# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 219249Orig1s000

# OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

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

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

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| Date of This Review: | October 9, 2024 |
| Requesting Office or Division: | Division of Oncology 1 (DO1) |
| Application Type and Number: | NDA 219249 |
| Product Name, Dosage Form, and Strength: | Itovebi (inavolisib) tablets, 3 mg and 9 mg |
| Applicant Name: | Genentech, Inc. |
| FDA Received Date: | September 24, 2024 and October 7, 2024 |
| TTT ID #: | 2024-9034-1 |
| DMEPA 2 Safety Evaluator: | Ngoc-Linh Do, PharmD |
| DMEPA 2 Team Leader: | Tingting Gao, PharmD |

## 1 PURPOSE OF MEMORANDUM

Genentech, Inc. submitted revised container label and carton labeling received on September 24, 2024 and October 7, 2024 for Itovebi. The Division of Oncology 1 (DO1) requested that we review the revised container label and carton labeling for Itovebi (Appendix A and Appendix B) 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

Genentech accepted all of our recommendations from the previous label and labeling review.[b] Genentech explained that they intend to use "MM YYYY (e.g., 09 2026)" as the expiration date format, and that "this expiration date format is specific to the packaging site and cannot be changed due to equipment setup. This expiration date format is applied across all U.S. product configurations produced at this specific site". We find the proposed expiration date format acceptable from a medication error perspective.

However, we noted that a placeholder, "Tradename" was included on the revised container labels and carton labeling. Thus, we provided a recommendation to Genentech to update the container labels and carton labeling with the conditionally acceptable proprietary name, Itovebi,[c] and DO1 communicated this recommendation to Genentech on September 27, 2024.[d]

In addition, DO1 Review Team added the statement, "Swallow tablets whole. DO NOT chew, crush, or split tablets" to Section 2.3 of the Itovebi Prescribing Information. Hence on October 7, 2024, Genentech submitted another updated container labels and carton labeling to include the statement, "Swallow tablets whole. DO NOT chew, crush, or split tablets" on the principal display panel of the container labels and carton labeling[e], to align with Section 2.3 of the Prescribing Information.

## 3 CONCLUSION

The October 7, 2024 Itovebi container labels and carton labeling are acceptable from a medication error perspective. We have no additional recommendations at this time.

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[a] Do, N. Label and Labeling Review for Itovebi (NDA 219249). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 JUL 12. TTT ID: 2024-9034.

[b] FDA Revised Draft Labeling received 17 September 2024. Inavolisib (RO7113755, GDC-0077). NDA 219249. South San Francisco (CA): Genentech, Inc. 2024 SEPT 24. Available from: \\CDSESUB1\EVSPROD\nda219249\0042\m1\us\clinical-information-amendment.pdf.

[c] Proprietary Name Granted Letter – Itovebi (NDA 219249). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 AUG 23. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80763d5b&showAsPdf=true.

[d] Hamidi, Z. FDA Labeling Revisions for NDA 219249-Round 3. Silver Spring (MD): FDA, CDER, OND, DO1 (US); 2024 Sept 27. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8077087a.

[e] FDA Revised Draft Labeling received 2 October 2024. Inavolisib (RO7113755, GDC-0077). NDA 219249. South San Francisco (CA): Genentech, Inc. 2024 OCT 7. Available from: \\CDSESUB1\EVSPROD\nda219249\0048\m1\us\clinical-information-amendment.pdf.



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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:** October 1, 2024

**To:** Zohal Hamidi, Regulatory Project Manager, Division of Oncology I (DO1)

**From:** Courtney Leach, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** Rachael Conklin, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for ITOVEBI (inavolisib) tablets, for oral use

**NDA**: 219249

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**Background:**
In response to DO1's consult request dated April 3, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for ITOVEBI (inavolisib) tablets, for oral use.

**PI:**
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on September 26, 2024, and our comments are provided below.

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

**Carton and Container Labeling**:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on October 1, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Courtney Leach at (301) 796-1044 or Courtney.Leach@fda.hhs.gov.

**PI**:

| Section | Statement from Draft (if applicable) | OPDP Comments |
|---|---|---|
| **2 DOSAGE AND ADMINISTRATION** | | We note there is not information regarding how to take ITOVEBI in the PI and PPI. For example: Swallow tablets whole. Do no chew, crush, or split the tablets. We defer to DO1 for the inclusion of this information in the PI and PPI. |
| **14.1 Locally Advanced or Metastatic Breast Cancer** | "The study excluded patients with Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring ongoing (b) (4) at the start of study treatment." (emphasis added) | For clarification, what is (b) (4)? Does this refer to any antihyperglycemic medication?<br><br>OPDP recommends specifying the meaning of (b) (4) If "(b) (4)" refers to any antihyperglycemic medication, consider revising to, "The study excluded patients with Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring ongoing hyperglycemic treatment at the start of study treatment." |

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

# PATIENT LABELING REVIEW

| | |
|---|---|
| Date: | October 1, 2024 |
| To: | Zohal Hamidi, PharmD, MS<br>Regulatory Project Manager<br>**Division of Oncology I (DO1)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)**<br><br>Barbara Fuller, MSN, BSN, RN<br>Team Leader, Patient Labeling<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Helen Young, MSN, MPH, CRRN, PHN, RN<br>Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)**<br><br>Courtney Leach, PharmD, BCCCP, BCPS<br>Regulatory Review Officer<br>**Office of Prescription Drug Promotion (OPDP)** |
| Subject: | Review of Patient Labeling: Patient Package Insert (PPI) |
| Drug Name (established name): | ITOVEBI (inavolisib) |
| Dosage Form and Route: | tablets, for oral use |
| Application Type/Number: | NDA 219249 |
| Applicant: | Genentech, Inc. |

# 1 INTRODUCTION

On March 27, 2024, Genentech, Inc. submitted for the Agency's review an original New Drug Application (NDA) 219249 for ITOVEBI (inavolisib) tablets. The proposed indication for this NDA is as follows:

(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 I (DO1) on April 3, 2024 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ITOVEBI (inavolisib) tablets.

# 2 MATERIAL REVIEWED

- Draft ITOVEBI (inavolisib) tablets PPI received on March 27, 2024, and received by DMPP and OPDP on September 17, 2024 and September 26, 2024.
- Draft ITOVEBI (inavolisib) tablets Prescribing Information (PI) received on March 27, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 17, 2024 and September 26, 2024.
- Approved PIQRAY (alpelisib) tablets comparator labeling dated January 18, 2024.
- Approved TRUQAP (capivasertib) tablets comparator labeling dated September 23, 2024.

# 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6$^{th}$ to 8$^{th}$ grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8$^{th}$ 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 size 10 font.

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.

(b) (4)

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**Clinical Inspection Summary**

| | |
|---|---|
| **Date** | 29 August 2024 |
| **From** | Elena Boley, MD, MBA<br>Good Clinical Practice Assessment Branch<br>Division of Clinical Compliance Evaluation<br>Office of Scientific Investigations |
| **To** | Zohal Hamidi, PharmD, MS, BCSCP, RPM<br>Suparna Wedam, MD, Clinical Reviewer<br>Preeti Narayan, MD, Team Leader |
| **NDA #** | NDA 219249 |
| **Applicant** | Genentech, Inc. |
| **Drug** | Inavolisib |
| **NME** | Yes |
| **Proposed Indication** | (b) (4) |
| **Consultation Request Date** | 30 Apr 2024 |
| **Summary Goal Date** | 3 Sep 2024 |
| **Action Goal Date** | 10 Sep 2024 |
| **PDUFA Date** | 27 Nov 2024 |

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Im, Musolino, and Dalenc were inspected in support of NDA 219249. The inspections covered Protocol WO41554. Based on these inspections, the Study WO41554 overall appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

## II. BACKGROUND

NDA 219249 was submitted on March 27, 2024, to support the efficacy and safety of inavolisib tablets when administered orally (b) (4)

(b) (4) The single Phase 3 clinical study supporting the application was the following:

- Protocol WO41554: "A Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of inavolisib plus palbociclib and fulvestrant versus placebo plus palbociclib and fulvestrant in patients with PIK3CA-mutant, hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer"

**Protocol WO41554**

This was a Phase 3, randomized, double blind, placebo-controlled, multicenter, and global trial in adults with patients with PIK3CA-mutated, HR-positive, HER2- negative locally advanced or metastatic breast cancer whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy and who had not received prior systemic therapy for locally advanced or metastatic disease. The primary objective was to evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of progression-free survival (PFS), defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1.

Eligible subjects were male or female and at least 18 years of age. Female subjects were required to be postmenopausal or premenopausal or perimenopausal. All subjects were to have begun treatment with luteinizing hormone-releasing hormone (LHRH) agonist therapy at least 2 weeks prior to the first day of the study treatment (Day 1 of Cycle 1) and continue it for the duration of study treatment. All subjects were required to have the following documentation for their adenocarcinoma of breast: 1) histological or cytological confirmation; 2) ER– positivity and/or progesterone receptor-positivity and HER2-negativity; 3) evidence of locally advanced or metastatic disease that was not amenable to surgical or radiation therapy with curative intent; 4) PIK3CA-mutated tumor status confirmed by valid results from either central testing of blood or local testing of blood or tumor tissue showing eligible PIK3CA mutations; and 5) progression during adjuvant endocrine treatment or within 12 months of completing adjuvant endocrine therapy with an aromatase inhibitor or tamoxifen. For those who had a CDK4/6 inhibitor included as part of neoadjuvant or adjuvant therapy, the progression event had to be > 12 months since completion of CDK4/6 inhibitor portion of neoadjuvant or adjuvant therapy. Finally, disease was required to be measurable by per RECIST v1.1. See protocol for full inclusion criteria.

Patients were excluded if they had prior systemic therapy for metastatic breast cancer, a history of leptomeningeal disease or carcinomatous meningitis, prior treatment with fulvestrant or any selective estrogen-receptor degrader (with the exception of patients that had received fulvestrant or any selective estrogen receptor degrader as part of neoadjuvant therapy only and with treatment duration of no longer than 6 months), or prior treatment with any PI3K, AKT, or mTOR inhibitor, or any agent whose mechanism of action was to inhibit the PI3K-AKT-mTOR pathway. See protocol for full exclusion criteria.

The study was comprised of four periods: a screening period (up to 28 days), a blinded treatment period, a post-treatment follow-up period (which included a "30-day safety follow-up" for all patients and, when applicable, a "post-treatment hyperglycemia follow-up," and/or a "post-treatment tumor assessment follow-up with [patient reported outcome]…collection"), and a survival follow-up period.

*Screening period and blinded treatment period*

After informed consent was obtained and screening was completed, eligible subjects were randomized in a 1:1 ratio (with stratification by visceral disease [yes or no], endocrine resistance [primary or secondary according to European Society for Medical Oncology Advanced Breast Cancer 4 (ESMO ABC4) 2018 guidelines], and geographic region [North America/Western Europe, Asia, other]) to one of the two following treatment groups:

- Inavo+Palbo+Fulv
    - Inavolisib: 9 mg tablet taken PO QD on Days 1-28 of each 28-day cycle, beginning on Day 1 of Cycle 1
    - Palbociclib: 125 mg capsule taken PO QD on Days 1-21 of each 28-day cycle, beginning on Day 1 of Cycle 1
    - Fulvestrant: 500 mg administered by IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle, or approximately every 4 weeks

- Pbo+Palbo+Fulv
    - Placebo: tablet taken PO QD on Days 1-28 of each 28-day cycle, beginning on Day 1 of Cycle 1
    - Palbociclib: 125 mg capsule taken PO QD on Days 1-21 of each 28-day cycle, beginning on Day 1 of Cycle 1
    - Fulvestrant: 500 mg administered by IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle, or approximately every 4 weeks

After the date of randomization and throughout the blinded treatment period and the rest of the study, tumor assessments were performed according to RECIST v1.1. to assess for response every 8 weeks (±7 days) during the first 2 years of study treatment and every 12 weeks (±7 days) thereafter (regardless of dose delay, treatment interruption or early treatment discontinuation, and until disease progression). The method of bone imaging (computed tomography [CT] scan, magnetic resonance imaging [MRI], or photographic measurements) used for a patient at screening was required to be the same throughout the study.

Patients received study treatment until unequivocal disease progression (as determined by the Investigator), unacceptable toxicity, patient withdrawal of consent, loss to follow-up, death, or study termination. Patients who discontinued study treatment for reasons other than disease progression or death were to continue to have tumor assessments performed every 8 weeks (±7 days) for the first 2 years from randomization and every 12 weeks (±7 days) thereafter, and complete PRO assessments at those timepoints ("post-treatment tumor

assessment follow-up with PRO collection"), until disease progression was documented, or another anti-cancer therapy was initiated, whichever occurred first.

*Post-treatment follow-up period*

Following the blinded treatment period, patients were to be followed for safety for 30 days (including a 30-day follow-up visit), or until the initiation of another anti-cancer therapy, whichever occurred first.

As part of the post-treatment follow-up period, patients on anti-hyperglycemic agents for the treatment of hyperglycemia during the study treatment period and those patients with ongoing events of hyperglycemia at the end of the 30-day safety follow-up were to undergo additional monthly safety follow-up assessments ("post-treatment hyperglycemia follow-up") until their fasting glucose returned to baseline levels, down-titration of their anti-hyperglycemic medications was complete, or up to approximately 3 months after the final dose of study treatment (even if the patient initiated another anticancer therapy subsequent to study treatment discontinuation).

*Survival follow-up period*

After study treatment discontinuation or post-treatment follow-up, all patients were to be followed for survival. These data were to be collected via telephone calls and/or clinic visits approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor, whichever occurred first.

Safety monitoring was to be performed throughout the study. Safety assessments were to include interval history since the previous assessment, physical examinations, and laboratory studies. All serious adverse events and adverse events of special interest (AESI) were to be reported in "real time" (within 24 hours of the event) via the electronic data capture (EDC) system.

The primary efficacy analyses were based on the tumor assessments performed by the local radiologists or Investigators. To support the primary endpoint of investigator-assessed PFS, a blinded independent central review (BICR) of tumor assessment data was to be performed. All radiological data (e.g., CT scan, MRI, or bone scan) and photographs for skin lesions obtained at baseline, during the treatment period, at the time of disease progression, and at the time of study treatment discontinuation (if not the same as disease progression) were to be sent to a central imaging vendor (contracted by the sponsor) within 2 weeks of imaging to enable retrospective BICR.

Important efficacy endpoint:

- ***Primary efficacy endpoint:*** Progression-free survival (PFS), defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first), according to RECIST v1.1 criteria.

**Details relevant to Study WO41554**

Study WO41554 was conducted at 123 centers that screened subjects in 28 countries including China, Russia, Spain, Republic of Korea, Thailand, United States, Canada, Italy, Poland, Turkey, France, Taiwan, Ukraine, Australia, Greece, Hungary, Singapore, Hong Kong, Germany, Malaysia, United Kingdom, Argentina, Portugal, Georgia Republic, Belgium, Denmark, Brazil, and New Zealand. The first subject was enrolled on January 29, 2020, and the last subject was enrolled on September 14, 2023. The study was ongoing. Of the 325 subjects that were randomized, 161 subjects were randomized to the Inavo+Palbo+Fulv arm, and 160 subjects (99.4%) received any study drug (inavolisib, palbociclib, or fulvestrant). Of the 164 subjects randomized to the Pbo+Palbo+Fulv arm, all patients (100%) received any study drug. The original protocol was dated August 12, 2019, there were seven protocol amendments, and the last amendment was dated March 8, 2023.

## II. RESULTS (by site):

1. **Seock Ah Im, M.D., Ph.D.**
   **Site # 323897**
   **Protocols:** WO41554
   Seoul National University Hospital
   101 Daehak-Ro, Jongno-Gu
   Seoul 3080
   South Korea
   *PDUFA Inspection Dates:* July 8-12, 2024

At this site for Protocol WO41554, 35 subjects were screened, 16 subjects were consented, 8 were enrolled and randomized. At the time of the inspection, the disposition of the subjects was the following:

- Subject # (b) (6) (inavolisib): Enrolled and receiving treatment
- Subject # (b) (6) (inavolisib): Enrolled and receiving treatment
- Subject # (b) (6) (inavolisib): Enrolled and receiving treatment
- Subject # (b) (6) (placebo): Discontinued treatment due to disease progression and remained enrolled
- Subject # (b) (6) (placebo): Discontinued treatment due to disease progression and remained enrolled
- Subject # (b) (6) (inavolisib): Discontinued treatment due to disease progression and subsequently expired during follow-up period
- Subject # (b) (6) (inavolisib): Discontinued treatment due to completion of the study
- Subject # (b) (6) (inavolisib): Discontinued treatment due to completion of the study

The inspection evaluated the study records for the 8 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; independent ethics committee approvals; subject eligibility criteria; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations;

drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation. Informed consent process was also reviewed, and the documentation was reviewed for all 16 of the consented subjects.

There was no evidence of under-reporting of adverse events. Data related to the primary efficacy endpoint, progression-free survival (PFS, defined as the time from randomization to the first occurrence of disease progression or death from any cause [whichever occurs first], according to RECIST v1.1 criteria) were verified against the data line listings provided by the sponsor for all 8 of the randomized subjects. No discrepancies were noted.

2. **Antonino Musolino, M.D.**
   **Site # 323146**
   **Protocol:** WO41554
   Universitaria Di Parma
   Via Gramsci 14
   43126 Parma, Emilia-Romagna
   Italy
   *PDUFA Inspection Dates:* July 8-12, 2024

At this site for Protocol WO41554, 22 subjects were screened, 7 subjects were consented, and 6 subjects were enrolled and randomized. At the time of the inspection, the disposition of the subjects was the following:

- Subject # (b) (6) (inavolisib): Enrolled and receiving treatment
- Subject # (b) (6) (placebo): Discontinued treatment due to progressive disease and withdrew from study
- Subject # (b) (6) (inavolisib): Lost to follow-up approximately 2 months after enrollment
- Subject # (b) (6) (inavolisib): Discontinued treatment due to stomatitis and lost to follow-up
- Subject # (b) (6) (placebo): Discontinued treatment due to progressive disease and subsequently expired
- Subject # (b) (6) (placebo): Discontinued treatment due to progressive disease and subsequently expired

The inspection evaluated the study records for the 6 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; independent ethics committee approvals; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation.

There was no evidence of under-reporting of adverse events. Data related to the primary efficacy endpoint, progression-free survival (PFS, defined as the time from randomization to the first occurrence of disease progression or death from any cause [whichever occurs first],

according to RECIST v1.1 criteria) were verified against the data line listings provided by the sponsor for all 6 of the randomized subjects. No discrepancies were noted.

3. **Florence Dalenc, M.D., Ph.D.**
   **Site # 323629**
   **Protocol:** WO41554
   Institut Universitaire Du Cancer De Toulouse-Oncopole
   1, Avenue Irene Joliot Curie
   31059 Toulouse
   France
   *PDUFA Inspection Dates:* July 29, 2024, through August 2, 2024

*At the time of the summary, the inspection report for Dr. Dalenc was not available. Therefore, the information below was conveyed in an email summary sent by the field investigator after the inspection. An addendum to this summary will be provided should the final inspection report reveal any significant new information.*

At this site for protocol WO41554, 32 subjects were screened, 9 subjects were consented, and 5 subjects were enrolled and randomized. At the time of the inspection, the disposition of the subjects was the following:

- Subject # (b) (6) (inavolisib): Enrolled and receiving treatment
- Subject # (b) (6) (inavolisib): Enrolled and receiving treatment
- Subject # (b) (6) (placebo): Discontinued treatment due to progressive disease and remained enrolled
- Subject # (b) (6) (inavolisib): Discontinued treatment due to progressive disease and remained enrolled
- Subject # (b) (6) (inavolisib): Discontinued treatment due to progressive disease and subsequently expired

The inspection evaluated the study records for the 5 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; independent ethics committee approvals; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs; financial disclosures; investigator agreements; and other regulatory documentation.

There was no evidence of under-reporting of adverse events. Data related to the primary efficacy endpoint, progression-free survival (PFS, defined as the time from randomization to the first occurrence of disease progression or death from any cause [whichever occurs first], according to RECIST v1.1 criteria) were verified against the data line listings provided by the sponsor for all 5 of the randomized subjects. No discrepancies were noted.

It was observed during the inspection that in two instances, the wrong kit was dispensed to a subject. In the first instance, subject # (b) (6) was dispensed by the research pharmacy a kit (placebo) that was not the kit to which the subject had been randomized by the IWRS.

Although the sponsor initially decided to discontinue the subject from treatment and requested that the subject return the box of the kit dispensed in error, the sponsor instead decided to have the subject return to the site and be issued a new kit allocated with a new IWRS. The new IWRS allocation was (coincidentally) the exact kit that had been issued in error. As a result, the sponsor reversed its decision to discontinue the subject and instead kept her in the study.

In the second instance, subject # (b) (6) was administered study medication (fulvestrant) that was instead assigned to a research subject enrolled in a different study. However, the study medication that the subject # (b) (6) did receive was identical (in dose and route) to the medication that they were intended to receive.

*Reviewer's comment: Although these are important deviations, review of the clinical investigator's response to the observations (details of which are included in the descriptions above) showed that in neither instance was subject safety or data reliability compromised.*

{See appended electronic signature page}

Elena Boley, M.D., M.B.A.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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CONCURRENCE:

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Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch

Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm. NDA 219249
DP/Senior Project Manager/Zohal Hamidi
DP/Clinical Reviewer/ Suparna Wedam
DP/Clinical Team Leader/ Preeti Narayan
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Elena Boley
OSI/GCPAB/Program Analyst/Yolanda Patague

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# Interdisciplinary Review Team for Cardiac Safety Studies

# QT Study Review

| | |
|---|---|
| Submission | NDA 219249 |
| Submission Number | 1 |
| Submission Date | 3/27/2024 |
| Date Consult Received | 5/3/2024 |
| Drug Name | Inavolisib |
| Indication | Locally advanced or metastatic phosphatidylinositol 3-kinase (PIK3CA) mutant, hormone receptor (HR)-positive, HER2 negative breast cancer |
| Therapeutic Dose | 9 mg QD in combination with palbociclib (b) (4) |
| Clinical Division | DO1 |
| Protocol Review | See links to previous IRT reviews |

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 5/3/2024 regarding the Applicant's QT evaluation. We reviewed the following materials:

- Previous IRT reviews for IND 130909 dated 06/20/2019 and 07/10/2023 in DARRTS;
- CQT study report (NDA 219249 / SN0001; link);
- Clinical study report of study GO39374 (NDA 219249 / SN0001; link);
- Study protocol of GO39374 (NDA 219249 / SN0001; link);
- Proposed label (NDA 219249 / SN0001; link); and
- QT evaluation checklist including highlights of clinical pharmacology and cardiac safety (NDA 219249 / SN0009; link).

## 1 SUMMARY

Inavolisib is unlikely to cause ≥ 20 msec mean increase in QTc interval based on this alternative QT assessment pathway – see Table 1 for overall results.

The clinical study GO39374 was a first-in-human, Phase I, open-label, dose-escalation study. The highest dose provided 0.8-fold clinical exposure. Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that inavolisib is associated with large mean increases in the QTcF interval (refer to section 4.5). However, the QT assessment has the following limitations:

1. The (b) (4) therapy (inavolisib is 9 mg QD in combination with palbociclib and endocrine therapy) was studied in Arm B (inavolisib + palbociclib

+ letrozole), Arm E (inavolisib + palbociclib + fulvestrant), and Arm F (inavolisib + palbociclib + fulvestrant + metformin for obsessed patients). The combination therapy in Arm E was used in the pivotal phase 3 study WO41554. However, Arm E and Arm F had limited ECG time collections (only predose and 24 hours postdose on multiple days), thus the data were not included in the reviewer's concentration-QTc analysis.

2. According to the Applicant's predictions, subjects with moderate or severe renal impairment are expected to have 2-3-fold the inavolisib exposure compared to healthy subjects. The currently proposed label has no dose adjustment, contraindication, or avoiding use in patients with moderate to severe renal impairment. The predicted exposure in patients with moderate or severe renal impairment is outside the studied range in study GO39374.

In the double-blind, placebo-controlled, pivotal phase 3 study WO41554, there were no imbalances in TdP/QT prolongation (broad SMQ) between the inavolisib (4.9%) and the placebo group (3.1%). More subjects experienced electrocardiogram QT prolonged in inavolisib (3.7%) than placebo (0.6%). None of the events were SAEs. One event was Grade 3 (QTcF 487 msec, change from baseline > 30 msec) but the subject had electrolyte imbalance during the time of QTc prolongation. The incidence of TdP/QT prolongation was similar in GO39374 (4.7%) and WO41554 (4.9%) (section 4.6).

**Table 1: Summary of findings**

<table>
<tr><td>QT assessment pathway</td><td>☐ Thorough QT study<br>☐ Substitute for thorough QT study (5.1)<br>☒ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• The anticipated high clinical exposure scenario is in subjects with moderate -to- severe renal impairment where exposure is predicted to increase up to 3-fold. Although renal impairment study is ongoing, the Applicant does not recommend contraindication nor dose adjustment in these subjects (section 3.1).<br>• The highest geometric mean Cmax in the clinical QTc assessment covers geometric mean therapeutic Cmax by 0.8-fold. This is considered sufficient coverage since the therapeutic Cmax is within range of individual Cmax in QTc assessment.
<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>Geometric mean Cmax at the steady state following inavolisib at 9 mg QD administered alone</td><td>75.1</td><td>4.2</td><td>(2.1 to 6.3)</td></tr>
</table>
</td></tr>
</table>

| | |
|---|---|
| **In vitro/ in vivo findings** | Integrated non-clinical QT assessment was not conducted |

### 1.1 RESPONSES TO QUESTIONS POSED BY APPLICANT

Not applicable.

### 1.2 COMMENTS TO THE REVIEW DIVISION

None.

## 2 RECOMMENDATIONS

### 2.1 ADDITIONAL STUDIES

Not applicable.

### 2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SN0001 (link) from the CS-IRT.

*Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Additionally, we are omitting section x, as we do not have any edits to that section. 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) At the recommended TRADENAME dose, a mean increase in the QTc interval of > 20 ms (b) (4) is unlikely.

***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).*

*The currently proposed label has no dose adjustment, contraindication, or avoiding use in patients with moderate to severe renal impairment. The predicted exposure in patients with moderate or severe renal impairment is outside the exposure range in the QTc assessment.*

## 3 APPLICANT'S SUBMISSION

### 3.1 OVERVIEW

Inavolisib (RO7113755, GDC-0077) is a kinase inhibitor indicated in combination with palbociclib and (b) (4) for the treatment of adult patients with PIK3CA mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on

or after adjuvant therapy [redacted] (b) (4) The recommended dose of inavolisib is 9 mg (tablets) taken orally once daily (QD) with or without food. Section 14 (clinical studies) in the proposed label was based on the phase 3 trial INAVO120 (WO41554, inavolisib + palbociclib + fulvestrant) and the FIH study GO39374 Arm B (inavolisib + palbociclib + letrozole), E (inavolisib + palbociclib + fulvestrant), and F (inavolisib + palbociclib + fulvestrant + metformin).

The CS-IRT reviewed the QT assessment plan twice.

In the review dated 06/20/2019, we reviewed the Applicant's preliminary concentration-QTc (CQT) analysis of data from study GO39374 (ongoing at the time) and found that the provided information was inadequate. The Applicant did not provide details about the modeling approach and there was not enough information to evaluate whether pooling data from different combination therapies was reasonable. We encouraged the Applicant to use the white paper model, to conduct by-time and categorical analysis, and to submit the CQT report.

In the review dated 07/10/2023, we acknowledged that the Applicant planned to use the white paper model and to conduct by-time and categorical analysis of study GO39374. The CQT report was not submitted. The Applicant still proposed to conduct a pooled analysis without additional information. We noted that timing of ECG collection varies considerably among arms. Per amendment 9 of the study protocol, ECG collection in arms E and F was limited, i.e., Day 1 (predose, 4, and 24 hours) and Day 15 (predose and 24 hours postdose) for arm E and Day 15 (predose and 24 hours postdose) for arm F, which are unlikely to support analysis of the triple combination.

In this submission, the Applicant submitted the CQT report based on study GO39374. Study GO39374 was a first-in-human, Phase I, open-label, dose-escalation study designed to evaluate the safety, tolerability, and pharmacokinetics of inavolisib as a single agent in patients with locally advanced or metastatic PIK3CA-mutated solid tumors and in combination with endocrine and/or targeted therapies in patients with locally advanced or metastatic, PIK3CA mutated breast cancer.

A total of 190 subjects were treated in a dose-escalation stage (Stage I, Arm A-C) and an expansion stage (Stage II, Arms B to F). Stage I used a 3+3 dose-escalation design. Arms included in the QT assessment are listed in Table 2. Stage I, Arm A and C could enroll backfill cohorts. In Stage I Arm A, a single dose of inavolisib was given on C1D1. QD dosing began on C1D8. In Stage 1 Arm A backfill cohorts and Arm B and C, and Stage II Arms B, C, D, and E, QD dosing started on C1D1. Arm F enrolled obese and pre-diabetic subjects who would receive metformin starting C1D1 and inavolisib starting C1D15. Hyperglycemia is included in W&P of the proposed label and metformin prophylaxis was recommended for patients with risk factors in the INAVO120 study. Cycle 1 in Stage I Arm A was 35 days in length; all other cycles and all other cohorts (including Arm A backfill) were 28 days in length.

Inavolisib should be taken on an empty stomach (1 hour before or 2 hours after a meal), except on days of extensive PK sampling (C1D1 and C1D15, or C2D1 for Arm C) when administration will be under fasted conditions (8 hours before dosing and 3 hours postdose). The first 20 subjects in Arm D would participate in a food effect assessment

who would receive inavolisib under fed conditions (high fat meal) on either Day 1 (odd-numbered subjects) or Day 8 (even-numbered subjects).

Palbociclib was dosed as 125 mg PO QD 3 week on 1 week off in each 28-day cycle. Letrozole was dosed as 2.5 mg QD in a 28-day cycle. Fulvestrant was dosed 500 mg IM injection on C1D1 and C1D15 and on Day 1 of each subsequent 28-day cycles. Metformin was dosed as 500 mg PO starting at C1D1 and was increased by 500 mg every 3 days as tolerated up to a total daily dose of 2000 mg PO by C1D15.

Prior QT assessments of palbociclib and letrozole (125 mg palbociclib QD for 3 weeks on/1 week off in combination with 2.5 mg letrozole QD) suggest no large mean increases (i.e., 20 msec, link). We are not aware of a dedicated QT assessment for fulvestrant or metformin, which were approved prior to ICH E14.

The Applicant's primary analysis is concentration-QTc based on data pooled from Arms A-F.

**Table 2. Study Arms in GO39374[1]**

| Arm | Combination therapy | Dose of inavolisib | ECG and matching PK |
|---|---|---|---|
| A | Single agent | 6 mg (n=7), 9 mg (n=9), 12 mg (n=4), total 20<br>Cmax = 53 ng/mL (9 mg) | C1D1 and C1D15: predose, 2, 8, 24 hours postdose. Backfill cohorts had fewer time points on C1D1 (predose and 2 hours postdose) |
| B | Palbociclib and letrozole | 3 mg (n=3), 6 mg (n=3), 9 mg (n=7+20)[2], total 33<br>Cmax = 61 ng/mL (9 mg) | Same as Arm A |
| C | Letrozole | 6 mg (n=7), 9 mg (n = 10+20)[2], total 37<br>Cmax = 53 ng/mL (9 mg) | C1D1: predose, 3, 6, 24 hours postdose; C2D1: predose, 2, 8, 24 hours postdose. Same for backfill |
| D | Fulvestrant | 9 mg (n = 20+40)[3]<br>Cmax = 36 ng/mL | First 20 subjects, C1D1 and C1D15: predose, 2, 8, 24 hours postdose. Last 40 subjects: C1D1 predose |
| E | Palbociclib and fulvestrant | 9 mg (n = 20)<br>Cmax = 29 ng/mL | C1D1: predose and 24 hours postdose[4]; C1D15: predose and 24 hours postdose |
| F | Palbociclib, fulvestrant, and metformin | 9 mg (n = 20)<br>Cmax = 30 ng/mL | C1D15: predose and 24 hours postdose |

[1] In all arms, ECGs were only available for predose after Cycle 1
[2] Escalation stage + expansion stage
[3] Food effect assessment + non-food effect assessment
[4] Protocol included a 4-hour postdose on C1D1, but dataset did not include that time point.

### 3.1.1 Clinical pharmacology

See highlights of clinical pharmacology and cardiac safety.

Following single oral administration of 9 mg (approximately 200 μCi) of [14C]-inavolisib in the human mass balance study, the parent compound represented 99.5% of extractable radioactivity in the plasma. Inavolisib was eliminated to a similar extent via urinary and fecal pathways. Unchanged inavolisib in the urine accounted for 40.4% of the dose.

Following 9 mg administered as a single agent, median Tmax is 3 hours (n=6). Terminal half-life is 16 hours (n = 5). Cmax accumulation ratio is 2-fold (n = 9).

No impact of mild renal impairment (based on baseline CrCL; n= 124) on the exposure of inavolisib. A dedicated renal impairment study in subjects with moderate or severe renal impairment is ongoing.

No impact of mild hepatic impairment (based on NCI criteria; n= 111) on the exposure of inavolisib. No dedicated hepatic impairment study is planned.

Inavolisib has been studied clinically in combinations with letrozole, palbociclib, and fulvestrant. PK data suggest no DDI between inavolisib and these combination agents either as victim or perpetrator.

No clinically relevant food effect (high-fat meal) was observed on inavolisib PK in Study GO39374. After multiple dosing in the fed vs fasted state, geometric mean Cmax was 9% lower and AUC was 12% lower.

Steady-state AUC is comparable between Phase I and Phase III formulations. Although there are some numerical differences in Cmax values between these formulations, there is a large overlap in the ranges observed. As such, the Phase I and Phase III formulations are considered generally comparable.

According to the Applicant's predictions, subjects with moderation or severe renal impairment are expected to have 2-3-fold higher inavolisib exposure than normal subjects. For this reason, the Applicant excludes such subjects in the ongoing clinical trials. The label stated that (b) (4) There is no dose adjustment, contraindication, or avoiding use in patients with (b) (4) severe renal impairment.

**Table 3: Summary of dose and exposure assessment**

| | | **Mean $C_{max}$** |
|---|---|---|
| **Highest therapeutic or clinical trial dosing regimen** | 9 mg QD at steady state as single agent, oral tablets | 75.1 ng/mL ($C_{max,ss}$)* |
| **Applicant's High clinical exposure scenario** | 2 to 3-fold increase predicted in patients with moderate/severe renal impairment** | 225 ng/mL |

| | | |
|---|---|---|
| **Highest dose in QT assessment** | Arm B Inavolisib 9 mg + Palbociclib + Letrozole | 61.2 ng/mL |
| **$C_{max}$ Ratio** | 0.8-fold for clinical exposure<br>0.3-fold for high clinical exposure | |

*The geometric mean Cmax calculated from the PP dataset and provided by the Applicant in the table of highlights of clinical pharmacology and cardiac safety.
** A dedicated renal impairment study is ongoing. In the table of clinical pharmacology highlights the sponsor predicts 2-3-fold increase in exposure due to moderate/severe renal impairment. Although the applicant excluded subjects with moderate and severe renal impairment from clinical trials, the current label does not recommend contraindication nor dose adjustment in this population.

### 3.1.2 Nonclinical Safety Pharmacology Assessments

Inavolisib does not show significant inhibition of cardiac human ether-à-go-go-related gene (hERG), sodium, or calcium channels in vitro at clinically relevant concentrations. The IC50 for inhibition of hERG current was > 1700x the human plasma Cmax [unbound] (0.116 µM) at the 9 mg dose, which suggests a low potential for clinically significant QT interval prolongation.

In the single-dose cardiovascular safety pharmacology study in dogs (15-3293), inavolisib-related cardiovascular effects included generally dose-dependent, reversible, and non-adverse decreases in heart rate, increases in arterial pressure and contractility, lengthening of PR and QT intervals (likely driven by the decreased heart rates), and minimally lengthened QTc at doses ≥ 0.3 mg/kg. The Cmax [total] at the no observed adverse effect level (NOAEL) of 3 mg/kg was 679 ng/mL (9.0x the steady state Cmax of 75.1 ng/mL at 9 mg in patients in study GO39374).

No cardiovascular findings were observed in the GLP 1- and 3-month repeat-dose toxicity study in dogs using external ECG and blood pressure measurements. The inavolisib exposures were comparable in the telemetry and repeat-dose dog studies.

***Reviewer's Comment:*** *Study 15-3355 tested the effects of GDC-0077 on hERG currents in voltage-clamped HEK293 cells at two concentrations of GDC-0077 (10 and 200 µM) at near physiological temperature (33 to 35 ºC). GDC-0077 inhibited hERG current by 7.0 ± 0.7% at 10 µM and 10.4 ± 0.8% at 200 µM versus 3.2 ± 0.1% in control (Mean ± SEM; n = 3). Concentrations greater than 200 µM were not evaluated due to the estimated solubility limit. The hERG safety margin (IC50 > 200 µM, MW: 407.37 g/mol) over free (PB: 37%) clinical exposure (75.1 ng/mL) is over 1700-fold.*

## 3.2 APPLICANT'S RESULTS

### 3.2.1 By-Time Analysis

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

For unscheduled timepoints, Arm B (3 mg or 9 mg inavolisib) and Arm E, the upper bounds of 90% CI were larger than 10 msec.

***Reviewer's comment:*** *The Applicant provided descriptive boxplots of ΔQTcF versus time for overall and by treatment arm and dose. The reviewer conducted MMRM for Arm B (9 mg inavolisib) only because Arm B is label indicated therapy and has adequate ECG*

*timepoints. Thus, it is not directly comparable. Additionally, for the analyses at unscheduled timepoints, since it is hard to interpret for lumping the unscheduled timepoints together, the reviewer didn't include unscheduled timepoints in our MMRM model. Please see section 4.3 for more details.*

#### 3.2.1.1 Assay Sensitivity

Not applicable.

##### *3.2.1.1.1 QT Bias Assessment*

The Applicant did not conduct bias assessment.

### 3.2.2 Categorical Analysis

There were no significant outliers per the Applicant's analysis for QTc (i.e., >500 msec or >60 msec over baseline). There were few significant outliers for PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline).

***Reviewer's comment:*** *The Applicant didn't conduct categorical analysis for HR. For HR, there were few outliers in the reviewer's results. For QTc, PR, and QRS, the Applicant's results are similar to the reviewer's results. Please see section 4.4 for more details.*

### 3.2.3 Exposure-Response Analysis

The Applicant pooled data from stage I (dose escalation in Arms A, B, and C) and stage II (dose expansion in arms B, C, D, E, and F) for their C-QTc analysis. A total of 1476 PK/ECG pairs from 172 patients were used in the Applicant's C-QTc analysis. The Applicant did not use the recommended white paper model. The Applicant included hours 6 and 8 post-dose (i.e., QTcF at these time points were considered different from baseline while QTcF at all other time points were considered same as baseline). The Applicant also included a steady state covariate (i.e., all other time points except C1D1) to estimate difference in ΔQTcF between C1D1 and steady state. The Applicant's final model is presented in Equation 1 below. Where $C_{ij}$ is inavolisib concentration, $Time_j$ is 6- and 8-hours after dose as categorical covariates, $SS$ is steady state condition as categorical covariate, and $\left(QTcF_{i,j=0} - \overline{QTcF_0}\right)$ is individual baseline adjusted by mean of baseline QTc.

**Equation 1. Applicant's final C-QTc model.**

$$\Delta QTcF_{ij} = (\theta_0 + \eta_{0i}) + (\theta_1 + \eta_{1i}) \times C_{ij} + \theta_{2j} \times Time_j + \theta_3 \times SS + \theta_4 \times \left(QTcF_{i,j=0} - \overline{QTcF_0}\right) + \varepsilon_{ij}$$

Predose was used as baseline. PK-ECG pairs were excluded if time difference exceeded 30 minutes in 0-12 hours postdose in Cycle 1 and Cycle 2, or time difference exceeded 2 hours after 12 hours postdose in all cycles.

The results of the Applicant's analysis show concentration dependent increase in QTc interval but unlikely to cause large mean increase in QTc interval (i.e., excludes ≥ 20 msec). The estimated intercept ($\theta_0$) and slope ($\theta_1$) of the model (95 % CI) were -1.85 (-3.64 – -0.064) msec and 0.0556 (0.0151 – 0.0961) msec/(ng/ml) respectively. According to the Applicant, the highest observed mean Cmax in adequate sample size (n > 3) was 61.2 ng/mL (Arm B, n= 27, Inavolisib 9 mg + Palbociclib + Letrozole). The Applicant

predicted ΔQTcF (95%CI) at the highest mean Cmax (61.2), at 6- and 8-hours post-dose was 7.59 (5.76 – 9.42) msec.

The Applicant also conducted CQT model by treatment arm and dose levels (CQT report Appendix Figure 12.5.3); Arm C appears to have a different CQT relationship than the other arms (see section 4.5).

***Reviewer's Comment:*** *Reviewers used a model recommended in the white paper. Despite a different model, reviewer's findings are consistent with those of the sponsor (see section 4.5.1).*

### 3.2.4 Safety Analysis

The most robust and comprehensive safety data is available from WO41554 and GO39374 (cutoff date 29 Sep 2023 and 27 Mar 2023, respectively).

In study GO39374, triplicate ECG recordings with corresponding plasma drug concentrations were obtained for all study arms (see Table 2). In the pivotal phase 3 trial WO41554 (INAVO120), inavolisib 9 mg QD or matching placebo was given in combination with palbociclib 125 mg PO QD 3 week on 1 week off in each 28-day cycle and fulvestrant 500 mg IM injection on C1D1 and C1D15 and on Day 1 of each subsequent 28-day cycle. Triplicate 12-lead ECG recordings were obtained at baseline and single 12 lead ECG recordings were obtained on Day 1 of each cycle. The MedDRA SMQ "Torsade de pointes/QT Prolongation" and the preferred term of "Seizure", was utilized to analyze cardiac-related events in study WO41554 and GO39374.

In Study WO41554 (n = 162:162 to inavolisib and placebo), 8 patients in the Inavo+Palbo+Fulv arm experienced cardiac safety adverse events (electrocardiogram QT prolonged [6 patients, 3.7%], syncope [1 patient, 0.6%] and seizure [1 patient, 0.6%]). None of the events led to study drug discontinuation and there were no events of sudden death reported.

In Study GO39374 (n = 190), 9 patients experienced a cardiac safety adverse event (electrocardiogram QT prolonged [5 patients, 2.6%], syncope [3 patients, 1.6%] and seizure [1 patient, 0.5%]). None of the events led to study drug discontinuation and there were no events of sudden death reported.

***Reviewer's comment:*** *See section 4.6 for reviewer's analysis.*

## 4 REVIEWERS' ASSESSMENT

The main analysis presented in this report was based on both digital and digitized ECGs. By-time analysis was based on Arm B 9 mg dose cohort only, which was the only arm of label indicated therapy that had adequate ECG timepoints and sample size. Concentration-QTc analysis was based on pooled data from Arm A to Arm C, which had intensive PK/ECG time points and were either monotherapy of inavolisib or with combination of therapies with known QTc effect (palbociclib and/or letrozole). Arm D had only predose ECG time points for the fasted cohorts. Arm E and Arm F had limited ECG time points as well (predose and 24-hour postdose on multiple days). Sensitivity analysis was also conducted for concentration-QTc analysis (1) on Arms A to C, separately, and (2) on digital ECGs only.

## 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 12-lead triplicated digital ECG waveforms and non-digital ECG waveforms (digitized ECGs) were submitted for review. Digitized ECG waveforms were semi-automatically read. Readers were noy blinded. Since the submission includes digitized ECG waveforms, sensitivity analysis was performed with and without digitized ECGs for concentration-QTc analysis and there were no noteworthy differences in the results. Thus, the results for digital ECG only were not included in the report.

### 4.2.2 QT Bias Assessment

The reviewer did not conduct bias assessment. Instead, sensitivity analysis was conducted (see section 4.2.1).

## 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 statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. Since there is only one treatment (Arm B, 9 mg inavolisib) in the analysis, the model includes time (as a categorical variable) as a fixed effect, and baseline as a covariate. The model also includes an unstructured covariance matrix to explain the associations among repeated measures within the treatment.

### 4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for Arm B (9 mg inavolisib). The maximum ΔQTcF values by treatment are shown in Table 4.

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

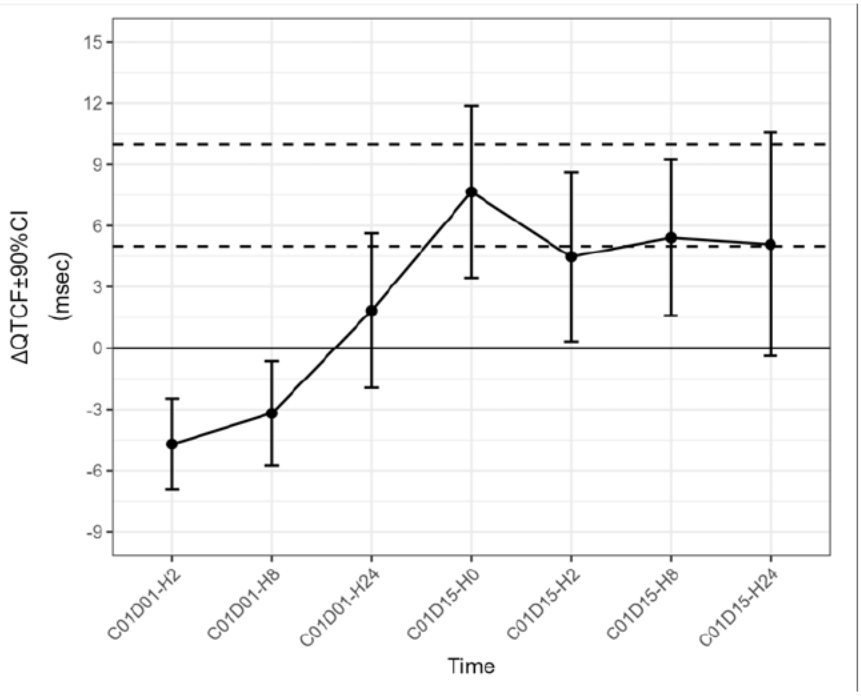



**Table 4: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF**

| Treatment | Visit | Analysis Nominal Period Day (C) | N | Time (hour) | ΔQTCF (msec) | 90.0% CI (msec) |
|---|---|---|---|---|---|---|
| Arm B, 9 mg INAVOLISIB + PALBOCICLIB + LETROZOLE | C01D01 | 1 | 24 | 24.0 | 1.8 | (-1.9 to 5.6) |
| Arm B, 9 mg INAVOLISIB + PALBOCICLIB + LETROZOLE | C01D15 | 15 | 24 | 0.0 | 7.7 | (3.4 to 11.9) |

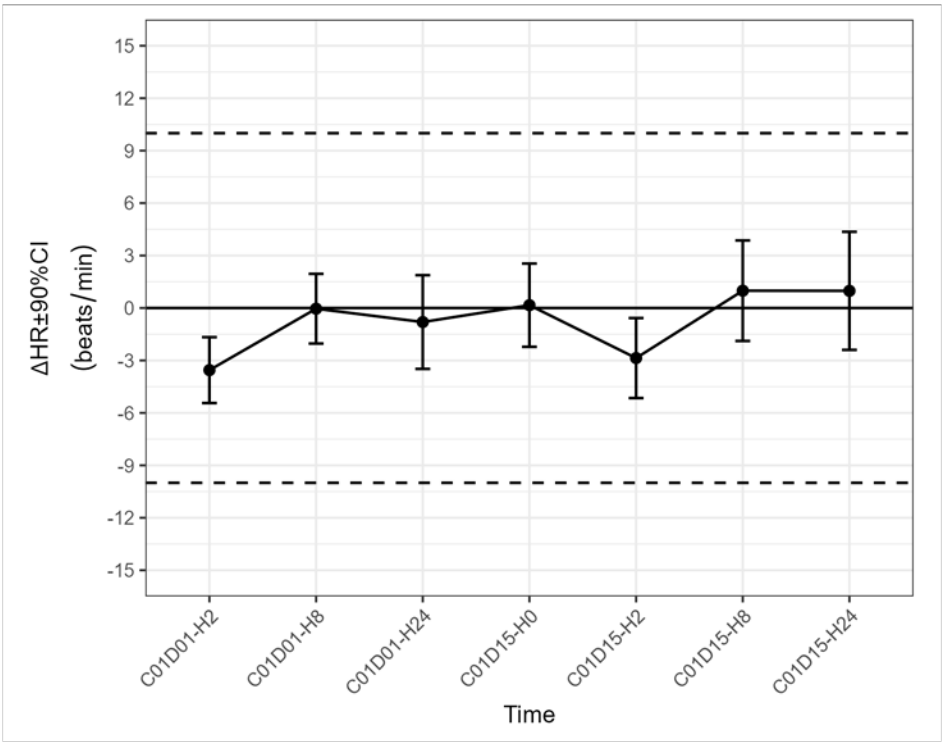
#### 4.3.1.1 Assay Sensitivity

Not applicable.

### 4.3.2 HR

Figure 2 displays the time profile of ΔHR for Arm B (9 mg inavolisib).

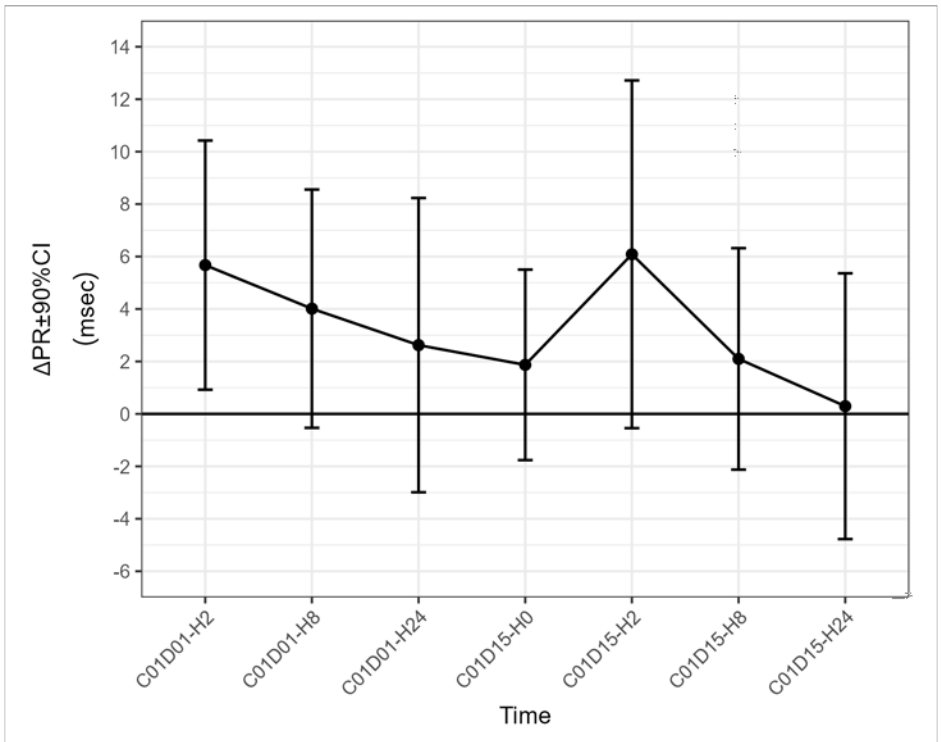
**Figure 2: Mean/Median and 90% CI of ΔHR Time-course**




### 4.3.3 PR

Figure 3 displays the time profile of ΔPR for Arm B (9 mg inavolisib).

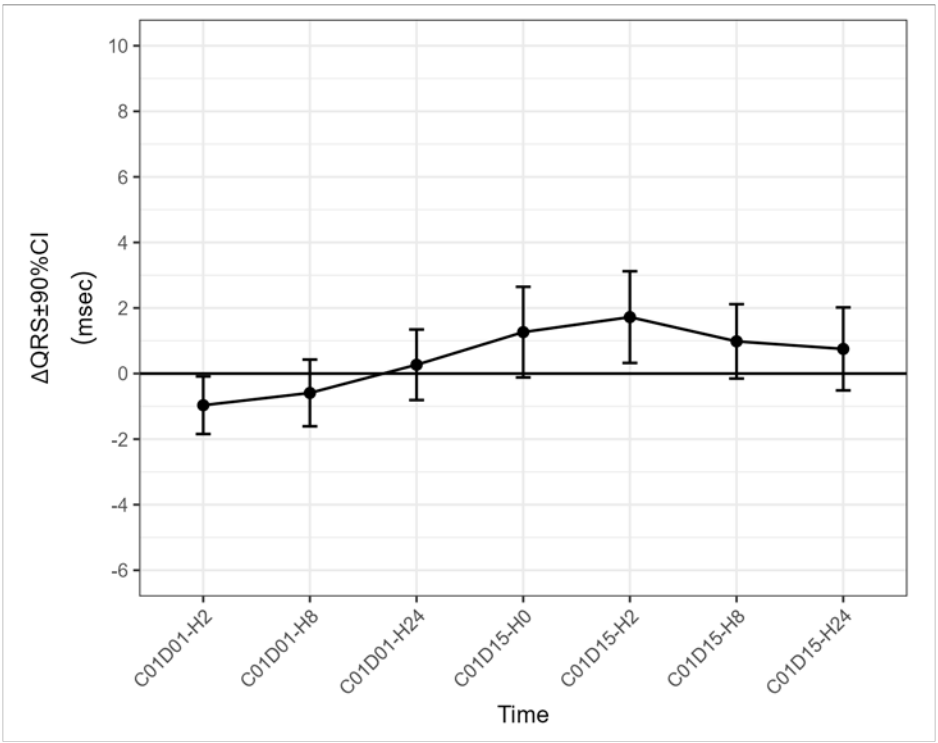
**Figure 3: Mean/Median and 90% CI of ΔPR Time-course**



### 4.3.4 QRS

Figure 4 displays the time profile of ΔQRS for Arm B (9 mg inavolisib).

**Figure 4: Mean/Median 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. In the following categorical tables, an omitted category means that no subjects had values in that category.

### 4.4.1 QTc

There were no subjects who experienced QTcF >480 msec or ΔQTcF >60 msec.

### 4.4.2 HR

HR values >100 beats/min were observed in Arm A 6 mg (1 subject, 14.3%), Arm A 9 mg (3 subjects, 33.3%), Arm B 3 mg (1 subject, 33.3%), Arm B 9 mg (4 subjects, 14.8%), Arm C 6 mg (1 subject, 14.3%), Arm C 9 mg (5 subjects, 17.2%), Arm D (3 subjects, 5.6%), Arm E (4 subjects, 20.0%), Arm F (3 subjects, 16.7%), and Arm G (1 subject, 14.3%).

### 4.4.3 PR

Table 6 lists the categorical analysis results for PR (<200 msec, >200 and ≤220 msec, and >220 msec; with and without 25% increase over baseline). For the treatment of Arm B (9

mg inavolisib), there were two subjects (7.4% in this dose group) who experienced PR values >220 msec with 25% increase over baseline.

### 4.4.4 QRS

Table 7 lists the categorical analysis results for QRS (≤120 msec, and >120 msec; with and without 25% increase over baseline). For the treatment of Arm E, there was one subject (5.3% in this dose group) who experienced QRS values >120 msec with 25% increase over baseline.

## 4.5 EXPOSURE-RESPONSE ANALYSIS

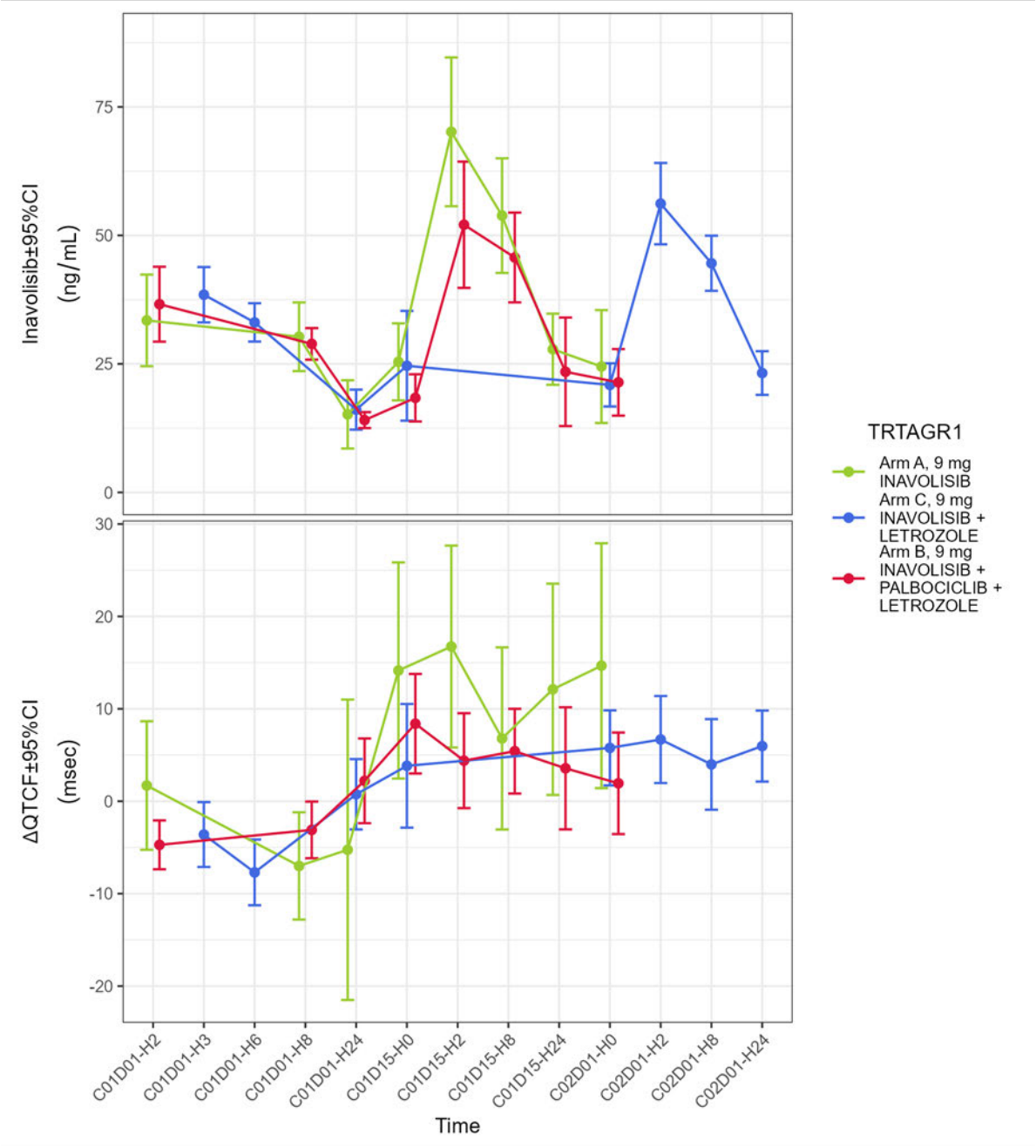
Exposure-response analysis was conducted using pooled data from stage I and II of Arms A, B, and C. Data from all treatment Cycles were used in the analysis. Other arms were excluded because they mixed in food effect or had insufficient PK/ECG sampling schedules. Only subjects with baseline and at a least one post-baseline ECG, with time-matched PK were used for exposure-QTc analysis. The final dataset included 20, 33, and 36, subjects from Arms A, B, and C respectively.

### 4.5.1 QTc

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

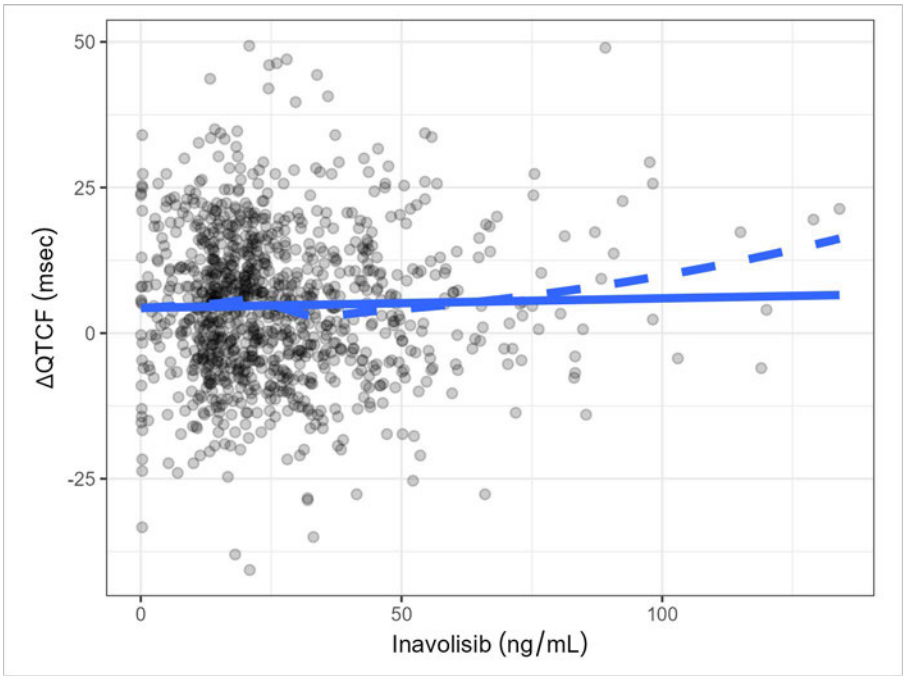
Figure 2 shows the time-course of ΔHR, with an absence of significant ΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔQTcF, with no appearance of significant hysteresis for Arms B and C but some hysteresis for Arm A on Day 15. The figure also indicates QTc shortening on Day 1 but QTc prolongation on Day 15 in Arm A. The reason for the discrepant profiles among the treatment arms is unclear but could be due to noise. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

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




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

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




Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 5.

**Figure 7: Goodness-of-fit Plot for QTcF**

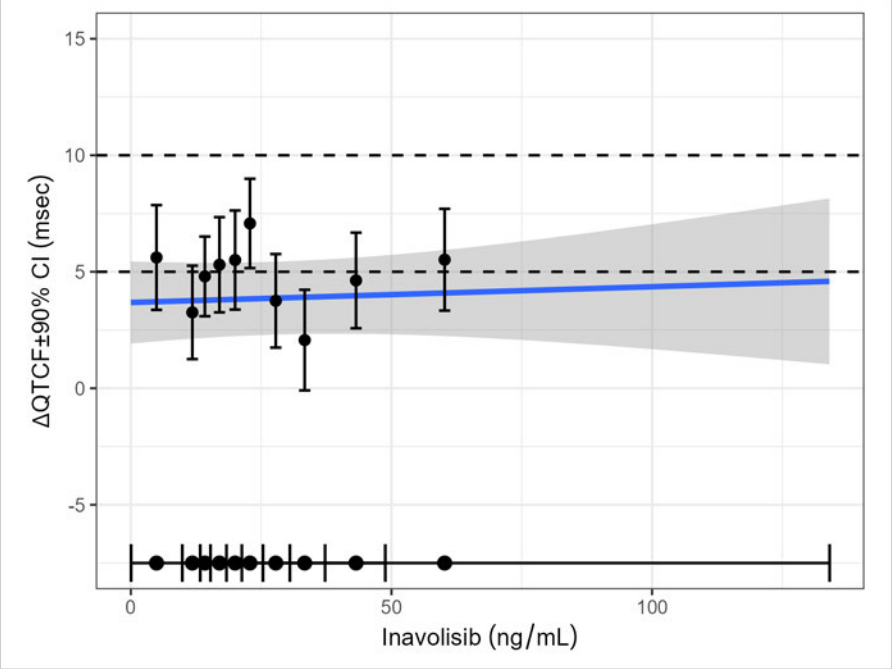
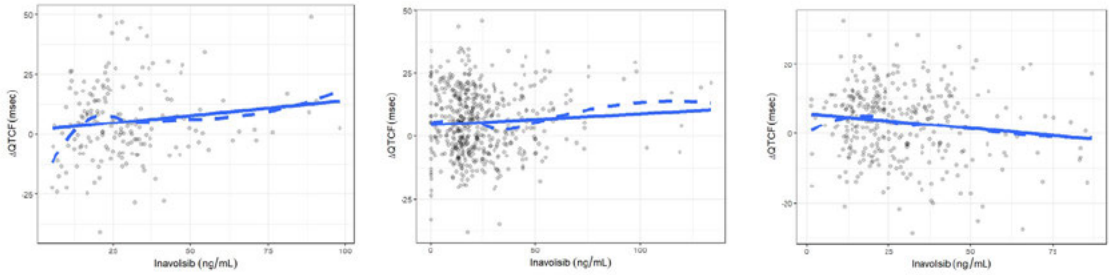


**Table 5: Predictions from Concentration-QTcF Model**

| Treatment | Analysis Nominal Period Day | Inavolisib (ng/mL) | ΔQTCF (msec) | 90.0% CI (msec) |
|---|---|---|---|---|
| Arm A, 9 mg INAVOLISIB | 1 | 40.3 | 4.0 | (2.3 to 5.6) |
| Arm A, 9 mg INAVOLISIB | 15 | 69.3 | 4.2 | (2.1 to 6.2) |
| Arm A, 12 mg INAVOLISIB | 1 | 47.4 | 4.0 | (2.3 to 5.7) |
| Arm A, 12 mg INAVOLISIB | 15 | 52.2 | 4.0 | (2.3 to 5.8) |
| Arm B, 9 mg INAVOLISIB + PALBOCICLIB + LETROZOLE | 1 | 45.5 | 4.0 | (2.3 to 5.6) |
| Arm B, 9 mg INAVOLISIB + PALBOCICLIB + LETROZOLE | 15 | 41.6 | 4.0 | (2.3 to 5.6) |
| Arm C, 9 mg INAVOLISIB + LETROZOLE | 1 | 56.8 | 4.1 | (2.3 to 5.9) |
| Arm C, 9 mg INAVOLISIB + LETROZOLE | 15 | 22.0 | 3.8 | (2.3 to 5.4) |
| Geometric mean Cmax at the steady state following inavolisib at 9 mg QD administered alone | | 75.1 | 4.2 | (2.1 to 6.3) |

The reviewer also conducted sensitivity analysis of Arm A to Arm C, separately. Arm A and Arm B showed positive slopes in the concentration-QTc relationship while Arm C showed a negative slope (Figure 8). Overall, the slopes were shallow and none of the arms showed significant QTc prolongation at therapeutic Cmax.

**Figure 8. Assessment of Linearity of the Concentration-QTcF Relationship of Arm A (Left), B (Middle), and C (Right)**




## 4.6 SAFETY ASSESSMENTS

The reviewer used the same query as the Applicant (broad SMQ of Torsade de pointes/QT prolongation + PT of seizure).

**WO41554**

Study WO41554 was a double-blind, placebo-controlled pivotal phase 3 study.

In general, there were no imbalances in TEAE of TdP/QT prolongation between the inavolisib and the placebo group (Table 6). More subjects had TEAE of

electrocardiogram QT prolonged in the inavolisib group than the placebo group. None of the electrocardiogram QT prolonged events on the inavolisib were SAEs. One was Grade 3 and the subject had electrolyte imbalance during the event (see case description below). The number of subjects with QTcF > 500 msec was balanced between the inavolisib group (4 subjects, 2.5%) and the placebo group (3 subjects, 1.9%).

**Electrocardiogram QT prolonged (Grade 3)**: Subject (b) (6) is a 46-year-old white female randomized to the Inavo+Palbo+Fulv arm. On Day 29, the subject experienced a Grade 3 Electrocardiogram QT prolonged (QTcF 487 msec) with normal HR (79 bpm), PR (132 msec), and QRS (92 msec). QTcF was 446 msec on Day -5 (average of 3 measurements) and 453 msec on Day 1. The subject had diarrhea (Grade 1) from Day 3 to Day 29 and hypocalcemia (Grade 2) from Day 15 to 85. On Day 29, potassium, sodium, and magnesium were normal and calcium was below normal (2.1 mmol/L, normal range 2.2-2.6). The event was resolving at the cutoff date and led to inavolisib dose reduction (from 9 mg QD to 6 mg QD on Day 64). The Applicant considered the event to be related to inavolisib.

**Seizure:** Subject (b) (6) is a 59-year-old Asian female randomized to the Inavo+Palbo+Fulv arm. On Day -48, the subject was diagnosed with metastatic breast cancer (ER/PR positive, and HER2 negative). Target lesion included liver (S3 and S6) and non-target lesion included liver. The subject experienced Grade 1 non-serious seizure from Day 111 to 142, assessed by the investigator as related to all study treatment. The event was reported as recovered/resolved at time of cutoff date and did not require dose modification to study treatment. The subject had a number of episodes of low-grade diarrhea prior to the onset of the event of seizure. QTcF was 491 msec on Day 142 (baseline 411 msec on Day -1) and was normal on Day 112 (427 msec). HR, PR, and QRS were normal on Day 112 and 142. The subject had Grade 4 hypokalemia from Day 142 to Day 151. Calcium was lower than normal on Day 112 and Day 142 (2.0-2.1 mmol/L, NR: 2.2-2.6). Magnesium was above normal on Day 142 (1.06 mmol/L, NR: 0.75-1.02). Potassium was below normal on Day 142 (2.16 mmol/L, NR: 3.5-5.0). The QTc prolongation on Day 142 was likely due to electrolyte imbalance.

**Table 6. Broad SMQ of Torsade de Pointes/QT Prolongation + Seizure, Safety Population, WO41554**

| Preferred term | Inavo+Palbo+Fulv n (%) N = 162 | Pbo+Palbo+Fulv n (%) N = 162 |
|---|---|---|
| Total | 8 (4.9) | 5 (3.1) |
| Cardiac arrest | 0 | 1 (0.6) |
| Electrocardiogram QT prolonged | 6 (3.7) | 1 (0.6) |
| Loss of consciousness | 0 | 1 (0.6) |
| Seizure | 1 (0.6) | 0 |
| Syncope | 1 (0.6) | 2 (1.2) |

**GO39374**

The incidence of broad SMQ of Torsade de pointes/QT prolongation + PT of seizure was similar in GO39374 (9/190, 5%) to WO41554 (8/162, 5%). See section 3.2.4. The reviewer's analysis confirms with the Applicant's numbers.

All the electrocardiogram QT prolonged events were observed in 5 subjects who received inavolisib at the 9 mg dose level (3 subjects in the Inavo+Let Arm, 1 in the Inavo+Fulv Arm, and 1 in the Inavo+Fulv+Palbo+Metf Arm). All of the events of electrocardiogram QT prolonged were Grade 1 and nonserious except for one Grade 2 serious event that led to drug interruption (QTcF 494 msec). The event was likely due to Grade 4 hypomagnesemia (serious) and Grade 3 hypocalcemia (non-serious). One subject experienced an SAE of seizure on the Inavo+Fulv+Palbo+Metf Arm. The subject was diagnosed with Grade 3 metastases to central nervous system 1 months prior to the seizure event. None of the syncope events were serious or led to dose change.

**Electrocardiogram QT prolonged (SAE)**: Subject (b) (6) is a 60-year-old white female in Stage II Arm F receiving Inavo+Fulv+Palbo+Metf. Approximately 5 years and 4 months prior to study entry, the participant was diagnosed with metastatic breast carcinoma. No target lesions were reported. Non-target lesions included bone (bony metastasis). On Day 617, during scheduled visit, a laboratory work-up revealed potassium 3.1 mmol/L (NR: 3.3-4.9 mmol/L), magnesium 0.16 mmol/L (NR: 0.7-1 mmol/L) and calcium 1.67 mmol/L (NR: 2.1-2.55 mmol/L). The subject was diagnosed with Grade 4 hypomagnesemia (serious) and Grade 3 hypocalcemia (non-serious). Prolonged ECG showed QTc prolongation of 494 msec and the subject was diagnosed with Grade 2 electrocardiogram QT prolonged. The subject was hospitalized for magnesium infusion and observations. She received treatment with magnesium sulfate and calcium carbonate for hypomagnesemia and hypocalcemia. No treatment was given for electrocardiogram QT prolonged. On Day 617, the event electrocardiogram QT prolonged was considered resolved. On Day 618, the participant was discharged from the hospital.

**Seizure (SAE):** Subject (b) (6) is a 54-year-old white female in Stage II Arm F receiving Inavo+Fulv+Palbo+Metf. On Day 464, a laboratory work-up showed blood glucose 371 mg/dL (NR: 70-110 mg/dL), and the subject was diagnosed with Grade 3 hyperglycemia (non-serious) and the event was considered resolved on Day 491. On Day 470, the subject experienced syncope and a brain MRI showed dural brain metastasis. The subject was diagnosed with Grade 3 metastases to central nervous system (serious) leading to hospitalization on the same day. On Day 472, the event of metastases to central nervous system was considered resolved and the subject was discharged from the hospital.

On Day 493, the subject was at her son's house when she experienced anxiousness and subsequently had generalized shaking. She had incontinence of bowel and bitten her tongue. The subject presented to emergency and a head CT showed no acute changes, besides her osseous lytic metastatic lesions in the calvarium and specifically in the left parietal region. The subject was diagnosed with Grade 1 seizure. A laboratory work-up showed blood glucose 565 mg/dL (normal range: 70-100 mg/dL), and the subject was diagnosed with Grade 4 hyperglycemia (non-serious). On Study Day 494, the event of hyperglycemia improved to Grade 3. A head CT scan revealed no change. No distinct new intracranial mass, infarct or hemorrhage was noted. She received treatment with levetiracetam, potassium chloride, dexamethasone and treatment with empagliflozin, sitagliptin, pioglitazone, glimepiride, and insulin degludec was ongoing. The subject was placed on seizure precautions and monitored with neuro checks. No further episodes of

seizure were noted during hospitalization. On Day 495, the event of seizure was considered resolved and the participant was discharged. On Study Day 520, the event of hyperglycemia was considered resolved.

# 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: GO39374<br><br>Population: Patients<br><br>Design: Other (Open label) | Digital: Yes<br><br>Central Read? Yes<br><br>Blinded? No<br><br>Replicates? Yes | Highest Dose: 9 mg<br><br>Placebo: No<br><br>Positive Control: No | Therapeutic | 172 for CQT modeling (primary analysis) | Baseline: Pre-dose baseline<br><br>Timing: See Table 2 |
| *Reviewer's comments: Although 12 mg was the highest dose in QT assessment (Arm A), only 2 subjects in this dose group were evaluated on day 15 and had geometric mean Cmax of 52.2 ng/ml. The next highest dose, 9 mg (in Arms A, B, and C) had the highest geometric mean Cmax in 9 subjects Arm A, Day 15 (i.e., 69.3 ng/ml), therefore this is considered as the highest dose in the QT assessment.* | | | | | |

## 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? | No |
| Is the data pooling appropriate? | No |
| *Reviewer's comments: The Applicant pooled data from all treatment groups even those which are not relevant for the target indication. The treatment arms differed in concomitant medications and intensity of PK/ECG sampling times. Despite these differences, the sponsor did not conduct heterogeneity assessment. To minimize heterogeneity, the reviewer's analysis focused on treatment arms representative of the target indication and rich PK/ECGs sampling.* | |
| **1.3 QT Correction Method** | |
| Is an HR increase or decrease greater than 10 beats/min? | No |
| Primary method for QT correction | QTcF |
| **1.4 Assay Sensitivity** | |
| Assay sensitivity methods proposed by Applicant | ☐ Moxifloxacin<br>☐ Exposure-margin<br>☐ QT bias assessment<br>☐ Other<br>☒ Not applicable (objective is large mean effects) |
| ***Reviewer's comments:*** *The study did not include placebo nor positive control and therefore QT effects is assessed using an alternative pathway.* | |
| **1.5 By-Time Analysis** | |
| **1.5.1 Investigational Drug** | |
| Primary analysis | No |
| Did the Applicant use IUT or descriptive statistics? | Descriptive statistics |

| | |
|---|---|
| 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? | N/A |
| 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? | N/A |
| **1.5.2 Positive Control** | |
| Primary analysis | N/A |
| Did the Applicant adjust for multiplicity? | N/A |
| **1.6 Exposure-Response Analysis** | |
| **1.6.1 Investigational Drug** | |
| Primary analysis | Yes |
| What is the dependent variable in the Applicant's model? | Single delta |
| White paper model? | No |
| Which concentration covariate(s) are included in the model? | Multiple |
| Which methods did the Applicant use for predicting the QT effect? | ☒ Model-based confidence intervals<br>☐ Bootstrap-derived confidence intervals |
| ***Reviewer's comments:*** *The sponsor included time effects and steady state covariate in the model. According to the white paper, time effect is not necessary if the study did not include placebo.* | |

| **1.7 Categorical Analysis** | | | |
|---|---|---|---|
| QTcF / ΔQTcF? | Yes | QRS? | Yes |
| PR? | Yes | HR? | No |

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LABEL AND LABELING REVIEW

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

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

| | |
|---|---|
| Date of This Review: | July 12, 2024 |
| Requesting Office or Division: | Division of Oncology 1 (DO1) |
| Application Type and Number: | NDA 219249 |
| Product Name, Dosage Form, and Strength: | GDC-0077[a](inavolisib) tablets, 3 mg and 9 mg |
| Product Type: | Single Ingredient Product |
| Rx or OTC: | Prescription (Rx) |
| Applicant Name: | Genentech, Inc. |
| FDA Received Date: | March 27, 2024 |
| TTT ID #: | 2024-9034 |
| DMEPA 2 Safety Evaluator: | Ngoc-Linh Do, PharmD |
| DMEPA 2 Acting Team Leader: | Tingting Gao, PharmD |

[a] Since the proprietary name for GDC-0077 has not yet been determined, "GDC-0077" is used throughout this review to refer to this product.

## 1 INTRODUCTION

As part of the approval process for GDC-0077 (inavolisib) tablets, the Division of Oncology 1 (DO1) requested that we review the proposed GDC-0077 Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 219249.

| Table 1. Materials Considered for this Label and Labeling Review | |
|---|---|
| Material(s) Reviewed | Appendix Section |
| Relevant Product Information | A |
| Labels and Labeling | B |
| Memorandum of Teleconference and Post-Approval Change Management Protocol | C |

## 3 CONCLUSION

We evaluated the proposed GDC-0077 Patient Package Insert (PPI) and determined that it is acceptable from a medication error perspective.

However, the proposed GDC-0077 Prescribing Information (PI), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Oncology 1 (DO1) in Section 4 and for Genentech, Inc. in Section 5.

## 4 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 1 (DO1)

A. Prescribing Information

1. Highlights of Prescribing Information

   a. We recommend deleting the statement, [redacted] (b) (4) to reduce clutter so that the recommended dosage is easily identified.

2. Section 2 Dosage and Administration

   a. For Section 2.2, we recommend the following revisions:

      i. For clarity and readability, combine the recommended dosage and duration of treatment statements to read as follows, “The recommended dosage of TRADENAME is 9 mg taken orally once daily with or without food, until disease progression or unacceptable toxicity”. We recommend removing the subheading [redacted] (b) (4) to reduce clutter.

ii. To increase prominence of information and readability, move the statements regarding referring to the Full Prescribing Information for endocrine therapy and palbociclib to its own line.

iii. For subsection Delayed or Missed Doses, for clarity, revise the statements to read, "Take TRADEMANE at approximately the same time each day. If a dose of TRADENAME is missed, take the missed dose as soon as possible within 9 hours. (b) (4)

If vomiting occurs after taking TRADENAME, do not (b) (4)

3. Section 17 Patient Counseling

   a. For the Dosing subsection, ensure to align the missing dosage statement with Section 2 Dosing subsection for consistency.

5 RECOMMENDATIONS FOR GENENTECH, INC.

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

1. As currently presented, the format for the expiration date is not defined; therefore, we are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)*.

2. On the side panel, we recommend revising the "Dosage" statement to "Recommended Dosage: see Prescribing Information." to ensure consistency with the terminology in the Prescribing Information.

B. Container Label(s)

1. As currently presented, the number sequences, “11016426 US” for the 3 mg and “11016234 US” are in close proximity to the expiration date and lot number. To minimize confusion with the actual lot number and reduce the risk for deteriorated drug medication errors, move these number sequences to a different location so that the “11016234 US” is not located in close proximity to the expiration date and lot number.

C. Carton Labeling

1. As currently presented, the product identifier is missing a placeholder for the machine-readable, 2D data matrix barcode format. Ensure the 2D data matrix barcode is included as part of the product identifier. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)*.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for GDC-0077 received on March 27, 2024 from Genentech, Inc.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for GDC-0077</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>inavolisib</td></tr>
<tr><td>Indication</td><td>(b) (4)</td></tr>
<tr><td>Dosage Form</td><td>tablets</td></tr>
<tr><td>Strength</td><td>3 mg and 9 mg</td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Dose and Frequency</td><td>9 mg once daily<br><br>Dose Reduction for Adverse Reactions
<table>
<tr><th>Dose Reduction Schedule</th><th>Dose Modified</th></tr>
<tr><td>Starting dose</td><td>9 mg daily</td></tr>
<tr><td>First dose reduction</td><td>6 mg daily</td></tr>
<tr><td>Second dose reduction</td><td>3 mg daily</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td>it is supplied in the following strengths and package configurations:
<table>
<tr><th>Package Configuration</th><th>Tablet Strength</th><th>NDC</th><th>Tablet Description</th></tr>
<tr><td>Bottle of 30 film-coated tablets</td><td>3 mg</td><td>50242-084-01</td><td>Red and round convex-shaped with an “INA 3” (b) (4) on one side</td></tr>
<tr><td>Bottle of 30 film-coated tablets</td><td>9 mg</td><td>50242-079-01</td><td>Pink and oval-shaped with an “INA 9” (b) (4) on one side</td></tr>
</table></td></tr>
<tr><td>Storage</td><td>Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F)</td></tr>
<tr><td>Container Closure</td><td>(b) (4)</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,[b] along with postmarket medication error data, we reviewed the following GDC-0077 labels and labeling submitted by Genentech, Inc.

- Prescribing Information and Patient Package Insert received on March 27, 2024, available from \\CDSESUB1\EVSPROD\nda219249\0001\m1\us\draft-labeling-text.docx
- Container label(s) received on March 27, 2024
- Carton labeling received on March 27, 2024

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

Container label(s)


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

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

## APPENDIX C. MEMORANDUM OF TELECONFERENCE AND POST-APPROVAL CHANGE MANAGEMENT PROTOCOL

On April 22, 2024, Genentech proposed to change the tablet count per bottle from 30 to 28 to align with the 28-day regimen for Palbociclib, to avoid patient confusion and enhance convenience. FDA communicated that no proposed changes should be made at this time and asked Genentech to submit proposed changes as a 'Comparability Protocol' instead. See Memorandum of Teleconference, April 24, 2024, available from https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8073ddbe&showAsPdf=true, and Post-Approval Change Management Protocol, received on May 23, 2024, available from \\CDSESUB1\EVSPROD\nda219249\0011\m3\32-body-data\32r-reg-info\regional-information12.pdf.

Genentech intends to submit a Change Being Effected (CBE-0) supplement for a 28-tablet bottle package configuration.

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