CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218550Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 120500

MEETING PRELIMINARY COMMENTS

Genentech, Inc.
Attention: Sonia De Rubeis
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Ms. De Rubeis:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for entrectinib.

We also refer to your January 11, 2023, correspondence, received January 11, 2023, requesting a meeting to discuss the planned sNDA which proposes a new route and method of administration and the planned NDA which proposes the use of an age-appropriate formulation for the treatment of neurotrophic tyrosine receptor kinases (NTRK) (b) (4).

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

[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.

If you have any questions, call me at 240-402-4558 or email opeyemi.udoka@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Opeyemi Udoka DPT, CSM
Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for Division of Oncology 2
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-sNDA and NDA
Meeting Date and Time:	March 8, 2023; 3:30PM – 5:00PM EST
Meeting Location:	Videoconference
Application Number:	IND 120500
Product Name:	entrectinib.
Indication:	treatment of [redacted] (b) (4) with *NTRK* fusion-positive, locally advanced or metastatic solid tumor (extracranial and primary CNS tumors)
Sponsor Name:	Genetech, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)

Martha Donoghue, M.D., Acting Associate Director for Pediatric Oncology, Office of Oncologic Diseases (OOD)
Steven Lemery, M.D., Division Director, Division of Oncology 3, DO3
Nicole Drezner, M.D., Acting Deputy Division Director, Division of Oncology 2 (DO2)
Amy Barone, M.D., MSC., Acting Cross Disciplinary Team Leader, DO2
Marjilla Seddiq, M.D., Clinical Reviewer, DO2
Jason Moore, Ph.D., Team Leader, Division of Clinical Pharmacology II (DCPII)
Miao Zhao, Ph.D., Clinical Pharmacology Reviewer, DCPII
Anup Amatya, Ph.D., Acting Biostatistics Team Leader, DBM
Michelle Marcovitz, Ph.D., Biostatistics Reviewer, DBM
Xing Wang, Ph.D., CMC Team Leader, Division of New Drug Products I (DNDPI)
Olen Stephens, Ph.D., Drug Product Assessor, ONDP1/OPQ
Rohi Kolhatkar, Ph.D., CMC Team Leader, Office of Life Cycle Drug Products (OLDP)
Qi Liu (Charles), Ph.D., CMC Assessor, OLPD
Opeyemi Udoka, D.P.T., Regulatory Health Project Manager, Division of Regulatory Operations for Oncologic Diseases (DRO-OD)

SPONSOR ATTENDEES

Gabriele Bieska, Pediatric Global Regulatory Leader, Product Development Regulatory
Alison Cardenas, R.N., Pediatric Global Regulatory Leader, Product Development Regulatory
Hubert Caron, M.D., Ph.D., Safety Director, Product Development Safety
Bo Ci, Ph.D., Global Development Leader for Pediatric Oncology, Product Development Oncology
Lauren Dam, M.S. Senior Statistical Scientist, Product Development Data
Clare Devlin, Ph.D., Regulatory Program Manager, Product Development Regulatory
Cinzia Gazziola, Ph.D., Principal Clinical Scientist, Product Development Oncology
Katherine Jin, Pharm.D., Technical Regulatory Affairs Manager

Qinshu Lian, Ph.D., Associate Regulatory Labeling Manager, Product Development Regulatory
Qiqi Lin, Pharm.D., Principal Statistical Scientist, Product Development Data
Georgina Meneses-Lorente, Ph.D., Regulatory Program Management Intern, Product Development Regulatory
Sid Patel, M.D., Clinical Pharmacology Lead, Clinical Pharmacology Oncology
Brian Simmons, M.S., Pharm.D., Lead Medical Director, Product Development Oncology
Zachary Taylor, Global Development Leader for Adult Oncology, Product Development OncologyThomas Wodey, Pharm.D., Regulatory Associate Director, Product Development Regulatory
Jade Wulff, M.D., Regulatory Program Director, Product Development Regulatory
Medical Monitor, Product Development Oncology)

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 8, 2023, 3:30PM – 5:00PM between Genentech, Inc., and the Division of Oncology 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

On January 11, 2023, Genentech, Inc., (Genentech) submitted a meeting request to obtain feedback on the acceptability of the data package to support entrectinib for the treatment of (b) (4) with neurotrophic tyrosine receptor kinases (*NTRK)* fusion-positive, locally advanced or metastatic solid tumor (extracranial and primary CNS tumors) and to align on the proposed content and format for (planned submission Q2 2023):

- NDA to introduce F15 (“coated granules”) as a new dosage form for entrectinib and clinical data to support the extension of the current NTRK solid tumor indication for (b) (4)

- sNDA to support the new route and method of administration for entrectinib capsule suspension.

The meeting package was received on February 10, 2023.

Regulatory

On August 15, 2019, FDA granted accelerated approval to entrectinib (Rozlytrek) (entrectinib) 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. As part of the accelerated approval, post-marketing requirement (PMR) 3689-2 was issued:

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.

On May 2, 2022, a Type B Pre-NDA meeting was held with the Division of Oncology 3 to discuss the proposed sNDA for the treatment of NTRK (b) (4) and the acceptability of the pediatric formulation. Genentech proposed submission of a marketing application based on 25 pediatric patients with *NTRK* fusion-positive solid tumors, of whom 10 had < 6 months of follow-up. FDA stated that the proposed follow-up duration was insufficient to characterize the effect of entrectinib in the proposed patient population. Genentech subsequently proposed submission of a marketing application based on a later data cutoff date (August 2, 2022); FDA agreed that the longer follow-up time would likely be sufficient and stated that the adequacy of the updated study results to support registration will be discussed upon submission of the topline data in the context of a pre-NDA meeting.

Clinical

To support the expansion of the *NTRK* indication to patients (b) (4) years of age, provide confirmation of benefit for patients ≥ 12 years of age, and to support approval of a new formulation F15, Genentech plans to submit updated data from the clinical cutoff date CCOD of August 2, 2022, from pediatric patients in study STARTRK-NG which will form the basis of the NDA. The application will also include results from two supportive studies: STARTRK-02 and TAPISTRY.

The efficacy-evaluable population includes a total of 33 patients (STARTRK-NG: n=31; TAPISTRY: n=2) and the safety-evaluable population includes a total of 76 patients (STARTRK-NG: n=68; TAPISTRY: n=6; STARTRK-02: n=2).

- STARTRK-NG is a multipart, dose-finding (pediatric patients with relapsed or refractory extracranial solid tumors; Part A) and expansion study in patients with primary brain tumors harboring *NTRK* or *ROS1* gene fusions (Part B), and extracranial solid tumors harboring *NTRK* or *ROS1* gene fusions (Part D). Part A was completed in December 2017 and determined that the maximum tolerated dose (MTD) and Recommended Phase 2 Dose (RP2D) of the entrectinib F1 formulation is 550 mg/m^2 daily.

  In the expansion cohorts, several formulations at the RP2D were used (i.e., F1 550 mg/m^2 daily, F06 300 mg/m^2 daily, and F15) based upon the patients' ability to swallow.

  The primary objective of the expansion cohorts was to evaluate the efficacy of entrectinib as assessed by overall response rate (ORR) in the efficacy-evaluable patients using the Response Assessment in Neuro-Oncology Criteria (RANO) criteria for primary CNS tumors and Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in patients with extracranial solid tumors, as assessed by a blinded Independent Review Committee (BICR). The efficacy-evaluable population was defined as all patients with measurable (or evaluable) disease at baseline who received at least 1 dose of entrectinib and were enrolled at the RP2D (using F1, F06, or F15).

- STARTRK-02 is a study of pediatric patients with solid tumors with or without prior treatment that were enrolled in baskets according to their genetic aberration (*NTRK1/2/3*, *ROS1, or ALK*) with an additional basket for patients with non-evaluable gene types. In addition, for patients who had molecular testing but were not enrolled, there was a natural history follow-up cohort. The primary objective of the study was to determine the ORR of entrectinib, as assessed by BICR, in each patient population based on type of solid tumor. Entrectinib was administered orally at a dose of 600 mg per day (three 200 mg capsules per day).

- TAPISTRY is a global, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or in combination in patients with unresectable, locally advanced or metastatic solid tumors determined to harbor specific oncogenic genomic alterations, including *NTRK*, or who are tumor mutation burden-high (TMB-H).

Efficacy Results

The efficacy-evaluable population is defined as all patients <18 years old with *NTRK* Fusion-positive tumors who received at least 1 dose of entrectinib and were enrolled at the RP2D (using F1, F06, or F15) determined in Cohort A or in the expansion portion of the study. A total of 31 patients from STARTRK-NG (including 5 patients included in the original marketing application for entrectinib) and 2 patients from TAPISTRY. The

median duration of follow-up was 15.0 months (range: 1–57 months). Of the 33 efficacy-evaluable patients, 9 were infants (0 to < 2 years), 19 were children (≥ 2 to < 12 years), and 5 were adolescents (≥ 12 to < 18 years). Tumor types enrolled included primary CNS tumors (n=29), sarcoma (n=15) and skin cancer (n=1)

Table 1 displays the key efficacy results from the updated analysis (CCOD: August 2, 2022). Responses were observed across all age groups. Of the 23 responses, 5 occurred in infants, 15 occurred in children and 3 in adolescents. Responses were also observed in both CNS tumors (9 of 23) and non-CNS tumors (14 of 23).

Table 1- Summary of Efficacy in the Efficacy-Evaluable Population (CCOD: August 2, 2022)

	Total (N=33)
ORR, n (%) (95% CI)	23 (70%) (51, 84)
CR, n (%) (95% CI)	14 (42%) (25, 61)
PR, n (%) (95% CI)	9 (27%) (13, 46)
Median DOR, months (95%CI)	25.4 (14.3, NE)

DOR: duration of response; NE: not evaluable; CR: complete response; PR: partial response

Table 2 Summary of response data for patients with NTRK fusion tumors (DCO August 2022) across STARTRK-NG and TAPISTRY

Disease Type/Histology	ORR by BICR n (%)	DOR (months), range
Astrocytoma (N=1)	1 (100)	9.5
Infantile fibrosarcoma (N=8)	7 (88)	3.7, 24
Spindle cell (N= 6)	6 (100)	3.7, 12.9
Sarcoma other (N=1)	0	NA
Melanoma (N=1)	1 (100)	42.5
Glioblastoma (N=4)	2 (50)	14,3, 25.4
Glioma (N=6)	2 (33)	11.8, 12.9
Anaplastic ganglioglioma (N=1)	1 (100)	11.8
Medulloblastoma (N=1)	0	NA
Diffuse midline glioma (N=1)	0	NA
Anaplastic astrocytoma (N=1)	1 (100)	30.4
Glioneuronal tumor (N=1)	1 (100)	11.1
Ganglioneuroblastoma of CNS (N=1)	1 (100)	5.5

Genentech proposes to submit updated efficacy and safety data within 90 days after the NDA submission (planned for the second quarter of 2023), providing approximately 7 months of additional data.

Safety Results

The safety-evaluable population comprises 76 pediatric patients who received at least one dose of entrectinib in STARTRK-NG (n=68), TAPISTRY (n=6), and STARTRK-02 (n=2). Of the 76 pediatric patients, 14 are 0 to < 2 years, 49 are ≥ 2 to < 12 years, and 13 are ≥ 12 to <18 years. The median duration of treatment was 8.7 months (range: 0.2 – 44.7 months).

Genentech states that no new safety concerns were identified. The safety profile remains consistent with what was previously observed in pediatric patients. Grade 3-4 adverse events (AEs) occurred in 70% of patients and serious AEs occurred in 45% of patients. No Grade 5 AEs occurred. A total of 13% of patients had an AE leading to treatment discontinuation, 21% of patients had an AE leading to dose reduction, and 40% of patients had an AE leading to treatment interruption. The most frequently reported AEs were weight increased (45%), vomiting (43%), constipation (42%), pyrexia (42%) and anemia (42%).

Bone fracture events occurred in 25% of patients; 15% were Grade 1-2 in severity and 11% were Grade 3 in severity.

Formulations

Multiple formulations have been developed during the clinical development of entrectinib. The initial formulation used in pediatrics was the F1 capsule, (b) (4) Subsequently, a capsule formulation (F06) (b) (4) and is the current approved commercial formulation. Both F1 and F06 (available as 100 mg and 200 mg dose strengths) are used in pediatrics.

Later in clinical development, an age-appropriate formulation for younger children with difficulty swallowing was developed, which is a (b) (4) formulation described as “granules” in the meeting package and as (b) (4) in the IND (F15/F17, 20 x 2.5 mg tablets to yield a 50 mg strength) to be sprinkled over soft food, which will be proposed in the NDA submission. In addition, the sNDA will include a new suspension presentation, prepared from content of the capsule formulation (F06) for pediatric patients who are unable to swallow food which may be administered via nasogastric tube.

SPONSOR QUESTIONS AND FDA RESPONSES

Clinical/Safety

1. Does the Agency agree that the efficacy and safety results from studies STARTRK-NG, STARTRK-02, and TAPISTRY provide adequate clinical

evidence and demonstrate an acceptable benefit-risk profile to support registration for entrectinib in pediatric patients of all ages with NTRK fusion-positive locally advanced or metastatic solid tumors?

FDA Response: Yes, we agree; however, a final determination will be made upon review of the data submitted in the NDA including the data provided in the 90-day safety and efficacy update. In making benefit-risk determinations, we will consider the totality of the data and information submitted in the application, including the magnitude and duration of the responses in the context of safety. See additional comments below.

Regulatory

2. During the review of the dossier, would the Agency accept supplemental data that would include 7 additional months of efficacy and safety data (CCOD: March 2023) at the time of the 90-day safety update?

FDA Response: Yes; the proposal to submit supplemental data is acceptable. Whether or not the additional data will be included in the product label will be a review issue.

3. Does the Agency agree with the proposed content and format of the:
   a) NDA (NTRK line extension for entrectinib in (b) (4), including new coated granules formulation) and

FDA Response: No, we do not agree with the proposed content and format of the clinical pharmacology portion of the proposed NDA. Submit an updated population PK study report and exposure-response analysis reports for efficacy and safety with all available data to support the proposed dosage regimen in different age groups. We also reiterate that the acceptance of the proposed dosage regimens will be assessed at the review of the NDA submission.

   b) sNDA (new route and method of administration for entrectinib capsule suspension)?

FDA Response: No, we do not agree with the proposed content and format of the clinical pharmacology portion of the proposed sNDA. Submit an updated population PK study report and exposure-response analysis reports for efficacy and safety with all available data to support the proposed dosage regimen in different age groups. We also reiterate that the acceptance of the proposed dosage regimens will be assessed at the review of the sNDA submission.

4. For bioavailability study GP44192, does the Agency agree to receive a data memo at the time of the NDA submission and the final CSR upon study completion (expected July 2023)?

   FDA Response: We agree that a data memo for the relative bioavailability study GP44192 is acceptable at the time of sNDA submission. However, the final CSR for study GP44192 should be submitted as early as possible, preferably within 60 days of sNDA submission, to facilitate the filing review. In addition, the PBPK models should be updated to incorporate study results from GP44192 at the time of sNDA submission.

Additional FDA Comments:

Clinical

5. Clarify how many of the 23 responders in the primary efficacy population were followed for at least 6 months post response and provide the proportions of actual responders (e.g., not by Kaplan Meier estimation) with response duration ≥ 6 months after onset of response and ≥ 12 months after onset of response.

6. For each of the 76 patients in the safety evaluable population, provide a line-item listing of the entrectinib dose and formulation received by each patient. The NDA submission should address whether any differences in toxicity were observed across the different formulations.

7. In order to more definitively characterize the risk of fracture in pediatric patients, for each event of fracture, provide the following information in the NDA submission: narrative description of the event, location of the fracture, action taken with entrectinib (e.g. discontinued, interrupted, reduced), time to fracture in relation to start of entrectinib, time to recovery, outcome of rechallenge if applicable, if the fracture was related to trauma, radiographic findings, and any growth information available for that patient. Additionally, please clarify how fractures were identified (e.g., through routine prespecified surveillance or by clinical symptoms).

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

If at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VII. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days

after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[2]

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric

[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[3]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project

[3] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[4]

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[5]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[6]

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

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[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[5] http://www.fda.gov/ectd
[6] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[7] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[8]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs,

[7] https://www.fda.gov/media/84223/download
[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[9]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[10]

[9] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[10] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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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.

/s/

OPEYEMI O UDOKA
03/06/2023 02:23:41 PM

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 120500
Request Receipt Date	30 March 2017
Product	Entrectinib
Indication	Treatment of Advanced Solid Tumors with NTRK Fusions
Drug Class/Mechanism of Action	Adenosine triphosphate (ATP)-competitive, selective inhibitor of tropomyosin-related kinases (TRKA, TRKB, and TRKC)
Sponsor	Ignyta, Inc.
ODE/Division	DOP2/OHOP
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	29 May 2017

Section I:

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

Entrectinib is indicated for the treatment of NTRK fusion-positive, locally advanced or metastatic solid tumors in adult (b) (4), including those with disease in the central nervous system, who have either progressed following prior therapies or who have no available standard therapies.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Consideration of Breakthrough Therapy Criteria:**

a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g., only high-level summary of data provided, insufficient information About the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints Are not well-defined and the natural history of the disease is not Relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious Aspect of the disease (e.g., alopecia in cancer patients, erythema chromium migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5%

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. **Provide below a brief description of the deficiencies for each box checked above in Section 3b:**
   Not applicable.

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. **Clearance and Sign-Off (no MPC review)**

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. **A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history.**

   Entrectinib is an orally bioavailable, inhibitor of tyrosine kinases TRKA (encoded by the gene NTRK1), TRKB (encoded by the gene NTRK2), TRKC (encoded by the gene NTRK3), ROS1 (encoded by the gene ROS1), and ALK (encoded by the gene ALK).

   Human TRK (tropomyosin-related kinase) is a receptor tyrosine kinase family of neurotrophin receptors that are found in multiple tissues types. Three classes of TRK have been described: TRKA, TRKB, and TRKC; these are coded by the NTRK1, NTRK2, and NTRK3 genes, respectively. Following ligand binding, adjacent TRK receptors dimerize and become catalytically active by phosphorylating various tyrosine moieties within the cytoplasmic-facing region of its dimer counterpart. The propagation of these signals may stimulate growth, survival, and differentiation. Among many pathways known to be stimulated by the activated TRK receptors, major ones include the PI3 kinase pathway, phospholipase C-ɣ, the Erk 1 and 2 mitogen-activated protein (MAP) kinase pathways, and the Erk5 MAP kinase pathway.

   The incidence of NTRK activated rearrangements is unknown, and varies among tumor types, including non-small cell lung cancer (NSCLC), papillary thyroid cancer, spitzoid melanoma, glioma, colorectal cancer (CRC), salivary gland cancer (including mammary analog secretory carcinoma or MASC), cholangiocarcinoma, sarcomas, secretory breast cancer, congenital fibrosarcoma, and pediatric nephroma. NTRK rearrangements are below 1% in the most common cancer types such as lung, prostate, breast, and colon, but more frequently observed in rarer cancers (e.g., 90-100% in MASC, a rare form of salivary gland cancer), which in turn represents less than 1% of all cancer malignancies.

   Based on literature reports, the following table summarizes the estimated frequency of these rearrangements (table copied from the BTDR).

   Table 1: Estimated frequency of NTRK rearrangements across solid tumor histologies

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[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Tumor Histology	*NTRK1*	*NTRK2*	*NTRK3*
Astrocytoma		3%[12]	
Breast (secretory)			92%[41]
Cholangiocarcinoma	4%[35]		
Congenital fibrosarcoma			90-100%[44, 45]
CRC	1-2%[17, 19, 31]		1%[39]
Glioblastoma	1-3%[37, 38]		
Head & neck cancer		<1%[39]	<1%[39]
Inflammatory myofibroblastic tumor (IMT)			3%[50]
Melanoma (Spitz)	16%[34]		
Mesoblastic nephroma			90%[44]
Myosarcoma	1%[39]		
NSCLC	<1%[31, 32, 33]	<1%[39]	
Papillary thyroid	5-13%[36]		2-24%[42, 43, 49]
Pediatric glioma	7% combined[25]		
Pediatric sarcomas	<1%[40]		
Salivary gland: mammary analog secretory carcinoma (MASC)			90-100%[46, 45]
Salivary gland-not otherwise specified (NOS)			2%[48]

There are no drugs approved for the treatment of tumors with NTRK gene fusions. Eligibility requirements for all entrectinib trials include locally advanced or metastatic malignancies, previously treated with standard of care therapy appropriate for the tumor type and stage of disease or are unlikely to tolerate or derive clinical benefit from appropriate standard of care therapy. Entrectinib agreed (b) (4) .

Regulatory History Highlights:

- New IND 120500 submitted Feb 2014
- Granted orphan drug designation and rare pediatric disease designation for treatment of neuroblastoma 22 Dec 2014
- Granted orphan drug designation by FDA for treatment of TrkA-positive, TrkB-positive, TrkC-positive, ROS1-positive, or ALK-positive NSCLC and treatment of TrkA-positive, TrkB-positive, TrkC-positive, ROS1-positive, or ALK-positive CRC 3, 12 Feb 2015

7. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

Overall tumor response rate (ORR) with a sufficient duration as determined by RECIST v1.1 criteria and RANO criteria (for CNS tumors) from 4 single-arm trials are being used to support this breakthrough therapy designation request.

For accelerated approval (or tumors harboring rare mutations), OHOP considers ORR of a sufficient magnitude and with an acceptable duration of response as a surrogate reasonably likely to predict clinical benefit in this refractory patient population. An effect on ORR could also support, depending on study results (magnitude of

effect, duration of response, effects on different histologies, etc.) regular approval in this refractory population. Randomized trials will likely be difficult to conduct in these rare groups (especially given the response rates observed to date; see below). Nevertheless, consideration of regular approval for a "tissue agnostic" indication may require enrollment of additional patients in order to better characterize the treatment effects in different patients groups.

b. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

Not applicable

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

Standard of care differs for each type of cancer. Eligible patients will be those with locally advanced or metastatic malignancy harboring an NTRK1, NTRK2 or NTRK3 gene fusion, previously treated with standard of care therapy appropriate for the tumor type and stage of disease or patients who are unlikely to tolerate or derive clinical benefit from appropriate standard of care therapy. Note that some tumor types (e.g., MASC) can have an indolent course.

There are no drugs that have been approved for this indication nor are there off label drugs used in this indication.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

Not applicable

10. Information related to the preliminary clinical evidence:

Clinical Trials Submitted for BTDR Entrectinib in original submission

1. ALKA-372-001 (ALKA): Single-arm, open-label study in patients with solid tumors with TRKA/B/C, ROS1, or ALK molecular alterations; ongoing in Italy at 2 clinical sites.

2. RXDX-101-01 (STARTRK-1): Single-arm, open-label study in patients with solid tumors with NTRK1/2/3, ROS1, or ALK molecular alterations; ongoing in the U.S. and South Korea.

3. RXDX-101-02 (STARTRK-2): Global, single-arm, open-label multicenter basket study in patients with solid tumors with NTRK1/2/3, ROS1, or ALK gene rearrangements; ongoing in the U.S., EU, and Asia-Pacific.

4. RXDX-101-03 (STARTRK-NG): Open-label, multicenter dose escalation study in children and adolescents with relapsed or refractory extracranial solid tumors (Part A), with expansion cohorts in subjects with primary brain tumors harboring NTRK1/2/3, ROS1, or ALK molecular alterations (Part B), neuroblastoma (Part C) and other non-neuroblastoma, extracranial solid tumors harboring NTRK1/2/3, ROS1, or ALK gene fusions (Part D); ongoing in the U.S. *NOTE: none were summarized in this BTDR as none had NTRK1/2/3 gene fusions.*

The current dose administered to adults in clinical trials is 600 mg once day daily, on a continuous daily dosing regimen. The recommended pediatric dose has not yet been determined.

Nineteen patients with NTRK fusion cancers have been enrolled across four trials across 10 tumor histologies in adults and 1 tumor type in pediatrics: mammary analogue secretory cancer (MASC) of the salivary glands, lung

cancer, colon cancer, soft tissue sarcoma (STS), secretory breast cancer, uterine carcinoma, neuroendocrine tumor, primary brain tumor, and infantile fibrosarcoma (IFS).

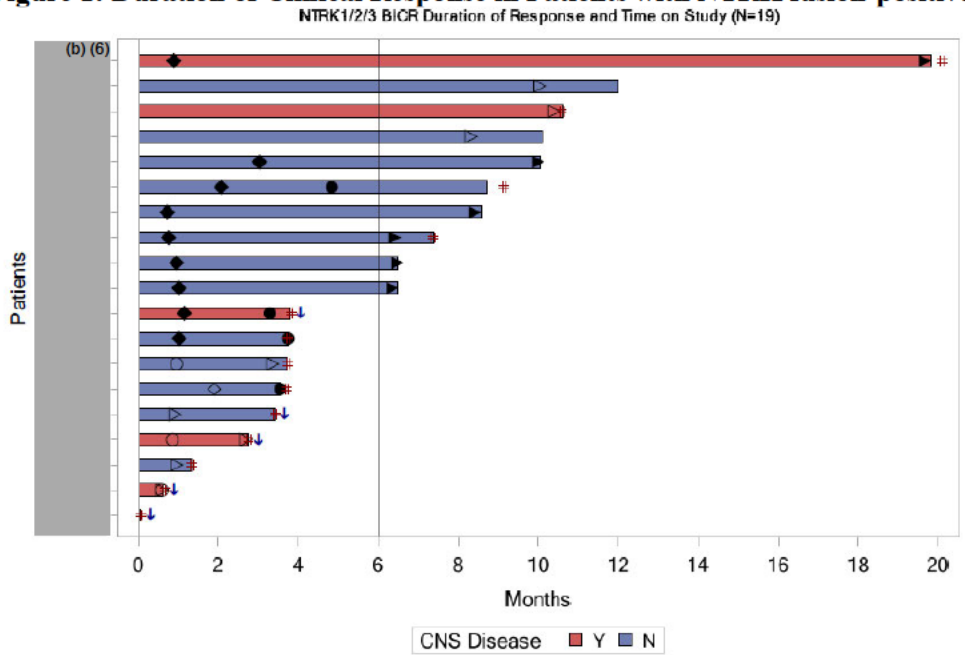
Nine of the 19 evaluable patients are partial responders (per independent review) = **ORR 47.4% (95% CI: 24.5%, 71.1%)**, and there are no patients with a complete response (CR). Clinical activity in patients with CNS disease consists of 2 out of 6 (33%) patients (1 stable disease and 1 partial response). **Median duration of response (mDoR) (**duration of follow up from time of response) **was 6.3 months (95% CI: 5.6, 7.7).** All responders were centrally reviewed. As of 29 March 2017, 7 (31.6%) patients were ongoing on study. Thirteen patients discontinued: 8 patients from disease progression (42.1%), 2 patients from patient decision (10.5%), 2 patient from adverse events (10.5%), and 1 patient from death (5.3%; pediatric patient).

Table 2: Efficacy for NTRK-mutated subjects on Entrectinib across all trials (copied from submission)

No.	Study/PID/Age/Sex/ECOG/CNS	Tumor Type	Number of Prior Systemic Therapies	Gene Fusion	BOR		DOR (m)		TOT (m)	On Study	Notes
					INV	BICR	INV	BICR			
Adult Population											
1	ST-1 (b) (6) M/1/Y	NSCLC	4	*SQSTM1-NTRK1*	PR	PR	18.82	18.82*	19.84	N	CNS CR
2	ST-1 (b) (6) M/0/Y	PBT	0	*BCAN-NTRK1*	SD	SD	NA	NA	10.39	N	Lesions 60% 3D-vol assessment^
3	ST-1 F/1/N	MASC	4	*ETV6-NTRK3*	PR	PR	4.64	2.80	8.72	N	
4	ST-2 (b) (6) F/1/N	Ovarian	4	*ETV6-NTRK3*	SD	SD*	NA	NA	12.01	Y	BICR non-measurable at baseline
5	ST-2 M/1/N	NET	1	*ETV6-NTRK3*	PD	SD	NA	NA	10.10	Y	
6	ST-2 M/1/N	MASC	2	*ETV6-NTRK3*	PR	PR	5.66*	5.66*	7.37	N	
7	ST-2 F/1/N	Uterine	2	*ETV6-NTRK3*	SD	PR	NA	6.97*	10.03	Y	
8	ST-2 F/1/N	STS	2	*TPM3-NTRK1*	PR	PR	7.73*	7.73*	8.59	Y	
9	ST-2 F/1/N	mCRC	1	*ETV6-NTRK3*	PD	PD	NA	NA	3.72	N	
10	ALKA (b) (6) F/1/N	mCRC	3	*LMNA-NTRK1*	PR	PD	2.63	NA	3.56	N	BICR missing Cycle 1 scan
11	ST-2 (b) (6) M/1/N	STS	3	*PEAR1-NTRK1*	uSD	uSD	NA	NA	3.42	N	
12	ST-2 M/0/N	STS	0	*TPM3-NTRK1*	PR	PR	2.76	2.76	3.72	N	
13	ST-2 F/2/N	Breast	4	*ETV6-NTRK3*	PR	PR	5.56*	5.56*	6.48	Y	
14	ST-2 M/1/Y	Gastric	4	*MDM4-NTRK1*	PD	PD	NA	NA	2.76	N	
15	ST-2 F/0/N	NSCLC	1	*ETV6-NTRK3*	PR	PR	6.05*	5.36*	6.48	Y	
16	ST-2 M/2/N	NSCLC	3	*ETV6-NTRK3*	uSD	uSD	NA	NA	1.35	N	Squamous NSCLC
17	ST-2 F/3/Y	PBT	1	*unk-NTRK1*	PD	PD	NA	NA	0.59	N	ECOG 3 at baseline
18	ST-2 F/3/Y	MASC	3	*ETV6-NTRK3*	ND	ND	NA	NA	0.07	N	ECOG 3 at baseline
Pediatric Population											
19	(b) (6) 18mo/M/4/Y	IF	2	*ETV6 NTRK3*	uPR	PR	NA	2.17	3.78	N	ECOG 4-equivalent at baseline

* = ***DOR censored***

Figure 1: Duration of Clinical Response in Patients with NTRK fusion-positive tumors per BICR



♦ = confirmed PR/CR; ► = ongoing response; ○ PD = in a non-responder; ● = PD in a responder; # end-of-treatment; ↓=patient death, open triangle = ongoing in non-responder, ◊ = unconfirmed PR/CR

The most common (>10% incidence) treatment-related adverse events are fatigue (36.7%), dysgeusia (34.9%), nausea (23.3%), paresthesia (24.2%), dizziness (21.9%), diarrhea (17.2%), myalgia (16.7%), vomiting (14.9%), arthralgia

(12.6%), constipation (14%), and weight increased (13%); there is no evidence of cumulative toxicity, renal or hepatic toxicity, or QTc prolongation.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting: NTRK rearranged tumors are rare, and there are no alternative therapies for these patients. Entrectinib shows promising activity (ORR 47.4%) and duration of response (6 months) in a variety of heavily pre-treated refractory tumors that harbor NTRK fusions.

☐DENY:

12. Division's next steps and sponsor's plan for future development:

Due to the rarity of these tumors, randomized trials are not likely to be feasible. The Sponsor is conducting the above U.S. trials designed for registration purposes. Based on study results and the population enrolled, entrectinib may be approved for NTRK-mutated tumors irrespective of the histology, or for specific tumor types with NTRK mutations. Regular approval may require enrollment on additional patients to confirm the treatment effect on ORR and DoR in different patient populations. Given the early response rate in rare tumors, the Division has already worked proactively with the company to encourage expanded access for patients who cannot enroll into a clinical trial (e.g., based on location) and that response rate data from expanded access requests could be considered to support approval. Furthermore, DOP2 has encouraged Ignyta to expand enrollment of their clinical trials where safely possible and to enroll patients as young as 12 years old in the "adult trial" and to continue to enroll patients in their pediatric trial.

The company has been advised and contacted CDRH for (b) (4)

13. List references, if any:

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page} Leigh Marcus
Team Leader Signature: {See appended electronic signature page} Steven Lemery
Division Director Signature: {See appended electronic signature page} Patricia Keegan

5-7-15/M. Raggio

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KAYLA J GARVIN
05/09/2017

PATRICIA KEEGAN
05/09/2017