NDA 212725

NDA APPROVAL

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

Dear Dr. Tao:

Please refer to your new drug application (NDA) dated December 18, 2019, 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.

This new drug application provides for the use of Rozlytrek (entrectinib), 100 mg and 200 mg capsules, for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are *ROS1*-positive.

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.

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 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 212725**." 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.

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 orphan drug designation, you are exempt from this requirement.

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.

[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 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 identify this serious risk.

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

3686-1 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 risk of cardiac toxicity and skeletal fractures and to assess a signal of a serious risk of 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:

3686-2 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 sequelae in patients exposed to entrectinib 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

3686-3 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 entrectenib 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

3686-4 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 final clinical protocol(s) and draft and final analysis plans to your IND 135124 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to this 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3686-5 Submit a report, including datasets, of clinical studies that further characterize the clinical benefit of entrectinib for the treatment of adult patients with *ROS1* fusion-positive metastatic NSCLC by providing a more precise estimation of the BICR-assessed overall response rate (ORR) and duration of response (DOR) in 92 *ROS*1 TKI-naive patients with *ROS1*-positive NSCLC and measurable disease enrolled across the ALKA, STARTRK-1 [NCT02097810] and STARTRK-2 [NCT02568267] studies.

Provide updated DOR results for the 40 responders in the efficacy evaluable population of 51 patients (primary analysis population) and for the additional 27 responders among the 41 additional patients with ROS1-positive NSCLC with measurable disease as of the original data cut-off date for the NDA. This report will be submitted after all responders have been followed for at least 18 months from the date of initial response.

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

Trial Completion: 09/2020

Final Report Submission: 06/2021

3686-6 Commit to providing adequate analytical and clinical validation results from clinical trial data to support labeling of the (b) (4) test to detect ROS1 rearrangements for identifying patients who may benefit from entrectinib. The analytical validation should consist of precision, limit of detection, and accuracy studies for the ROS1 indication. The clinical validation should be supported by a clinical bridging study comparing (b) (4) and the clinical trial enrollment assays.

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

Final Report Submission: 12/2019

Submit the final report 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 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. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

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

Alternatively, you may submit a request for advisory comments 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.[3]

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.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

REPORTING REQUIREMENTS

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

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.[7]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products 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.

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.

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[3] 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.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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

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/

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