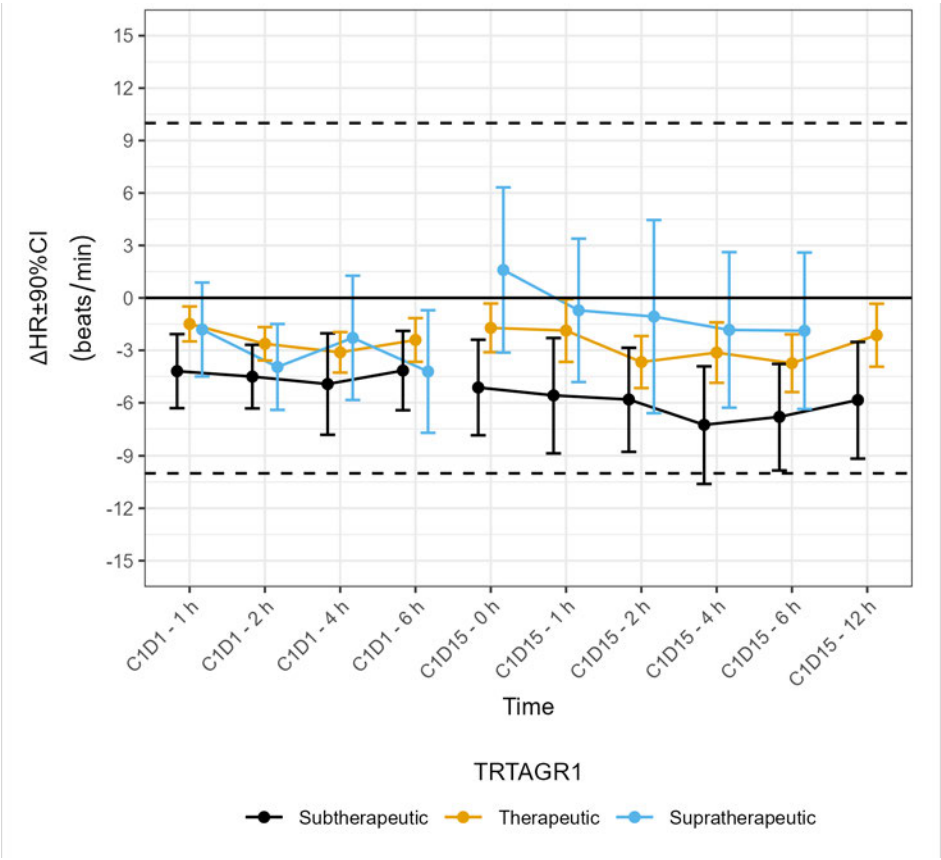
4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 3 displays the time profile of ΔHR for different treatment groups on Day 1 and Day 15 of Cycle 1. A mean decrease in ΔHR was observed, which was numerically largest for the lowest dose group pool. Similarly, the Applicant also reported a mean decrease in HR.

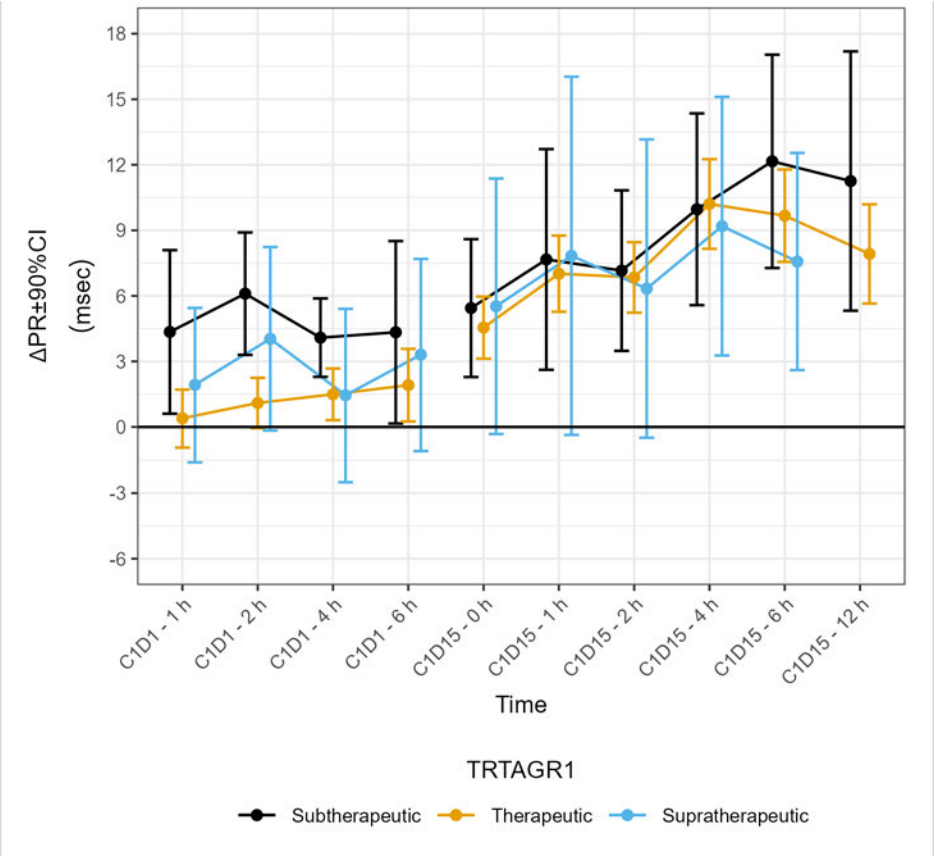
Figure 3. Mean and 90% CI of ΔHR Time-Course



4.3.3 PR

Figure 4 displays the time profile of ΔPR for different treatment groups on Day 1 and Day 15 of Cycle 1. A mean increase in ΔPR was observed on Day 15 of Cycle 1. This is consistent with the Applicant's findings. There is no apparent dose dependency in the increase in ΔPR.

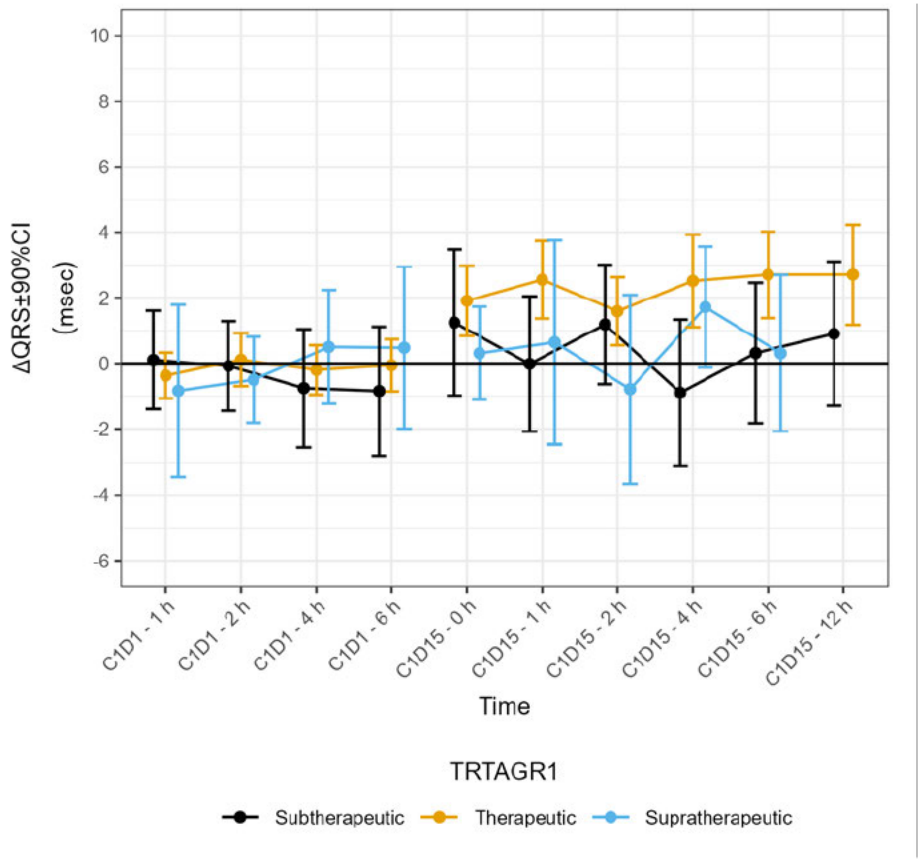
Figure 4. Mean and 90% CI of ΔPR Time-Course



4.3.4 QRS

Figure 5 displays the time profile of ΔQRS for different treatment groups on Day 1 and Day 15 of Cycle 1. No significant changes in mean ΔQRS were observed.

Figure 5. Mean and 90% CI of ΔQRS Time-Course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs.

4.4.1 QTc

There were no subjects having observed QTcF above 480 msec in any of the treatment groups.

Table 3 lists the categorical analysis results for ΔQTcF (<30 msec, >30 and <60, and >60 msec). There was one subject in the subtherapeutic treatment group, one subject in the therapeutic treatment group, and one subject in the supratherapeutic treatment group having observed maximum ΔQTcF above 60 msec.

Table 3. Categorical Analysis for ΔQTcF (Maximum)

TRTAGR1	Total (N)		Value <=30 msec		30 msec < Value <=60 msec		Value >60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Subtherapeutic	45	1127	37 (82.2%)	1099 (97.5%)	7 (15.6%)	25 (2.2%)	1 (2.2%)	3 (0.3%)

TRTAGR1	Total (N)		Value <=30 msec		30 msec < Value <=60 msec		Value >60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Therapeutic	169	4255	141 (83.4%)	4175 (98.1%)	27 (16.0%)	79 (1.9%)	1 (0.6%)	1 (0.0%)
Supratherapeutic	37	1133	30 (81.1%)	1102 (97.3%)	6 (16.2%)	30 (2.6%)	1 (2.7%)	1 (0.1%)

4.4.2 HR

Table 4 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). There were 9 subjects in the subtherapeutic treatment group, 37 subjects in the therapeutic treatment group, and 21 subjects in the supratherapeutic treatment group having observed HR above 100 beats/min. Among them, three subjects in the subtherapeutic treatment group, fourteen subjects in the therapeutic treatment group, and seven subjects in the supratherapeutic group were 25% increase over baseline.

Table 4. Categorical Analysis for HR (Maximum)

TRTAGR1	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Subtherapeutic	45	1127	36 (80.0%)	1079 (95.7%)	9 (20.0%)	48 (4.3%)
Therapeutic	170	4269	133 (78.2%)	4158 (97.4%)	37 (21.8%)	111 (2.6%)
Supratherapeutic	37	1133	16 (43.2%)	1089 (96.1%)	21 (56.8%)	44 (3.9%)

4.4.3 PR

Table 5 lists the categorical analysis results for PR (<200 msec, >200 and ≤220 msec, and >220 msec; with and without 25% increase over baseline). There was one subject in the subtherapeutic treatment group, two subjects in the therapeutic treatment group, and one subject in the supratherapeutic group having observed PR above 220 msec with 25% increase over baseline.

Table 5. Categorical Analysis for PR

TRTAGR1	Total (N)		Value <=220 msec		Value >220 msec & <25%		Value >220 msec & >=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Subtherapeutic	45	1126	43 (95.6%)	1084 (96.3%)	1 (2.2%)	41 (3.6%)	1 (2.2%)	1 (0.1%)
Therapeutic	168	4234	161 (95.8%)	4187 (98.9%)	5 (3.0%)	45 (1.1%)	2 (1.2%)	2 (0.0%)

TRTAGR1	Total (N)		Value <=220 msec		Value >220 msec & <25%		Value >220 msec & >=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Supratherapeutic	37	1133	33 (89.2%)	1107 (97.7%)	3 (8.1%)	25 (2.2%)	1 (2.7%)	1 (0.1%)

4.4.4 QRS

Table 6 lists the categorical analysis results for QRS (≤120 msec, and >120 msec; with and without 25% increase over baseline). There were four subjects who had observed QRS >120 msec with 25% increase over baseline in the therapeutic treatment group.

Table 6. Categorical Analysis for QRS

TRTAGR1	Total (N)		Value <=120 msec		Value >120 msec & <25%		Value >120 msec & >=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Subtherapeutic	45	1127	45 (100.0%)	1127 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Therapeutic	169	4256	156 (92.3%)	4098 (96.3%)	9 (5.3%)	140 (3.3%)	4 (2.4%)	18 (0.4%)
Supratherapeutic	37	1133	34 (91.9%)	1093 (96.5%)	3 (8.1%)	40 (3.5%)	0 (0%)	0 (0%)

4.5 EXPOSURE-RESPONSE ANALYSIS

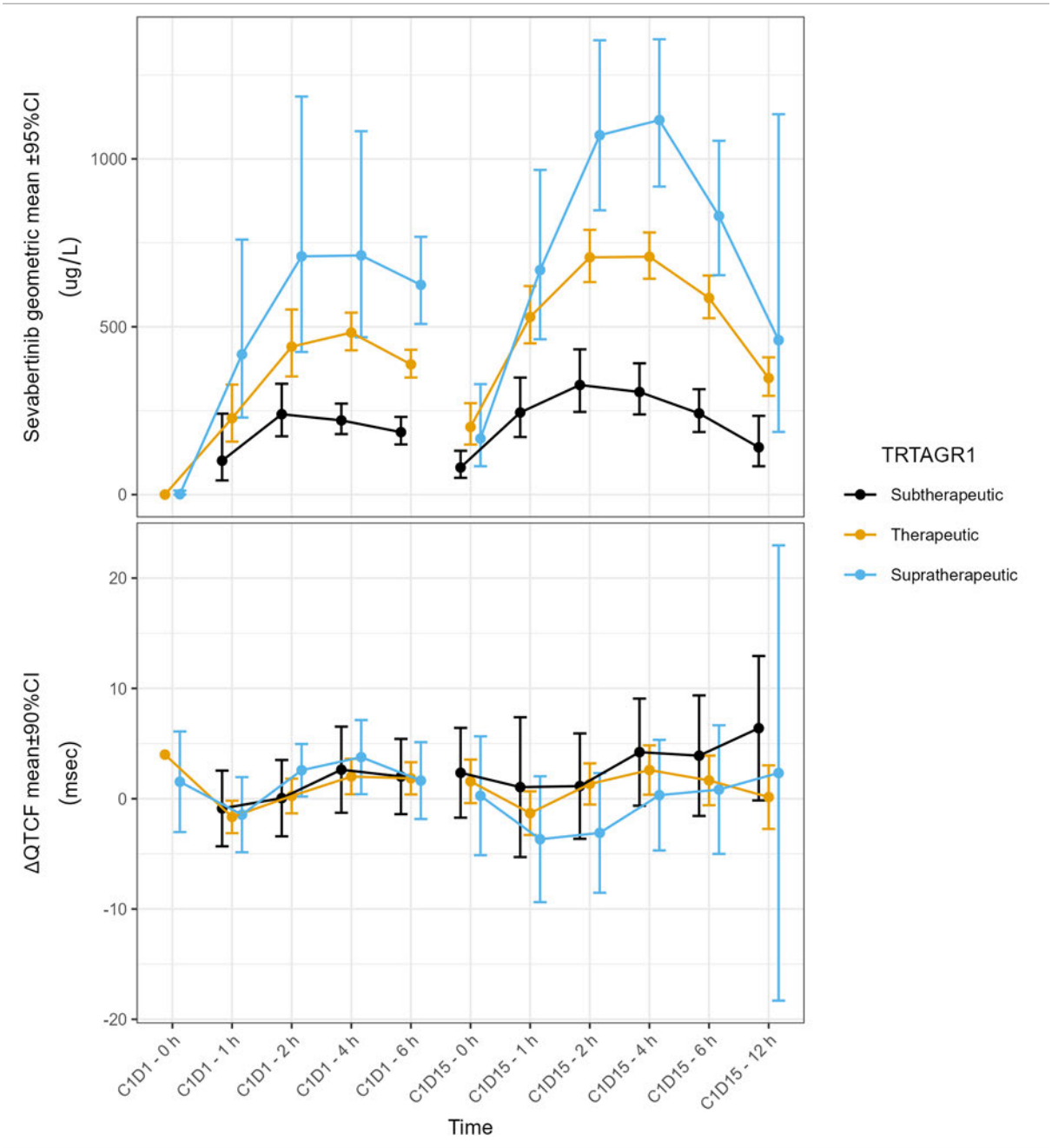
Exposure-response analysis was conducted for sevabertinib only as M1 concentrations data were not available for evaluation at this time. The analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK.

4.5.1 QTc

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

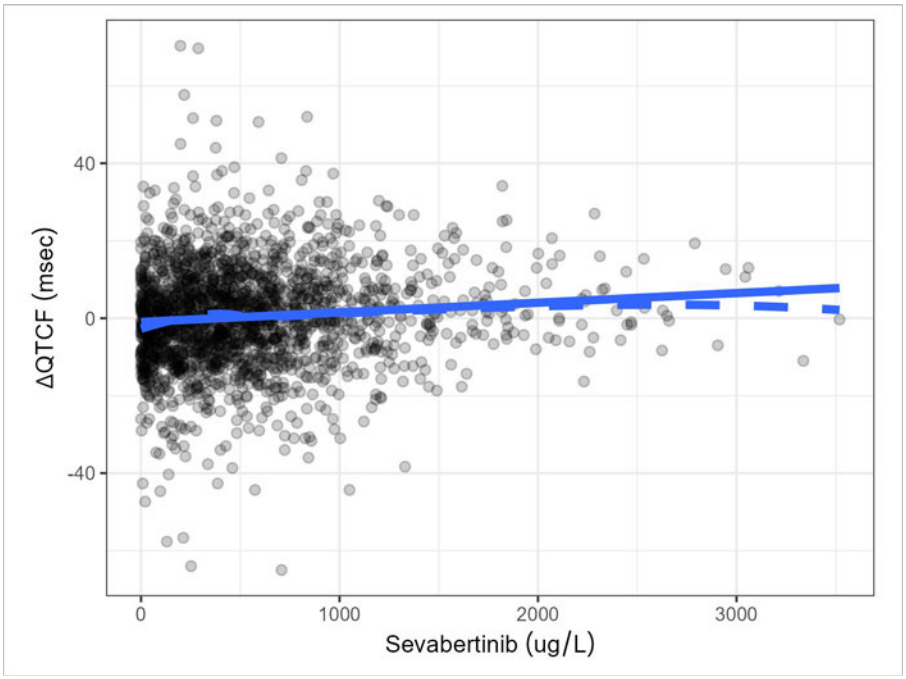
Figure 2 shows the time-course of ΔHR, with an absence of significant ΔHR changes. Figure 6 offers an evaluation of the relationship between time-course of sevabertinib concentration and ΔQTcF, with no appearance of significant hysteresis. As Tmax of M1 is between 4 – 7 hours, the lack of hysteresis indicate that M1 is less likely to cause QTc prolongation. Therefore, despite the lack of M1 concentration data, C-QTc analysis for sevabertinib alone is adequate to characterize QTc effects of sevabertinib treatment. Figure 7 shows the relationship between sevabertinib concentration and ΔQTcF and supports the use of a linear model.

Figure 6. Time-Course of Drug Concentration (Top) and QTcF (Bottom)[1]



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

Figure 7. 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 8. Predictions from the concentration-QTcF model are provided in Table 7.

Figure 8. Goodness-of-Fit Plot for QTcF

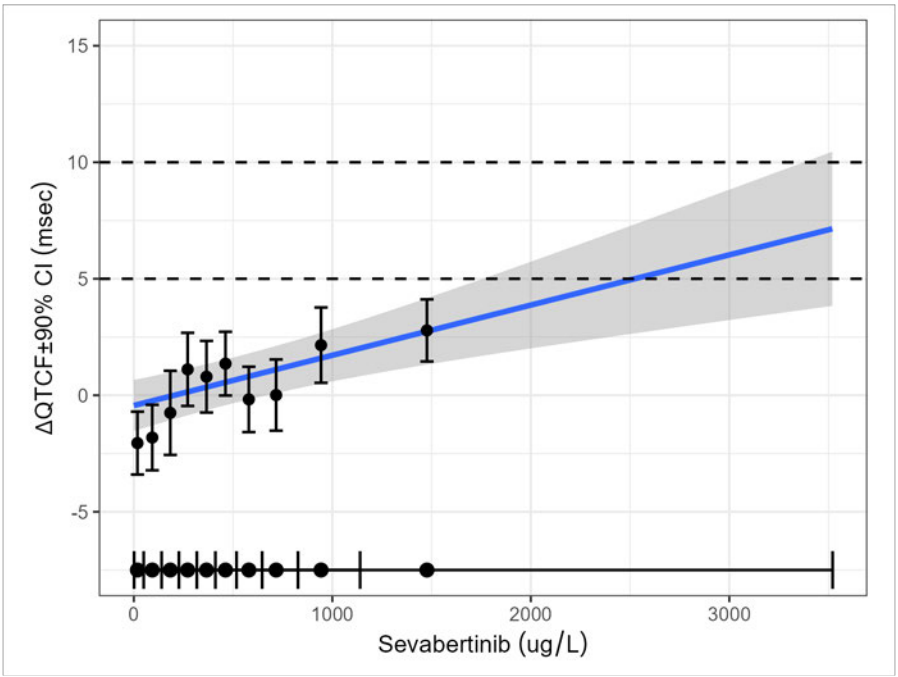


Table 7. Predictions From Concentration-QTcF Model

TRTAGR1	Sevabertinib (ug/L)	ΔQTCF (msec)	90.0% CI (msec)
Therapeutic	900.0	1.5	(0.4 to 2.6)
Highest dose in QT	2,020.0	3.9	(2.0 to 5.8)

The reviewers also conducted a sensitivity analysis with the concentration-QT model including , and the results were consistent with those obtained from the default white paper model. Therefore, only results from the white paper model are presented.

4.5.1.1 Assay Sensitivity

Not applicable as the study did not include a 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

Please see previous review dated 02/12/2024.

5.2 EVALUATION OF THE APPLICANT'S CLINICAL QT ANALYSIS PLAN

Please see previous review dated 02/12/2024.

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/

DEVI KOZELI on behalf of ELIFORD N KITABI
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Eliford is OOO

JING SUN
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QIANYU DANG
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MICHAEL Y LI
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ANNE E BUNNER
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LARS JOHANNESEN
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CHRISTINE E GARNETT
07/30/2025 01:45:01 PM

LABEL AND LABELING REVIEW

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

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

Date of This Review:	July 21, 2025
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 219972
Product Name, Dosage Form, and Strength:	Hyrnuo (sevabertinib) tablets, 10 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Bayer HealthCare Pharmaceuticals Inc.
FDA Received Date:	March 28, 2025
TTT ID #:	2025-13912
DMEPA 2 Safety Evaluator:	Adeola Oluwatimilehin, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 INTRODUCTION

As part of the approval process for Hyrnuo (sevabertinib) tablets, the Division of Oncology 2 (DO2) requested that we review the proposed Hyrnuo Prescribing Information (PI), Patient Package Insert (PPI), container label, 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 Hyrnuo Prescribing Information (PI), Patient Package Insert (PPI), container label, 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 Bayer HealthCare Pharmaceuticals Inc. in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. General Issues

   a. As currently presented, the proprietary name is denoted by the placeholder "TRADENAME". We reference our July 10, 2025 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, HYRNUO, was found conditionally acceptable. We recommend replacing the placeholder "TRADENAME" with the conditionally acceptable proprietary name, HYRNUO.

2. Highlights of Prescribing Information

   a. For brevity, revise the dosage statement in the Dosage and Administration section of the Highlights of PI from (b) (4) (b) (4) to "20 mg orally twice daily."

3. Section 2 Dosage and Administration

   a. For brevity, we recommend revising section 2.2 Recommended Dosage as follows:

(b) (4)

b. As currently presented, the missed dose information does not indicate when to skip the missed dose. Failure to provide clarity on when to skip the missed dose may result in dosing errors. We recommend revising the missed dose statement to include the number of hours between the first dose and the missed dose. For example, "If a dose of TRADENAME is missed, take the missed dose as soon as possible. If a dose is missed by more than X hours, skip the missed dose and take the next dose at the scheduled time. Do not take 2 doses at the same time to make up for the missed dose."

c. For brevity, we recommend revising Table 1 in section 2.3 Dosage Modifications for Adverse Reactions as follows:

(b) (4)

d. For brevity, we recommend revising section 2.4 as follows:

(b) (4)

We also recommend defining the "3 to 5 elimination half-lives" with the actual number of days for clarity.

B. Patient Package Insert (PPI)

1. As currently presented, the missed dose information does not indicate when to skip the missed dose. Failure to provide clarity on when to skip the missed dose may result in dosing errors. We recommend revising the missed dose statement to include the number of hours between the first dose and the missed. For example, "If you miss a dose of TRADENAME, take your prescribed dose as soon as you remember. However, if it is close to the time of your next dose (within x hours), take your next dose at your regular time. Do not take 2 doses at the same time to make up for a missed dose.".

5 RECOMMENDATIONS FOR BAYER HEALTHCARE PHARMACEUTICALS INC.

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

1. As currently presented, the proprietary name is denoted by the placeholder "TRADENAME". We reference our July 10, 2025 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Hyrnuo, was found conditionally acceptable. We recommend replacing the placeholder "TRADENAME" with the conditionally acceptable proprietary name, Hyrnuo, and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your label and labeling.
2. We recommend revising the Dosage statement to be consistent with the terminology in the Prescribing Information. For example, "Recommended Dosage: See Prescribing Information."

3. As currently presented, the negative statement “Do not cut, crush or chew tablet.” is bolded. Post-marketing reports have shown that negative statements (e.g., Do not) may have the opposite of the intended meaning because the word “not” is overlooked, and get misinterpreted as an affirmative action. Thus, we recommend adding the desired action “Swallow tablets whole.” in the beginning and unbold the negative statement so that the sentence reads “Swallow tablets whole. Do not cut, crush, or chew tablets.”

B. Container Label

1. As currently presented, it is unclear whether the container label will wrap around the HDPE bottle in a manner that may affect scannability of the barcode. Ensure the linear barcode is oriented on the container label such that it is not distorted or obstructed by the container curvature to improve scannability of the barcode.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Hyrnuo received on March 28, 2025 from Bayer HealthCare Pharmaceuticals Inc..

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Hyrnuo</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>sevabertinib</td></tr>
<tr><td>Indication</td><td>Treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.</td></tr>
<tr><td>Dosage Form</td><td>tablets</td></tr>
<tr><td>Strength</td><td>10 mg</td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Dose and Frequency</td><td>20 mg twice daily

Dose Reductions for Adverse Reactions
<table><tr><td>Dose Reduction</td><td>Dosage</td></tr><tr><td>First dose reduction</td><td>10 mg twice daily</td></tr><tr><td>Second dose reduction</td><td>10 mg once daily</td></tr></table></td></tr>
<tr><td>How Supplied</td><td>HDPE bottle of 120 tablets closed with a child-resistant screw cap</td></tr>
<tr><td>Storage</td><td>Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 2°C to 30°C (36°F to 86°F) [see USP Controlled Room Temperature].</td></tr>
<tr><td>Container Closure</td><td>Plastic bottle 45 mL HDPE (b) (4) closed with screw cap (b) (4) child-resistant with sealing insert</td></tr>
</table>

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 Hyrnuo labels and labeling submitted by Bayer HealthCare Pharmaceuticals Inc..

- Prescribing Information and Patient Package Insert received on March 28, 2025, available from \\CDSESUB1\EVSPROD\nda219972\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-uspi-and-ppi.docx
- Container label received on March 28, 2025
- Carton labeling received on March 28, 2025

B.2 Container Label and Carton Labeling Images

Container Label:

(b) (4)

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

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

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

/s/

ADEOLA O OLUWATIMILEHIN
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