NDA 212726

ACCELERATED APPROVAL

Genentech, Inc.
Attention: Florence Tao, Ph.D.
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Tao:[1]

Please refer to your new drug application (NDA) dated December 18, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rozlytrek (entrectinib) capsules, 100 mg and 200 mg.

We also refer to our approval letter dated August 15, 2019, which contained the following minor typographical error in the indication statement: "the new drug application provides for the use of adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion ***with*** a known acquired resistance mutation."

This replacement approval letter incorporates corrections of the minor typographical error noted above. The effective approval date will remain August 15, 2019, the date of the original approval letter.

This new drug application provides for the use of Rozlytrek (entrectinib) capsules, 100 mg and 200 mg for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy.

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.

[1] 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.

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.[2] 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.*[3]

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 submitted on June 7, 2019, 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 *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 212726**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Rozlytrek (entrectinib) was not referred to an FDA advisory committee because outside expertise was not necessary; the application did not raise significant safety or efficacy issues in the intended population and there were no controversial issues that would benefit from advisory committee discussion.

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

[2] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[3] 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.

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 two accelerated approval postmarketing requirements specified in your submission dated August 8, 2019. Fulfillment of both of these postmarketing requirements is needed to verify and confirm the clinical benefit of entrectinib. These requirements, along with the required completion dates, are listed below.

3689-1 Submit the final report, including datasets, from the first 54 patients with *NTRK*-fusion solid tumors enrolled across the ALKA, STARTRK-1 [NCT02097810], and STARTRK-2 [NCT02568267] studies to verify and describe the clinical benefit and further characterize the duration of response in patients who achieved a complete or partial response to entrectinib. All responding patients will be followed for at least 2 years from the onset of response or until disease progression, whichever comes first. Duration of response will be assessed by independent central review.

Trial Completion: 09/2020
Final Report Submission: 06/2021

3689-2 Submit the final report, including datasets, from ongoing and proposed trials conducted to verify and describe the clinical benefit of entrectinib, through more precise estimation of the overall response rate and mature response duration per independent review assessment, in adult and pediatric patients 12 years of age and older with solid tumors with a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion and without a known acquired resistance mutation; are metastatic or would require surgical resection that would result in severe morbidity; and have no satisfactory alternative treatment or that have progressed following treatment.

A sufficient number of patients will be evaluated to more precisely characterize response and durability of response for each of the following tumor types: pediatric solid tumors, colorectal cancer, central nervous system cancers, gynecological cancers, and melanoma.

A minimum of 40 patients with cancers other than pediatric solid tumors, colorectal cancer, central nervous system cancers, gynecological cancers, melanoma, soft tissue sarcoma, non-small cell adenocarcinoma lung cancer, mammary analogue secretory carcinoma, and secretory breast cancer will also be studied. Overall response rate and duration of response will be assessed by independent central review and all responding patients will be followed for at least 12 months from the onset of response.

Draft Analysis Plan Submission: 06/2020
Final Analysis Plan Submission: 09/2020
Trial Completion: 03/2026
Final Report Submission: 03/2027

Submit the draft and final analysis plans to your IND 120500 for this product. Submit the final reports as supplemental applications to NDA 212726. For administrative purposes, all submissions relating to these postmarketing requirements must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

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 NDA 212726. 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 trials, number of patients entered into each trial.

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 has orphan drug designation for this indication, 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 toxicity from Rozlytrek (entrectinib) effects on certain off-target receptors, transporters, and channels.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

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

3689-3 Determine functional activation or inhibition of off-target receptors, transporters, and/or channels that, at concentrations of 10 μM, showed greater than 50% inhibition by entrectinib or M5 in the secondary pharmacology studies submitted to NDA 212725 and 212726. As part of an integral safety assessment, include EC_{50} or IC_{50} data for target receptors, transporters, and channels that are still significantly affected at a concentration less than 1 μM, particularly those involved in suicidal intent and behavior, as described in Muller et al., 2015.

The timetable you submitted on August 8, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2019
Study Completion: 04/2020
Final Report Submission: 09/2020

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risks of cardiac toxicity and skeletal fractures, and to assess signals of a serious risk of adverse long-term effects on growth and neurodevelopment in pediatric patients and impaired hepatic function on the pharmacokinetics of Rozlytrek (entrectinib).

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

3689-4 Submit integrated safety analyses and supporting data from an adequate number of patients enrolled in clinical trial(s) designed to characterize the cardiac risks and its sequelae in patients exposed to entrectenib with reasonable precision; to identify risk factors for development of these sequelae; and to support labeling instructions for dose modification and monitoring. The design of the trial should include sufficient cardiac monitoring to achieve these objectives.

The timetable you submitted on August 8, 2019, states that you will conduct this trial according to the following schedule:

Draft Analysis Plan Submission: 06/2020
Final Analysis Plan Submission: 09/2020
Trial Completion: 06/2021
Final Report Submission: 06/2022

3689-5 Conduct clinical trial(s) of entrectinib in a sufficient number of pediatric patients 12 years of age and older with *NTRK*-fusion solid tumors to evaluate the potential serious risk of adverse long-term effects of entrectinib on growth and development, including neurological outcomes with reasonable precision. Patients will be monitored for growth and

developmental milestones using age-appropriate screening tools and undergo neurological examination at appropriate intervals. Evaluations will include neurological exams with neurocognitive assessment, Karnofsky/Lansky score, growth as measured by height, weight, height velocity, and height standard deviation scores (SDS), 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 August 8, 2019, states that you will conduct this trial according to the following schedule:

Draft Analysis Plan Submission: 06/2020
Final Analysis Plan Submission: 09/2020
Trial Completion: 02/2029
Final Report Submission: 08/2029

3689-6 Submit integrated safety analyses and supporting data from an adequate number of patients enrolled in clinical trial(s) designed to characterize the risk of fractures and its sequelae in patients exposed to entrectinib with reasonable precision; to identify risk factors for development of these sequelae; and to support labeling recommendations to mitigate the risk of skeletal fractures. The design of the trial should include sufficient bone monitoring to achieve these objectives, including but not limited to initial and serial assessment of bone mineral density (BMD) with dual x-ray absorptiometry (DXA) scans, and markers of bone formation, bone resorption, and calcium metabolism.

The timetable you submitted on August 8, 2019, states that you will conduct this trial according to the following schedule:

Draft Analysis Plan Submission: 06/2020
Final Analysis Plan Submission: 09/2020
Trial Completion: 03/2024
Final Report Submission: 03/2025

3689-7 Complete a pharmacokinetic trial to evaluate the effect of moderate and severe hepatic impairment on the pharmacokinetics and safety of Rozlytrek (entrectinib) compared to subjects with normal hepatic function 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*," available at: https://www.fda.gov/media/71311/download.

The timetable you submitted on August 8, 2019, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	08/2019
Trial Completion:	06/2021
Final Report Submission:	12/2021

Submit clinical protocol(s) and draft and final analysis plans to your IND 120500 with a cross-reference letter to NDA 212725. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to NDA 212725. 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3689-8 Commit to providing adequate analytical and clinical validation results from clinical trial data to support labeling of the F1CDx test to detect NTRK rearrangements for identifying patients who may benefit from entrectinib. The analytical validation should consist of precision, limit of detection, and accuracy studies for the NTRK indication. The clinical validation should be supported by a clinical bridging study comparing F1CDx and the clinical trial enrollment assays.

The timetable you submitted on August 8, 2019 states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2019

Submit final report to NDA 212725. 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 NDA 212725. 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. 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

Under 21 CFR 314.550, 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 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 314.550, 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 (PI)/Medication Guide/Patient Package Insert (as applicable).
Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

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, and other submissions should be addressed to the original **NDA 212725** 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.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[5]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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.

[4] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[5] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

We will schedule a post-approval feedback meeting in September 2019; the topics we wish to discuss will be communicated in separate correspondence to allow you to ensure that appropriate staff from Genentech will attend the meeting in person. Please email the Regulatory Project Manager for this application with your proposed dates for this post-approval feedback meeting within two weeks of receipt of our subsequent correspondence.

If you have any questions, please call Kelie Reece, Ph.D., Regulatory Health Project Manager, at (240) 402-6397.

Sincerely,

{See appended electronic signature page}

Gideon Blumenthal, M.D.
Deputy Center Director
Oncology Center for Excellence
Center for Drug Evaluation and Research

ENCLOSURE(S):

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

KELIE M REECE
08/15/2019 12:00:00 AM

GIDEON M BLUMENTHAL
08/15/2019 12:00:00 AM