NDA 219249

**NDA APPROVAL**

Genentech, Inc.
Attention: Robin Stewertson
Regulatory Program Management
1 DNA Way, MS 407B
South San Francisco, CA 94080

Dear Robin Stewertson:

Please refer to your new drug application (NDA) dated and received March 27, 2024, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Itovebi (inavolisib) tablets.

This NDA provides for the use of inavolisib in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth-factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.

## APPROVAL & LABELING

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

## WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

## CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, except with the minor revisions listed above [e.g., changes consistent with annual reportable changes under 314.70(d)], as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 219249**." Approval of this submission by the FDA is not required before the labeling is used.

## DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Itovebi (inavolisib) tablets shall be 24 months from the date of manufacture when stored below 30°C.

## COMPARABILITY PROTOCOL

The proposed comparability protocol to change the tablet count of the container configuration to a 28-tablet bottle package configuration is acceptable.

## ADVISORY COMMITTEE

Your application for inavolisib was not referred to an FDA advisory committee because the clinical trial design is acceptable and outside expertise was not necessary. There were no controversial issues that would benefit from advisory committee discussion.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. This is due to the rarity of patients with breast cancer and pediatric cancers with *PI3KCA* mutations. Across pediatric cancers, *PIK3CA* mutations are far less common in pediatric tumors and are primarily limited to central nervous system (CNS) tumors. Inavolisib is not expected to be effective in CNS tumors, because inavolisib is a substrate of P-glycoprotein and breast cancer resistance protein which limits accumulation and activity within the CNS.

## POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes the FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if the FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of severe hyperglycemia, stomatitis/mucosal inflammation, and diarrhea, and assess a serious potential risk of increased drug exposure in patients with severe renal impairment and inpatients with moderate or severe hepatic impairment.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, the FDA has determined that you are required to conduct the following trials:

4718-1 Conduct a multicenter, randomized clinical trial to further characterize known serious risks with inavolisib including severe hyperglycemia, stomatitis/mucosal inflammation, and diarrhea, and compare the safety and activity of inavolisib 9 mg daily versus a lower daily dose in patients with *PIK3CA*-mutant, hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer.

The timetable you submitted on October 8, 2024, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 04/2025 |
| Final Protocol Submission: | 10/2025 |
| Trial Completion: | 10/2028 |
| Final Report Submission: | 04/2029 |

4718-2 Complete the ongoing renal impairment clinical trial and evaluate the pharmacokinetics and safety of inavolisib in participants with normal renal

function and patients with severe renal impairment, to evaluate the serious potential risk of increased drug exposure. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

The timetable you submitted on October 8, 2024, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 08/2023 (completed) |
| Trial Completion: | 12/2024 |
| Final Report Submission: | 06/2025 |

Submit the datasets with the final report submission.

4718-3 Conduct a hepatic impairment clinical trial to evaluate the serious potential risk of increased drug exposure and determine a safe and appropriate dose of inavolisib in patients with moderate and severe hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

The timetable you submitted on October 8, 2024, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 03/2025 |
| Final Protocol Submission: | 07/2025 |
| Trial Completion: | 07/2028 |
| Final Report Submission: | 01/2029 |

Submit the datasets with the final report submission.

The FDA considers the term *final* to mean that the Applicant has submitted a protocol, the FDA review team has sent comments to the Applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND 130909 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

**Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to the FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

The FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

## POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4718-4 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of inavolisib on the single dose pharmacokinetics of a sensitive CYP3A substrate to inform appropriate management strategies for clinically relevant drug interactions. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.”

The timetable you submitted on October 8, 2024, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 04/2025 |
| Final Protocol Submission: | 08/2025 |
| Trial Completion: | 02/2027 |
| Final Report Submission: | 08/2027 |

4718-5 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of inavolisib on the single dose pharmacokinetics of a CYP2B6 substrate to inform appropriate management strategies for clinically relevant drug interactions. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Clinical Drug Interaction Studies

— Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

The timetable you submitted on October 8, 2024, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 04/2025 |
| Final Protocol Submission: | 08/2025 |
| Trial Completion: | 02/2027 |
| Final Report Submission: | 08/2027 |

4718-6 Complete the ongoing clinical trial, INAVO120 (Study WO41554), entitled "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", to provide the final overall survival (OS) analysis.

The timetable you submitted on October 8, 2024, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Trial Completion: | 07/2025 |
| Final Report Submission: | 01/2026 |

Submit the datasets with the final report submission.

4718-7 Conduct an integrated analysis containing data from clinical trials and post-marketing reports, observational studies (e.g., real-world evidence), and other sources to further characterize the pharmacokinetics (PK), pharmacodynamics (PD), safety and efficacy of inavolisib in racial and ethnic minority patients and older patients age >65 years with *PIK3CA*-mutant, hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer. The analyses should support comparative safety and efficacy outcome analyses and characterization of potential differences in PK and PD between racial and ethnic minority patients and White patients, and older and younger patients.

The timetable you submitted on October 8, 2024, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission (Analysis Plan): | 06/2025 |
| Final Protocol Submission (Analysis Plan): | 12/2025 |
| Study Completion: | 12/2029 |
| Final Report Submission: | 06/2030 |

4718-8 Conduct an appropriate analytical and clinical validation study using the INAVO120 clinical trial or other data adequate to support the development of an in vitro diagnostic device for tumor tissue that is essential to the safe and effective use of inavolisib for treatment of patients with *PIK3CA*-mutant, hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer.

The timetable you submitted on October 8, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 130909 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

## REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

## POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

## COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). The FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[7].

If you have any questions, call Zohal Hamidi, Senior Regulatory Project Manager, at 301-796-6383 or email zohal.hamidi@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Paul G. Kluetz, MD
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

[7] https://www.uspnf.com/

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**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.**

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/s/

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