NDA 214701

ACCELERATED APPROVAL

Blueprint Medicines Corporation
Attention: Megan Sanchez, MPH
Director, Regulatory Affairs
45 Sidney Street
Cambridge, MA 02139

Dear Ms. Sanchez:

Please refer to your new drug application (NDA) dated June 30, 2020, received June 30, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Gavreto (pralsetinib), 100 mg capsules.

This new drug application provides for the use of Gavreto (pralsetinib), 100 mg capsules for adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy; and adult and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

We note that your November 30, 2020, submission includes final printed labeling (FPL) for your Prescribing Information and Patient Package Insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

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, text for the Patient Package Insert). 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 via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed container labeling that is identical to the container labeling submitted on November 24, 2020, 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Container Labeling for approved NDA 214701**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Gavreto (pralsetinib), 100 mg capsules shall be 24 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

[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.

ADVISORY COMMITTEE

Your application for Gavreto was not referred to an FDA advisory committee because no review issues were identified that raised significant public health questions regarding the risk:benefit assessment of pralsetinib for the proposed indication.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirements specified in your submission dated November 18, 2020. These requirements, along with required completion dates, are listed below.

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

3959-2 Submit the final report of integrated studies and datasets, to verify and further characterize the clinical benefit of pralsetinib for the treatment of patients with RET fusion-positive thyroid cancer who have received radioactive iodine (if appropriate for their tumor histology) to provide a more precise estimation of the BICR-assessed overall response rate and duration of response in at least 50 patients in a variety of histologies after all responding patients have been followed for 12 months following onset of response or until disease progression, whichever comes first.

Draft Analysis Plan:	09/2021
Final Protocol (Analysis Plan) Submission:	03/2021
Trial Completion:	09/2024
Final Report Submission:	06/2025

Submit clinical protocols to your IND 131825 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of

each requirement 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 entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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.

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 identify an unexpected serious risk of long-term adverse effects on the growth and development of adolescent patients, the potential for carcinogenicity, and the impairment to male fertility in patients administered pralsetinib.

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.

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

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

3959-4 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.

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

Draft Protocol Submission:	06/2021
Final Protocol Submission:	12/2021
Study Completion:	07/2022
Final Report Submission:	01/2023

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.

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

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

3959-6 Conduct a rodent fertility study investigating treated male rats (vehicle control and high dose only) mated to untreated female rats to evaluate the potential for pralsetinib to impair male fertility.

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

Draft Protocol Submission:	03/2021
Final Protocol Submission:	09/2021
Study Completion:	05/2022
Final Report Submission:	11/2022

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 protocols to your IND 131825 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports 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 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.

[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 COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

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

PROMOTIONAL MATERIALS

Under 21 CFR 314.55, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.55, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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]

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

REPORTING REQUIREMENTS

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

We have now administratively closed this NDA. Therefore, all 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, promotional materials and other submissions should be addressed to the original **NDA 213721** for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling requested above.

If you have any questions, call Idara Udoh, Senior Regulatory Health Project Manager, at 301-796-3074.

Sincerely,

{See appended electronic signature page}

Julia Beaver, M.D.
Deputy Director (acting), Office of Oncologic Diseases
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

ENCLOSURE(S):

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

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/

JULIA A BEAVER
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