NDA 213721/S-014

SUPPLEMENT APPROVAL/
RELEASE FROM POSTMARKETING
REQUIREMENT/COMMITMENT/
NEW POSTMARKETING REQUIREMENT/COMMITMENT
FULFILLMENT OF POSTMARKETING REQUIREMENT/
WITHDRAWAL OF ACCELERATED APPROVAL INDICATION

Genentech, Inc.
Attention: Grace Gao, Pharm.D.
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Gao:

Please refer to your supplemental new drug application (sNDA) dated and received on June 30, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for GAVRETO (pralsetinib) capsule.

This Prior Approval sNDA provides for removal of the Advanced and Metastatic RET-mutant Medullary Thyroid Cancer (MTC) Indication, approved under accelerated approval, from GAVRETO United States Prescribing Information (USPI).

Following a meeting with FDA wherein the challenges associated with fulfilling the confirmatory study for the MTC indication were discussed, you requested withdrawal of approval of this indication and waived the expedited withdrawal procedures set forth in section 506(c)(3) of the Food, Drug, and Cosmetic Act, as amended by the Food and Drug Omnibus Reform Act of 2022. You would have to obtain FDA approval of an efficacy supplement in order to resume marketing the product for this indication.

APPROVAL & LABELING

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

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, Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using 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 from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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.

Because none of these criteria apply to your application, you are exempt from this requirement.

RELEASE FROM POSTMARKETING REQUIREMENTS

We have received your submission dated June 30, 2023, requesting release from the following postmarketing requirements listed in our December 1, 2020, approval letter under NDA 214701:

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

3959-1 Submit the final report including datasets from a multi-center, randomized, open-label trial comparing pralsetinib to investigator's choice of either cabozantinib or vandetanib in multi-kinase inhibitor naïve patients with advanced or metastatic RET-mutant medullary thyroid cancer to confirm the clinical benefit of pralsetinib with progression-free survival as a primary end point, as assessed by blinded independent central review.

Draft Protocol Submission:	06/2020 (completed)
Final Protocol Submission:	12/2020
Trial Completion:	07/2027
Final Report Submission:	01/2028

3959-5 Conduct a rodent carcinogenicity study of pralsetinib in rats to evaluate its potential for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

Draft Protocol Submission:	06/2023
Final Protocol Submission:	12/2023
Trial Completion:	01/2026
Final Report Submission:	07/2026

We have reviewed your submission and have determined that you are released from the above requirements as they are no longer needed because the advanced and metastatic RET-mutant medullary thyroid cancer (MTC) indication has been withdrawn from the label.

RELEASE FROM POSTMARKETING REQUIREMENT/COMMITMENT AND NEW POSTMARKETING REQUIREMENT/COMMITMENT

We have received your submission dated June 30, 2023, requesting release from the following postmarketing requirement and commitment listed in our December 1, 2020, approval letter under NDA 214701:

3959-3 Submit the final report, of an integrated safety analysis from clinical studies that characterize the potential serious risk of long-term adverse effects of pralsetinib on growth and development, including an assessment of growth plate abnormalities in a sufficient number of adolescent patients 12 years of age and older with RET mutant MTC and RET fusion-positive thyroid cancer. Patients will be monitored for growth and development using age-appropriate screening tools such as Tanner staging. Evaluations will include growth as measured by height, weight, height velocity and height standard deviation scores, age at adrenarche if applicable (males), age at menarche if applicable (females) and Tanner stage. Patient monitoring will be performed until discontinuation of study

treatment or a minimum of 5 years from start of treatment, whichever occurs first. Include the datasets with the final report. The results from this study may inform product labeling.

The timetable you submitted on November 18, 2020, states that you will conduct this study according to the following schedule:

Draft Analysis Plan Submission:	12/2021
Final Protocol Submission (Final Analysis Plan):	03/2022
Study Completion:	07/2032
Final Report Submission:	04/2033

3959-7 Submit a summary of the final report of an analytical and clinical validation study, using clinical trial data, that is adequate to support labeling of an in vitro diagnostic device that demonstrates the device is essential to the safe and effective use of pralsetinib for patients with RET gene fusion thyroid cancers and RET-mutation-positive medullary thyroid cancer. The results of the validation study may inform product labeling.

The timetable you submitted on November 18, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2024

We have reviewed your submission and have determined that you are released from the above postmarketing requirement and commitment for the following reasons: because the advanced and metastatic RET-mutant medullary thyroid cancer (MTC) indication has been withdrawn from the label.

The above postmarketing requirement and commitment will be replaced by the new postmarketing requirement and commitment as described below:

POSTMARKETING REQUIREMENTS UNDER 505(o)

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

As noted in the December 1, 2020, approval letter, since pralsetinib was approved on September 4, 2020, we determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA was not be sufficient to identify the unexpected serious risk of long-term adverse effects on the growth and development of adolescent patients with solid tumors.

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 this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk.

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

4475-1 Conduct an integrated safety analysis from all available clinical trial data that characterizes the potential serious risk of long-term adverse effects of pralsetinib on growth and development, including an assessment of growth plate abnormalities, in a sufficient number of adolescent patients 12 years of age or older with solid tumors treated with pralsetinib. Patients will be monitored for growth and development using age-appropriate screening tools such as Tanner staging. Evaluations will include growth as measured by height, weight, height velocity and height standard deviation scores, age at adrenarche if applicable (males), age at menarche if applicable (females) and Tanner stage. Patient monitoring will be performed until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first.

The timetable you submitted on July 14, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission (Analysis Plan):	08/2023
Final Protocol Submission (Analysis Plan):	11/2023
Study Completion:	07/2032
Final Report Submission:	04/2033

Submit the datasets with the final report.

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 131825, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing 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: **"Required Postmarketing Protocol Under 505(o)", "Required**

[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.

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 FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B 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.

FDA will consider the submission of your annual report under section 506B 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 OF SECTION 506B

4475-2 Conduct an analytical and clinical validation study, using clinical trial data, of an in vitro diagnostic device that demonstrates the device is essential to the safe and effective use of pralsetinib for patients with RET gene fusion thyroid cancers.

The timetable you submitted on July 14, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 10/2024

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.[4]

Submit clinical protocols to your IND 131825 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) include a status summary of each commitment in your annual report to this NDA. The status summary should include expected study completion and final report submission dates, any changes in plans since the last annual report, and, for studies/trials, the number of patients entered into

[4] 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.

each study/trial. All submissions, including supplements, relating to this postmarketing commitment should be prominently labeled **"Postmarketing Protocol," "Postmarketing Final Report," or "Postmarketing Correspondence."**

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated May 18, 2023, containing the final report for the following postmarketing requirement listed in the December 1, 2020, approval letter.

3959-4 Conduct a rodent carcinogenicity study of pralsetinib in mice to evaluate its potential for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there is a postmarketing requirement listed in the December 1, 2020, approval letter under NDA 214701, that is still open.

We remind you that accelerated approval PMR 3959-2 listed in the December 1, 2020, approval letter is still open. Pursuant to 21 CFR 314.510 (Subpart H), continued approval of the drug is contingent upon verification and description of clinical benefit and completion of the clinical trial for PMR 3959-2.

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.*[5]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the

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

Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

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

If you have any questions, contact Jacqueline Glen, Regulatory Health Project Manager, at Jacqueline.Glen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Harpreet Singh, M.D.
Director
Division of Oncology 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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

/s/

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