

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212725Orig1s000

212726Orig1s000

ADMINISTRATIVE AND CORRESPONDENCE
DOCUMENTS



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND120500
IND 135124

MEETING MINUTES

Jean-Philippe Crochard, M.Sc.
Pharma Technical Regulatory Program Management
F. Hoffmann-La Roche Ltd.
Grenzacherstrasse 124
CH-4070 Basel, Switzerland

Dear Mr. Crochard,

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 the meeting between representatives of your firm and the FDA on November 7, 2018. The purpose of the meeting was to discuss with the Agency the data to be presented in the future NDAs, including that to support the selection [REDACTED] ^{(b) (4)} for launch of entrectinib, and to capture agreements regarding the contents of a complete application under the PDUFA VI Program for the two NDAs to be submitted for entrectinib.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

{See appended electronic signature page}

Steven Kinsley, Ph.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA CMC Only

Meeting Date and Time: November 7, 2018 11:00 AM
Meeting Location: 10903 New Hampshire Avenue
White Oak Bldg 21; Room 1537
Silver Spring, Maryland 20903

Application Number: 120500 and 135124
Product Name: entrectinib
Indication: Treatment of NTRK fusion-positive, (b) (4)
metastatic solid tumors in adult and pediatric patients who have
either progressed (b) (4)
(b) (4)
Treatment of patients with *ROS1*-positive, (b) (4)
metastatic non-small cell lung cancer (NSCLC)

Sponsor/Applicant Name: Genentech, Inc.

Meeting Chair: Anamitro Banerjee
Meeting Recorder: Steven Kinsley

FDA ATTENDEES

Anamitro Banerjee, Ph.D.	Branch Chief, OPQ/ONDP/DNDPI/BII
Olen Stephens, Ph.D.	Drug Product Reviewer, OPQ/ONDP/DNDPI/BII
Charles Jewell, Ph.D.	Drug Substance Reviewer, OPQ/ONDP/DNDPAPI/BI
Elsbeth Chikhale, Ph.D.	Biopharmaceutics Team Lead (Acting), OPQ/ONDP/DB/BI
David Anderson, Ph.D.	Process/Facilities Reviewer, OPQ/OPF/DPAI/BII
Rakhi Shah, Ph.D.	Branch Chief, OPQ/OPF/DPAI/BII
Patricia Keegan, M.D.	Division Director, OND/OHOP/DOP2
Martha Donoghue, M.D.	Clinical Reviewer, OND/OHOP/DOP2
Marcus Leigh, M.D.	Clinical Reviewer, OND/OHOP/DOP2
Joyce Weaver, M.D.	OSE/DRISK
Kelie Reece	Project Manager, OND/OHOP/DOP2
Priyanka Kumar	Regulatory Business Process Manager
Steven Kinsley, Ph.D.	Regulatory Business Process Manager

SPONSOR ATTENDEES

(In Person)

Pankaj Rege, Ph.D.	Process Chemistry
Marvin Lloyd Woodhouse, M.Sc.	Formulation Development
Christiane Froehlich, Ph.D.	Pharma Technical Development Program Management
Jean-Philippe Crochard, M.Sc.	Pharma Technical Regulatory Program Management
Fabian Schwarb, Ph.D.	Pharma Technical Regulatory Program Management
Dharmendra Singhal, Ph.D.	Head of Pharma Technical Development Small Molecules
Gert Thurau, Ph.D.	Head Pharma Technical Regulatory Small Molecule Development Products

(Via Teleconference)

Muriel Cordon Federspiel, Ph.D.	Drug Substance Analytical Development
Dirk Spielvogel, Ph.D.	Manufacturing Science and Technology
Marc Lindenberg, Ph.D.	Drug Product Analytical Development
Susanne Kaiser, Ph.D.	Drug Product Analytical Development
Pirmin Hidber, Ph.D.	Material Science
Georgina Meneses-Lorente, Ph.D.	Clinical Pharmacology
Chung Ying (Florence) Tao, Ph.D.	Drug Regulatory Affairs Program Management
Marie-Claire Beurier, Diplom-Ingenieur	Drug Regulatory Affairs Program Management
Guillaume Bergthold, MD, Ph.D.	Pediatric Clinical Development Management

1.0 BACKGROUND

Entrectinib is reported as a CNS-active potent inhibitor of the 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), with IC50 values for kinase inhibition in the low nanomolar range (1.7, 0.1, 0.1, 0.2, and 1.6 nM, respectively).

Entrectinib drug substance synthesis was originally developed by NerPharMa (Nerviano, Italy). On May 12, 2017, Ignyta, Inc. was granted Breakthrough Therapy to entrectinib for the treatment of NTRK fusion-positive, locally advanced or metastatic solid tumors in adult and pediatric patients who have either progressed following prior therapies or who have no acceptable standard therapies. On July 5, 2017, entrectinib was granted orphan drug designation for NTRK fusion-positive tumors.

On February 8, 2018, Ignyta was acquired by Roche Holdings, Inc. (Roche) and remains a wholly owned subsidiary of Roche. On June 12, 2018, INDs 120500 (NTRK) and 134125 (ROS1) were transferred from Ignyta to Roche (Genentech).

The previous Sponsor (Ignyta) communicated to the Agency its intention to use a single manufacturer (b) (4) for bulk manufacture and packaging. Roche intends to use one additional packaging site (Roche Kaiseraugst).

In a “Written Only Response” meeting, dated August 28, 2018, provided feedback on updated drug product registration stability plans, and drug substance starting materials.

FDA sent an “Advice Letter,” dated October 9, 2018 to provide feedback on the acceptability of the proposed dissolution method.

Roche currently plans to submit two separate New Drug Applications for entrectinib (NTRK and ROS1 indications) in December of 2018.

A pre-NDA (CMC Only Meeting) was granted to Roche on August 30, 2018. The purpose of this meeting is to discuss the CMC data package to support two NDA submissions for entrectinib for the indications above. In particular, Roche would like to obtain feedback from the Agency on the drug substance (b) (4) selected for registration (b) (4), manufacturing process control strategy (b) (4), and plans envisioned to ensure robust supply.

A brief teleconference was held prior to the Pre-NDA CMC only meeting on October 26, 2018. At this teleconference, Roche clarified that the NDA applications would use only (b) (4) drug substance. FDA advised Roche that any comparability protocols could potentially have an impact on the review cycle and that Roche should communicate any comparability protocols as early as possible, preferably by submitting a draft comparability protocol to the IND.

FDA sent Preliminary Comments to Genentech, Inc. on October 30, 2018.

2. DISCUSSION

Question 1.

On the basis of the presented data package, does the Agency agree that the selection of drug substance (b) (4) is suitably justified for commercial registration?

FDA Response to Question 1:

Pending the results of experiments described in section 4.11.3 in the meeting package, selection of drug substance (b) (4) may be justified for commercial registration.

Roche Response:

The Sponsor acknowledges the Agency’s feedback. Please note that the results of the experiments described in section 4.11.3 of the PMP are presented in our Sponsor’s response to Question 2.

Discussion:

See discussion on Question 2

Question 2.

Does the Agency agree with the proposed control strategy for the drug substance (b) (4) destined to support the registration of entrectinib?

FDA Response to question 2:

The overall strategy is acceptable, however a specification attribute indicating (b) (4) is recommended for the drug substance release. The method should be validated to indicate suitable purity (b) (4). In your NDA application either add a specification for control of (b) (4) in the drug product or provide data and justification for omission of the specification.

Roche Response:

The Sponsor acknowledges the Agency's feedback and would like to discuss the following aspects of the control strategy (b) (4)

Drug substance

The identity of the desired (b) (4) will be included in the drug substance specification used for release and stability testing. The testing will be conducted by X-ray powder diffraction (XRPD).

(b) (4)

The identity test will include the verification of absence of any peak not belonging to (b) (4). Therefore, the Sponsor does not plan to implement a quantitative XPRD method for quality control.

Drug product

The drug product manufacturing process and the commercial container closure system were designed to ensure the integrity of the drug substance (b) (4).

The risk of drug substance (b) (4) in the drug product was determined to be very low, as elaborated below.

- a) (b) (4). In addition, the commercial container closure system (HDPE bottle (b) (4)) provides adequate protection (b) (4).

(b) (4)

c) Drug product stability data demonstrate the absence of (b) (4) on storage (see [Table 2](#) **Error! Reference source not found.** below). APPEARS THIS WAY ON ORIGINAL

On the basis of the very low risk of (b) (4) in the drug product, control of the drug substance (b) (4) in the drug product specification is deemed unnecessary.

Stability data

The Sponsor would like to provide an overview of the experimental results for drug substance (b) (4) characterization in the drug product (as described in Section 4.11.3 of the PMP; the corresponding data will be presented in Section 3.2.P.2 of the NDA).

These experiments, whose results are overviewed below in [Table 2](#), aim at confirming the integrity (b) (4) on storage of the drug product. The testing was conducted using a combination of analytical techniques, namely XRPD, Raman-imaging and NIR spectroscopy.

The following drug product registration batches were tested:

- Primary and site-specific drug product stability batches stored under ICH accelerated conditions (40°C/75% RH) in the primary packaging (HDPE bottles (b) (4)) for 6 months and 3 months, respectively.
- Site-specific drug product stability batches stored under open storage conditions (25°C/60% RH and 30°C/75% RH) for 3 months.

The results show that (b) (4) is stable in the drug product under all evaluated storage conditions (b) (4)

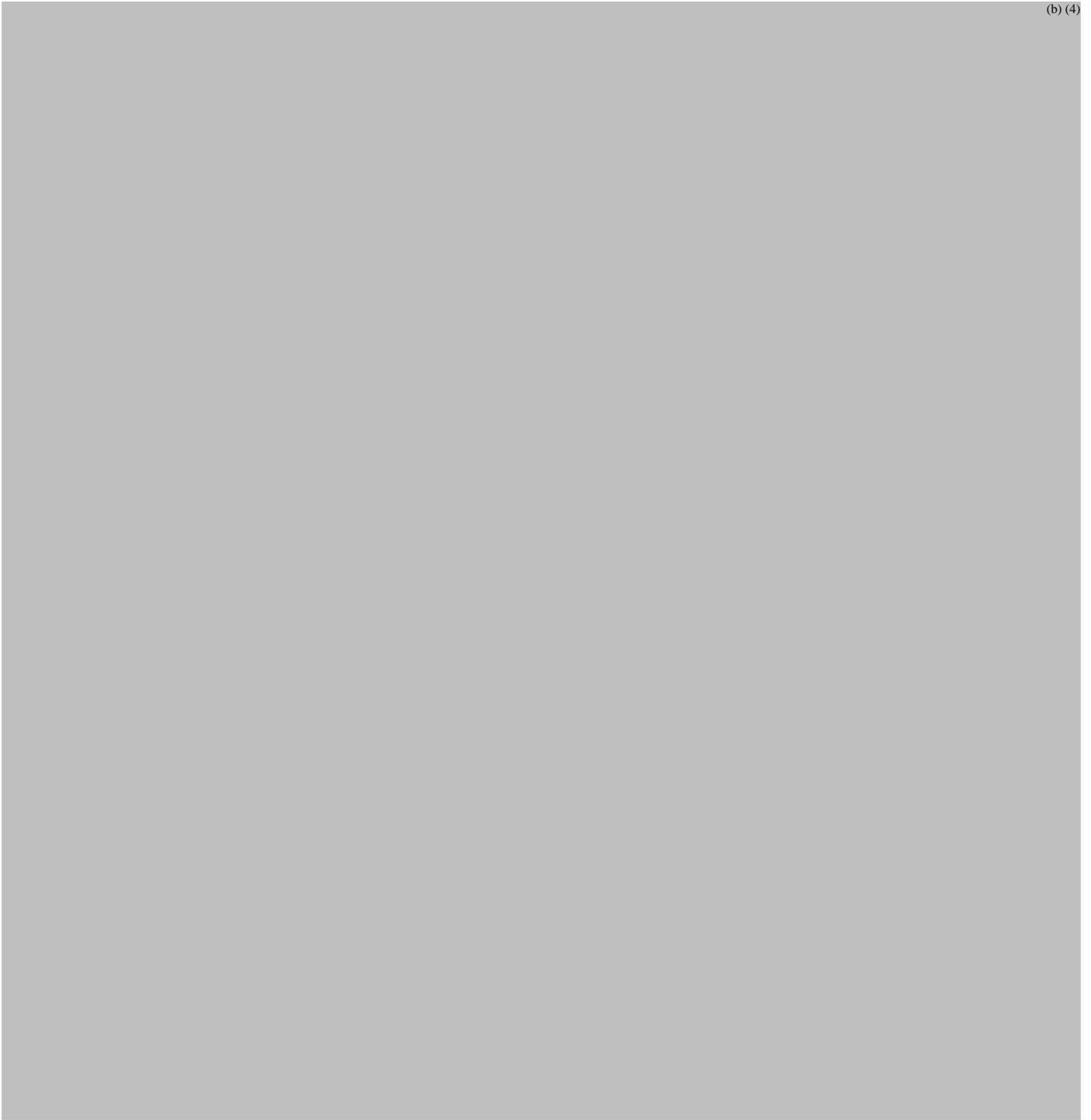


Table 3 Batch Correlation (Bulk Drug Product / Primary / Site-Specific)

Strength (F06)	200 mg			100 mg		
(b) (4) Batch	M10362	M10371	M10376	M10365	M10374	M10375
No. (Bulk)						
(b) (4) Batch	M10409	M10414	M10415	M10410	M10412	M10413
No. (Primary-Packaged)						
Roche Basel Batch No. (Primary-Packaged)	GEX0170	GEX0171	GEX0172	GEX0173	GEX0174	GEX0175

Abbreviations: (b) (4) Roche Basel = F. Hoffmann–La Roche Ltd, Basel, Switzerland

On the basis of the very low risk of (b) (4) in the drug product, control of the drug substance (b) (4) in the drug product specification is deemed unnecessary.

Discussion:

Roche stated that the risk (b) (4) of drug substance (b) (4) (b) (4) is low and will control (b) (4) with specifications in the drug substance. FDA stated that the approach appears acceptable, but the final decision on the acceptability of control (b) (4) in the drug substance will be based on the data and justification submitted in the NDA application. **FDA requests Roche provide any summary of validation data for the analytical methods used on the drug product showing that (b) (4) including XRPD. FDA also requests that a batch tree is given to show which drug substance batches used in the drug product batches and combine the control strategies into a single location in the NDA application.**

Question 3.

Does the Agency agree with the short- and mid-term actions proposed by Roche to ensure robust supply of entrectinib capsules to the patient?

FDA Response to question 3:

FDA understands that Roche will submit the NDA based on drug substance (b) (4). FDA offers the following guidance on the mid-term action proposed by Roche. (b) (4) (b) (4) bioavailability/bioequivalence of drug product manufactured with (b) (4) drug substance should be assessed relative to (b) (4) manufactured material. If the bioavailability is significantly different between these two products, clinical bridging may be necessary. This will also be contingent upon analytical methods (b) (4) in the drug product (b) (4) (b) (4)

Roche Response:

The Sponsor acknowledges the Agency's feedback and would like to take the opportunity of the meeting to discuss our high level strategy for the Comparability

Protocol. The latter aims at accelerating the introduction of the 2nd generation manufacturing process (b) (4) and additional drug substance manufacturer.

As a follow-up to discussions which occurred with the Agency during the teleconference of 26 October 2018, the Sponsor would like to present and discuss with the Agency its high-level plans for the comparability protocol intended to be included in the NDA.

During the teleconference, the Agency gave us feedback that such a comparability protocol should be submitted for evaluation ahead of the NDA submission due to the accelerated NDA review timelines expected under BTB. The Sponsor would therefore like to reach an agreement with regards to timing for pre-discussion/pre-evaluation (submission of a draft to the IND) and finalization (inclusion into the NDA) of the comparability protocol.

In order to support the discussion during the meeting, the Sponsor would like to use a slided presentation.

Discussion:

Roche stated that the process proposed for the potential new drug substance manufacturing site would be the same except for a change (b) (4). Roche stated that the new process (b) (4) would be the only process done at the new site, but the new process might also be run at the existing site. FDA requested that the proposed comparability protocol be submitted as early as possible to the IND to aid in the review process and feedback. FDA will determine the acceptability of the comparability protocol based on the totality of the information submitted to the NDA. FDA requested that details of the investigation and corrective actions related to the old process (b) (4) be submitted as early as possible. In addition, FDA requested a summary of robustness study data related to both the old and new process (b) (4) (b) (4) that demonstrate the risks (b) (4) also be submitted as early as possible. FDA reminds Roche that the final decision to determine the designation of a supplement as PAS or CBE will be made at the time of the submission of the supplement, and based on the data, information and facility status available at the time of submission of the supplement.

Question 4.

Does the Agency agree with Roche's plan to provide certificates of analysis for all relevant batches of the predecessor clinical formulations F1 and F2A in lieu of 3.2.P.5.4 Batch Analysis (i.e., populated tables with batch results) documents?

FDA Response to question 4:

No, for ease of review and batch comparison, provide the batch results for the predecessor formulations F1 and F2A as tabulated results in section 3.2.P.5.4. These relevant batches should be tabulated separate from the F06 batches and labeled clearly as supportive batch data.

Roche Response:

The Sponsor acknowledges the Agency's feedback. No further discussion at the meeting is needed.

Discussion:

There was no discussion of question 4.

Question 5.

Does the Agency agree with the list of manufacturing batch records that the Sponsor intends to include in the future NDA?

FDA Response to question 5:

No, FDA does not agree. In the briefing package you propose to submit executed batch records of one batch per strength, plus the bioequivalence batch records. According to 21CFR 314.50(d)(1)(ii)(b), for each primary stability batch, you will need to submit the batch production record.

Roche Response:

The Sponsor acknowledges the Agency's feedback. No further discussion at the meeting is needed.

Discussion:

There was no discussion of question 5.

ADDITIONAL COMMENTS:

1. In the NDA submission, in addition to tabulated data, provide stability charts that compile the registration and supportive stability data based on quality attribute with extrapolated trend lines and specification limits.
2. Table 20 appears to have an error for the total target capsule units for the 200 mg strength.
3. In the original NDA submission, provide a complete list of all testing, packaging, labeling, and manufacturing sites for the drug substance, drug product, and novel excipients on Form 356h.
4. In the original NDA submission, include the complete dissolution profile data for the registration batches at all stability time points.

Additional topics from Roche for discussion at the meeting.

1. Rolling submission

As follow-up to discussions that took place during the Clinical pre-NDA meetings for entrectinib, the Sponsor would like to inform the Agency that it will not use rolling submission for CMC submission documents.

Discussion:

There was no discussion.

2. Drug product process validation

Considering the small proposed batch size and the limited quantity of drug product required for commercialization, the Sponsor would like to highlight its intention to use concurrent validation for the drug product manufacturing process. This validation strategy is in line with the feedback received from the Agency by Ignyta (Type B CMC Meeting of 28 September 2017; minutes issued 16 October 2017, Reference ID: 4167862).

Discussion:

FDA agrees.

3.0 General Comments

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed and captured in the minutes for the meetings held on October 17, and November 7, 2018, for the NDA to seeking an indication for the treatment of *NTRK* (b) (4) fusion-positive (b) (4) metastatic solid tumors that have progressed (b) (4).

Genentech and FDA agreed that:

- The discipline-specific contents of the planned NDA are summarized in the minutes for the October 17, and November 7, 2018 meetings.
- The planned NDA will include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- All major components will be submitted in the original NDA application.

- Late submission of minor application components is limited to the eCRFs for the healthy volunteer clinical pharmacology studies, which will be submitted within 30 days of the original NDA submission.
- A REMS will not be required to file the planned NDA. FDA will make a final determination regarding the need for a REMS during the review of the NDA for entrectinib for the proposed indication of the for the treatment of *NTRK* (b) (4) fusion-positive (b) (4) metastatic solid tumors that have progressed (b) (4).
- Genentech will provide justification in the NDA if subsections for hepatotoxicity and interstitial lung disease (ILD) are not included in the Warnings and Precautions section of the proposed prescribing information.
- The content of a complete application was discussed and captured in the minutes for the meetings held on October 18, and November 7, 2018, for the NDA seeking an indication for the treatment of *ROS1*-positive metastatic, non-small cell lung cancer.

Genentech and FDA agreed that:

- The discipline-specific contents of the planned NDA are summarized in the minutes for the October 18, and November 7, 2018 meetings.
- The planned NDA will include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- All major components will be submitted in the original NDA application or in the cross-referenced NDA for the proposed indication for the treatment of *NTRK* fusion-positive, (b) (4) metastatic solid tumors in adult and pediatric patients who have either progressed (b) (4). The latter NDA will be submitted prior to or on the same day as the NDA for entrectinib for the proposed indication of the treatment of patients with *ROS1*-positive, (b) (4) (b) (4) metastatic NSCLC.
- Late submission of minor application components is limited to the eCRF for the healthy volunteer clinical pharmacology studies, which will be submitted within 30 days of the original NDA submission.
- A REMS will not be required to file the planned NDA. FDA will make a final determination regarding the need for a REMS during the review of the NDA for entrectinib for the proposed indication of the treatment of patients with *ROS1*-positive, (b) (4) metastatic NSCLC.
- Genentech will provide justification in the NDA if subsections for hepatotoxicity and interstitial lung disease (ILD) are not included in the Warnings and Precautions section of the proposed prescribing information.

- **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.

Because entrectinib was granted orphan drug designation for *NTRK* fusion-positive solid tumors by FDA's Office of Orphan Products Development on July 5, 2017, you are exempt from PREA requirements for this proposed indication. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your NDA application supporting this indication.

Because entrectinib was granted orphan designation for *ROS1*-positive NSCLC, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your NDA application supporting this indication.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

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.”

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.				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

5.0 ACTION ITEMS

[Insert any action items that were identify during the meeting. Include who is responsible to complete the action item and the due date. Responsible party should not be an individual, but either sponsor or FDA. Consider the use of a table to present the information]

Action Item/Description	Owner	Due Date
Provide draft comparability protocol	Sponsor	End of November
Submit draft 356h form for NDA (submit to IND)	Sponsor	End of November

6.0 ATTACHMENTS AND HANDOUTS

(b) (4)

2 Pages have been Withheld in Full as B4(CCI/TS)
Immediately Following this Page

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/

STEVEN A KINSLEY
11/26/2018



IND 135124

MEETING MINUTES

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 Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for entrectinib.

We also refer to the meeting between representatives of your firm and the FDA on October 18, 2018. The purpose of the meeting was to obtain Agency feedback on the planned NDA submission for entrectinib for the proposed indication of the treatment of patients with *ROS1*-positive, [REDACTED] ^{(b)(4)} metastatic, non-small cell lung cancer.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (240) 402-6397.

Sincerely,

{See appended electronic signature page}

Kelie Reece, Ph.D.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:

Meeting Minutes
“Pre-NDA ROS1 Responses to Preliminary Comments_final.pdf”



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: October 18, 2018, 3:00 PM – 4:00 PM
Meeting Location: White Oak Building 22, Conference Room 1315
Silver Spring, Maryland 20903

Application Number: IND 135124
Product Name: entrectinib
Proposed Indication: Treatment of patients with *ROS1*-positive, (b) (4)
(b) (4) metastatic non-small cell lung cancer
Sponsor Name: Genentech, Inc.

Meeting Chair: Erin Larkins, M.D.
Meeting Recorder: Kelie Reece, Ph.D.

FDA ATTENDEES

Patricia Keegan, M.D.	Division Director, DOP2/OHOP
Martha Donoghue, M.D.	Clinical Team Leader, DOP2/OHOP
Erin Larkins, M.D.	Clinical Team Leader, DOP2/OHOP
Luckson Mathieu, M.D.	Clinical Reviewer, DOP2/OHOP
Leigh Marcus, M.D.	Clinical Reviewer, DOP2/OHOP
Pallavi Mishra-Kalyani, Ph.D.	Statistics Team Leader, DBV/OB
Xiaoxue, Li, Ph.D.	Statistics Reviewer, DBV/OB
Whitney Helms, Ph.D.	Nonclinical Team Leader, DHOT/OHOP
Claire Myers, Ph.D.	Nonclinical Reviewer, DHOT/OHOP
Jeanne Fourie Zirkelbach, Ph.D.	Clinical Pharmacology Team Leader, DCPV/OCP
Xiling Jiang, Ph.D.	Clinical Pharmacology Reviewer, DCPV/OCP
Jiang Liu, Ph.D.	Pharmacometrics Reviewer, DPM/OCP
Banu Zolnik, Ph.D.	Biopharmaceutics Team Leader, DB/BBI
Parnali Chatterjee, Ph.D.	Biopharmaceutics Reviewer, DB/BBI
Olen Stephens, Ph.D.	Product Quality Reviewer, DNDPI/ONDPI
Reena Phillip, Ph.D.	Scientific Reviewer, CDRH/OIR/DMGP
Ozan Aygun, Ph.D.	Scientific Reviewer, CDRH/OIR/DMGP
Latonía Ford, M.B.A., BSN, RN	Safety Regulatory Project Manager, OSE/PMS
Monica Hughes, M.S.	Chief Project Manager Staff, DOP2/OHOP
Kelie Reece, Ph.D.	Regulatory Health Project Manager, DOP2/OHOP

SPONSOR ATTENDEES

Ignyta

Edna Chow-Maneval, Ph.D.	Sr. VP, Clinical Development
Ann Johnson, M.S.	Director, Biostatistics
Jennifer Shen, Ph.D.	Director, Regulatory

Roche

Ekaterina Bassett, Ph.D.	Sr. Project Leader, Companion Diagnostics
Marie-Claire Beurier	Diplom-Ingenieur Global Regulatory Lead
Na Cui, Ph.D.	Biostatistics Lead
Susan Eng, Pharm.D.	Safety Science Lead
George Gauthier, Ph.D., M.B.A.	Life Cycle Team Lead
Todd Riehl, Pharm.D.	Global Development Lead
Brian Simmons, Pharm.D., M.S.	Clinical Scientist
Chung Ying (Florence) Tao, Ph.D.	US Regulatory Partner
Gracy Crane, Ph.D.	Real World Data Scientist

(b) (4)

BACKGROUND

This application will be subject to “the Program”. The objective of the pre-New Drug Application (NDA) meeting to be held on October 18, 2018, is to obtain agreement between Genentech, Inc. (Genentech) and the FDA on the content and presentations of data to support the filing of the planned NDA for the following proposed indication.

Genentech’s Proposed Indication

Genentech is proposing submission of an NDA for the following indication:

Entrectinib is indicated for the treatment of ROS1-positive, [REDACTED] metastatic non-small cell lung cancer (NSCLC).

(b) (4)

The pre-meeting package for this October 18, 2018 interdisciplinary pre-NDA meeting, received on September 18, 2018, states that Genentech plans to file two NDAs for entrectinib: one for the treatment of adults with *ROS1*-positive NSCLC, in which clinical development occurred under IND 135124, and one for the treatment of adult and pediatric patients with *NTRK* fusion-positive solid tumors, in which clinical development occurred under IND 120500. The pre-meeting package further states that entrectinib will be supplied as hard capsules, with a proposed recommended dose of 600 mg given orally, once daily. IND 135124 contains a letter of cross reference to IND 120500 for a significant portion of the Chemistry, Manufacturing and Controls (CMC) developmental data. Genentech was granted orphan drug designation for entrectinib for

the “treatment of *TrkA*-positive, *TrkB*-positive, *TrkC*-positive *ROS1*-positive or *ALK*-positive non-small cell lung cancer” on February 3, 2015. Breakthrough Therapy Designation (BTD) has not been granted for entrectinib for this clinical development program/indication.

The CMC only pre-NDA meeting has been scheduled for November 7, 2018 to reach agreement on the content and format of the CMC components of both planned NDAs. At this meeting, Genentech and FDA will capture the agreements regarding the content and format of each NDA, acceptance of late submissions, and the need for risk evaluation and mitigation strategies (REMS) or other risk management actions.

A separate interdisciplinary pre-NDA meeting has been scheduled for October 17, 2018 under IND 120500 for the NDA that will support the proposed indication of entrectinib for the treatment of *NTRK* fusion-positive, (b) (4) metastatic solid tumors in adult and pediatric patients who have either progressed (b) (4). Breakthrough Therapy Designation was granted to Ignyta for the treatment of *NTRK* fusion-positive, locally advanced or metastatic solid tumors in adult and pediatric patients who have either progressed following prior therapies or who have no acceptable standard therapies on May 12, 2017. On July 5, 2017, orphan drug designation was granted to Genentech for entrectinib for the “treatment of *NTRK* fusion-positive solid tumors.”

Regulatory History

On February 27, 2014, Ignyta submitted IND 120500 for the initiation of clinical studies with entrectinib (RXDX-101) in the United States. Ignyta acquired RXDX-101 from Nerviano Medical Sciences (NMS), who initiated the first-in-human (FIH) dose escalation trial, Study ALK-372-001, in Italy in October 2012.

On February 3, 2015, Ignyta received orphan drug designation (#14-4629) for entrectinib “for the treatment of *TrkA*-positive, *TrkB*-positive, *TrkC*-positive, *ROS1*-positive, or *ALK*-positive NSCLC” under IND 120500.

On August 30, 2016, an Investigational Device Exemption (IDE G160133) for the planned companion diagnostic (Trailblaze Pharos™) to support appropriate selection of patients for treatment with entrectinib was approved under IND 120500. On November 10, 2016, the Ignyta Trailblaze Pharos™ assay, the proposed companion diagnostic test for selection of patients with either *TrkA*-positive, *TrkB*-positive, *TrkC*-positive, *ROS1*-positive, or *ALK*-positive cancers for treatment with entrectinib, was granted Expedited Access Pathway designation. Subsequently, Roche and Ignyta partnered with Foundation Medicine and plan to file a supplement premarketing approval application for the FICDx as the companion diagnostic test for entrectinib, to select for patients with *NTRK* fusion-positive solid tumors or *ROS1* fusion-positive NSCLC. This was noted in the Final Written Responses issued June 26, 2018, in response to the Type B meeting request submitted by Ignyta to IND 120500 on April 25, 2018.

On February 22, 2017, Ignyta submitted two analysis plans to pool efficacy data across three studies (Study RXDX-101-02 [STARTRK-2], the ALKA-372-001 study, and Study RXDX-101-01 [STARTRK-1]) in two subgroups: patients with *ROS1* fusion-positive NSCLC and adult and

pediatric patients with *NTRK1/2/3* fusion-positive extracranial solid tumors. Ignyta posed questions for each plan and requested FDA feedback on the acceptability of the analysis plans. The analysis plan for efficacy in the pooled efficacy analysis to be conducted in at least 56 patients with *ROS1* inhibitor-naïve, *ROS1* fusion-positive NSCLC was to calculate the overall response rate (ORR) as assessed by blinded independent central review (BICR). Ignyta proposed that an application could be supported by a demonstration of a BICR-assessed, confirmed ORR in which the lower limit of the 95% confidence limit (CI) would exclude 50% and the lower limit of the 95% CI for the BICR-assessed, median duration of response (DOR) would exclude 12 months. The proposed safety analysis plan would provide analyses of adverse events across ALKA-372-001, STARTRK-1, and STARTRK-2 in the following safety analysis populations:

- Patients with NSCLC, with or without a molecular alteration, treated with at least one dose of entrectinib at the recommended phase 2 dose
- Patients with NSCLC, with or without a molecular alteration, treated with at least one dose of entrectinib at any dose level
- All tumor types, with or without a molecular alteration, treated with at least one dose of entrectinib at any dose level

On March 31, 2017, FDA issued an Advice/Information Request letter under IND 120500, in response to the questions posed in the February 22, 2017 amendments containing these integrated statistical analysis plans. In that communication, FDA advised Ignyta that the data necessary to support the filing of a marketing application for the treatment of the proposed population (*ROS1* fusion-positive NSCLC) should be discussed in a meeting with clinical review staff from the Thoracic Malignancies team in the Division of Oncology Products 2.

On May 3, 2017, Ignyta submitted new IND 135124 for the development program supporting the proposed indication of the treatment of patients with *ROS1* fusion-positive, (b) (4) metastatic NSCLC, along with a request for 30-day waiver. A waiver of the 30-day review period for the original IND submission was granted on May 12, 2017.

On May 18, 2017, Ignyta submitted a meeting request under IND 135124 to seek feedback on the acceptability of the proposed integrated efficacy and safety analysis plan for data from patients with *ROS1* fusion-positive NSCLC who have not received prior treatment with an *ROS1* inhibitor, intended to support the filing of a planned NDA for the treatment of this patient population. In the meeting package, which was received on June 29, 2017, Ignyta proposed that patients must meet all of the following criteria to be included in the efficacy analysis population: have locally advanced or metastatic NSLC harboring an *ROS1* gene fusion; have not received prior *ROS1* inhibitor, have measurable disease at baseline as determined by investigator per RECIST v1.1; and have received at least one dose of entrectinib. In the Final Written Responses dated July 26, 2017, FDA stated the following:

- The proposed efficacy analysis population is not acceptable. In a single arm trial, the efficacy analysis population should be defined as the as-treated population (i.e., includes all patients who received at least one dose of entrectinib). Revise the analysis plan to incorporate a sensitivity analysis for ORR in the subset of patients with measurable disease at baseline.

- The proposed method for calculation of ORR and its 95% CI is acceptable. However, the timing of the final analysis must ensure an adequate assessment of durability of response. Therefore, the final analysis should occur when a minimum of 12 months follow-up **from the onset of response** in all responding patients has been reached.
- A determination of clinical benefit, based on the ORR and DOR, will depend upon both the magnitude of effect on the ORR and the DOR. A BICR-confirmed median DOR of 12.7 months, taking into account the 95% CI around this median, would not be considered an improvement over available therapy in this population. The risk:benefit assessment of entrectinib would be conducted in the context of available therapy.

On May 5, 2017, Ignyta submitted a request for preliminary Breakthrough Designation Request (BTDR) advice for a proposed indication of the treatment of patients with *ROS1* fusion-positive locally advanced or metastatic NSCLC, (b) (4). Ignyta presented analyses of ORR and DOR in 32 patients with *ROS1* fusion-positive NSCLC who had not received prior *ROS1* inhibitor, and 9 patients who had received crizotinib and had CNS-only progression using a data cut-off date of April 20, 2017. On May 23, 2017, a teleconference was held to provide advice on the preliminary BTDR data. FDA stated that the reported BICR-assessed ORR of 56% (95% CI: 38, 74) in crizotinib-naïve patients with *ROS1* fusion-positive, metastatic NSCLC did not suggest an advance over available therapy and, therefore, the data provided did not meet criteria for BTDR. In addition, based on the limited data provided for crizotinib-naïve patients with baseline CNS metastases (i.e., 7 patients with assessment of CNS response by BICR), FDA stated that a request for BTDR limited to this patient population was premature. Moreover, FDA informed Ignyta that the BTDR should contain adequate follow-up for durability of response and informed Ignyta that responders be followed for at least 6 months after the onset of response, to provide sufficient data on durability of response to support a BTDR.

On December 11, 2017, Ignyta submitted a BTDR for entrectinib for the treatment of *ROS1* fusion-positive NSCLC. FDA scheduled a teleconference on December 15, 2017, to discuss the request and stated during the teleconference that the submitted BTDR appeared premature, and that the data provided do not appear to be consistent with preliminary clinical evidence indicating that the entrectinib may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapy, as required to qualify for BTDR. Subsequently, on December 18, 2017, Ignyta withdrew the BTDR request.

On April 27, 2018, Ignyta submitted a request for preliminary BTDR advice for entrectinib for the treatment of *ROS1* fusion-positive locally advanced or metastatic NSCLC patients. On June 25, a teleconference meeting was held in which FDA informed the sponsor that the submitted data do not appear to demonstrate a substantial improvement of a clinically significant endpoint(s) over available therapy for the proposed indication, as required for BTDR. The ORR of 75% (95% CI: 63, 85), as assessed by independent review committee (IRC), was similar to that observed with crizotinib (ORR per IRC 66%), and the lower limit of the 95% CI did not exclude the ORR observed with crizotinib. Regarding intracranial ORR, data were available for only 16 patients with measurable CNS lesions at baseline; the CNS ORR in this subgroup of patients was 75% (CI: 48, 93). Data on the actual proportion of patients with CNS duration of response of ≥ 6 months and

≥12 months was unavailable during the discussion. Given the totality of the submitted data, FDA communicated to the sponsor that the reported results are unlikely to support BTD as there does not appear to be a transformative improvement over available therapy.

On June 12, 2018, Ignyta transferred sponsorship of IND 135124, and all rights and responsibilities related to the IND application to Genentech.

On August 9, 2018 FDA notified Genentech that the information required for the complete transfer of the orphan drug application (#14-4629) had been submitted.

On August 17, 2018, Genentech submitted a pre-NDA (clinical) meeting request to obtain Agency feedback on the planned NDA submission for entrectinib for the treatment of *ROS1*-positive (b)(4) metastatic NSCLC. The meeting package was received on September 18, 2018. FDA sent Preliminary Comments to Genentech on October 12, 2018.

CMC

IND 135124 cross references IND 120500, for a significant portion of the CMC developmental data. In IND 120500, Genentech stated that the drug product formulation, F06, is the intended commercial product. Formulation F06 is an immediate-release hydroxypropyl methylcellulose capsule available in 100 mg and 200 mg strengths. The two strengths are manufactured (b)(4). The formulations use United States Pharmacopeia/National Formulary compendial excipients and none of the excipients are novel. The drug product does not contain overages or overfills.

Nonclinical

Entrectinib is a pan-TRK, ROS1, and ALK kinase inhibitor. Based on information from the meeting package, Genentech has conducted repeat dose toxicology studies of up to 13 weeks in duration in dogs and rats, a full genotoxicity battery, a phototoxicity study, and several pharmacology studies including safety pharmacology studies for CNS, cardiovascular, and respiratory toxicity. An assessment of embryofetal toxicity was conducted in pregnant rats, and Genentech does not plan an additional study as the results were positive for embryofetal defects. In addition, a 13-week study was conducted in juvenile rats to characterize the toxicity in developing animals.

Clinical

Integrated Data Intended to support an NDA for entrectinib

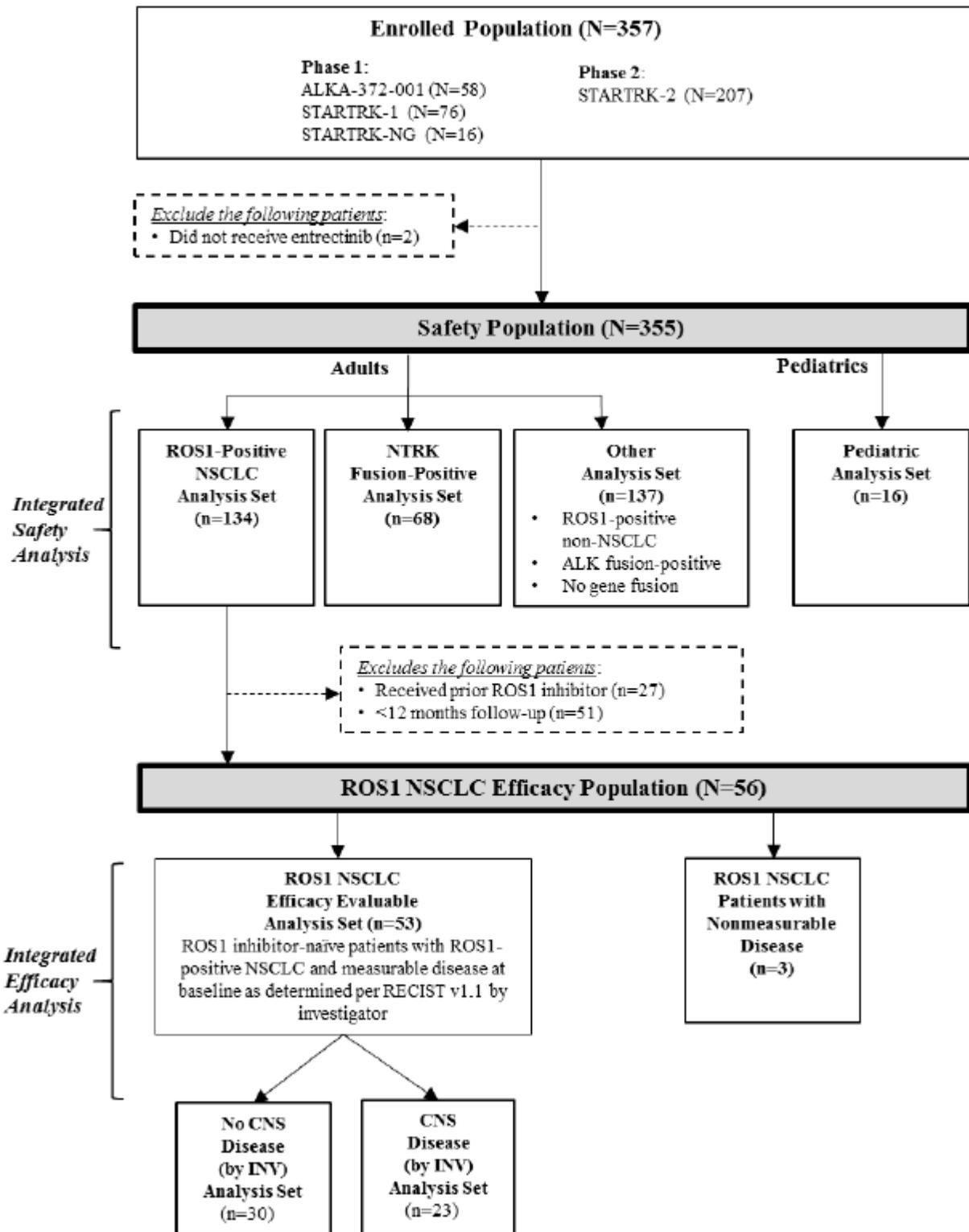
The safety and effectiveness of entrectinib for the treatment of *ROS1*-positive NSCLC and other *ROS1*-positive solid tumors is being studied in four ongoing clinical trials - ALKA-372-001, STARTRK-1, STARTRK-2, and Study RXDX-101-03/CO40778 (STARTRK-Next Generation [NG]).

- ALKA-372-001 is a FIH, open-label, multicenter, dose-escalation trial in sequential cohorts evaluating three different dosage schedules of entrectinib in adult patients with

locally advanced or metastatic solid tumors with identified molecular alterations of *NTRK*, *ROS1*, and *ALK*.

- STARTRK-1 is an open-label, multicenter, dose-escalation study, conducted in the U.S. and South Korea, evaluating entrectinib 600 mg once daily in adult patients with locally advanced or metastatic solid tumors with identified molecular alterations of *NTRK*, *ROS1*, or *ALK* molecular alterations.
- STARTRK-2 is an open-label, multicenter, global basket study of entrectinib for the treatment of patients with solid tumors that harbor an *NTRK*, *ROS1*, or *ALK* gene rearrangement. Patients are screened for gene rearrangement based on results from nucleic acid-based diagnostic testing methodologies for gene fusions, including Ignyta's Trailblaze Pharos and Foundation Medicine, Inc.'s Foundation One (laboratory developed test), as well as testing from local laboratories.
- STARTRK-NG is a single-arm, open-label, dose escalation and expansion study of entrectinib in children, adolescents, and young adults with recurrent or refractory solid tumors and primary CNS tumors, with or without *TRK*, *ROS1* or *ALK* fusions.

Genentech states that the planned NDA will contain pooled efficacy results from patients with *ROS1*-positive NSCLC who were enrolled in ALKA-372-001, STARTRK-1, or STARTRK-2 (see Figure 1 below).



Source: Figure 1 of the Meeting Package, pg. 20

The primary efficacy data intended were obtained in 53 “efficacy evaluable” patients (see Table 1) with *ROS1* fusion-positive, *ROS1* kinase inhibitor-naïve, metastatic NSCLC. The “efficacy evaluable” population is defined by Genentech as those patients who have not received a *ROS1* kinase inhibitor, have metastatic *ROS1* fusion-positive NSCLC with measurable disease per RECIST v1.1 by investigator assessment, received at least one dose of entrectinib, and have a follow-up duration of ≥ 12 months. The proposed NDA will include safety data from at least 355 patients who received at least one dose of entrectinib across ALKA-372-001, STARTRK-1, STARTRK-2, and STARTRK-NG, including 134 patients with *ROS1* fusion-positive NSCLC.

The meeting package presents the summary efficacy results based on a data cutoff date of May 31, 2018 (database lock / clinical cutoff date July 31, 2018).

In the “efficacy evaluable” population of 53 patients, the BICR-assessed ORR was 77.4% (95% CI: 63.8, 87.7), including three complete responses (CR 5.7%). The Kaplan-Meier (KM)-estimated median DOR per BICR-assessment is 24.6 months (95% CI: 11.4, 34.8). Genentech also presents an analysis of BICR-assessed ORR in the “as-treated” population (limited to patients with a follow-up duration of ≥ 12 months) which includes 3 patients determined to have non-measurable disease at baseline per investigator in addition to the 53 patients included in the “efficacy evaluable” population. In this “as-treated” population that is consistent with the FDA-defined primary analysis population as described in the May 18, 2017 meeting minutes, the BICR-assessed ORR is 75.0% (95% CI: 61.6, 85.6) and KM-estimated median DOR is 19.0 months (95% CI: 12.6, 34.8).

While ORR as assessed by investigator [75.5% (95% CI: 61.7, 86.2)] was similar to the BICR-assessed ORR, the KM-estimated median DOR per investigator assessment was 16.6 months (95% CI: 13.1, 21.4).

Genentech also presents BICR-assessed intracranial response data for 20 patients from the efficacy evaluable population determined to have CNS disease at baseline per BICR. The BICR-assessed intracranial ORR (IC-ORR) was reported to be 55% (95% CI: 31.5, 76.9). The IC-ORR among 12 patients with measurable CNS disease at baseline is 75.0% (95% CI: 42.8, 94.5).

A high-level summary of safety, abstracted from slides provided by Genentech, is presented in Table 3.

Table 3: Entrectinib Safety Summary

Patients w/	NTRK SE (N=68)	ROS-1 NSCLC SE (N=134)	Pediatric SE (N=16)	SE (N=355)
AE	68 (100.0%)	134 (100.0%)	16 (100.0%)	353 (99.4%)
Related AE	61 (89.7%)	125 (93.3%)	16 (100.0%)	325 (91.5%)
Serious AE	32 (47.1%)	50 (37.3%)	2 (12.5%)	137 (38.6%)
Related SAE	7 (10.3%)	15 (11.2%)	1 (6.3%)	30 (8.5%)
NCI-CTCAE ≥3 AE	50 (73.5%)	82 (61.2%)	8 (50.0%)	217 (61.1%)
Related NCI-CTCAE ≥3 AE	29 (42.6%)	46 (34.3%)	3 (18.8%)	110 (31.0%)
AE leading to Discon	9 (13.2%)	12 (9.0%)	1 (6.3%)	30 (8.5%)
Related AE leading to Discon	3 (4.4%)	6 (4.5%)	0	14 (3.9%)
AE leading to Dose Reduction	28 (41.2%)	46 (34.3%)	4 (25.0%)	100 (28.2%)
Related AE leading to Dose Reduction	27 (39.7%)	45 (33.6%)	4 (25.0%)	97 (27.3%)
AE Leading to Interruption	38 (55.9%)	60 (44.8%)	0	163 (45.9%)
AE leading to Death	6 (8.8%)	9 (6.7%)	0	20 (5.6%)

SE, safety evaluable population
Source: Genentech's Topline slides

The most common adverse events in the integrated safety population (n=355), occurring in ≥25% of patients, were constipation (46%), dysgeusia (44%), fatigue (38%), dizziness (35%), diarrhea, 35%), nausea (34%), dyspnea (30%), peripheral edema (29%), and anemia (28%). Grade ≥3 adverse events occurring in ≥5% of patients were anemia (11%), weight gain (7%), and dyspnea (6%). The most commonly reported serious adverse events (occurring in ≥2% of patients) were pneumonia (3.9%), dyspnea (3.7%), pleural effusion (3.4%), pulmonary embolism (2.3%), and pyrexia (2.0%).

DISCUSSION

GENERAL COMMENTS

FDA will not be able to reach agreements with Genentech on the contents of a complete application for an NDA for entrectinib for ROS1-positive, (b) (4) metastatic NSCLC (IND 135124) and for entrectinib for the treatment of NTRK fusion-positive, (b) (4) (b) (4) metastatic solid tumors in adult and pediatric patients, (b) (4) (b) (4) who have either progressed (b) (4) (IND 120500) under the PDUFA VI program, because the pre-NDA meeting for discussion of quality components has not been held. We acknowledge that a separate pre-NDA CMC Only meeting to discuss quality components for both NDAs is scheduled for November 7, 2018. During this meeting FDA and Genentech will need to reach agreement on the CMC, Clinical, Nonclinical, and Clinical Pharmacology information necessary to allow each NDA to be considered complete, reach agreement on the submission of late

components for each NDA, if any are planned, and to discuss the preliminary assessment of the need for a REMS.

Clinical/Statistics

Genentech's Background to Question 1 is provided on pages 34-35 of the meeting background document:

1. *Does the Agency agree that the available clinical data package provides sufficient clinical evidence to characterize the benefit and risk of entrectinib in patients with ROS1-positive (b)(4) metastatic NSCLC to support NDA filing?*

FDA's Response sent 10/12/18: The clinical data package intended to support an NDA filing for entrectinib for the treatment of patients with ROS1-positive metastatic NSCLC should include ORR data for all 134 entrectinib-treated patients (across ALKA-372-001, STARTRK-1, STARTRK-2) with ROS1-positive NSCLC.

The proposal to provide ORR and DOR in the population described on page 7 of the meeting package, in which Genentech states that ORR will be summarized "In 53 patients with ROS1-positive NSCLC who were followed for a minimum of 12 months from first response..." is acceptable only if Genentech also provides data from the first 56 patients with ROS1 inhibitor-naïve, ROS1-positive NSCLC-treated, in whom all responders had a follow-up duration of at least 12 months from the onset of response.

While the final wording of the indication is a review issue, FDA notes that the currently available data are (b)(4) >90% of patients with ROS1-positive NSCLC enrolled to the relevant studies had metastatic disease. In addition, FDA notes that efficacy data will focus on patients who are ROS1 kinase inhibitor naïve and does not stipulate that the patients must be identified by an FDA-approved test. The final indication will consider the totality of the evidence and any tests necessary for selection of the indicated population.

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback.

As previously agreed with the Agency at the Type C meeting on July 26, 2017, the efficacy analysis population should have a minimum of 12 months follow up from the onset of first response. Following this criterion, the Sponsor plans to submit data from 53 patients with measurable disease at baseline as the primary analysis population defined in the integrated SAP, as well as data from 3 additional patients with non-measurable disease to constitute the As-Treated population of 56 patients.

We would like to clarify that the 134 ROS1-positive NSCLC patients in the integrated safety population include (see updated Figure below):

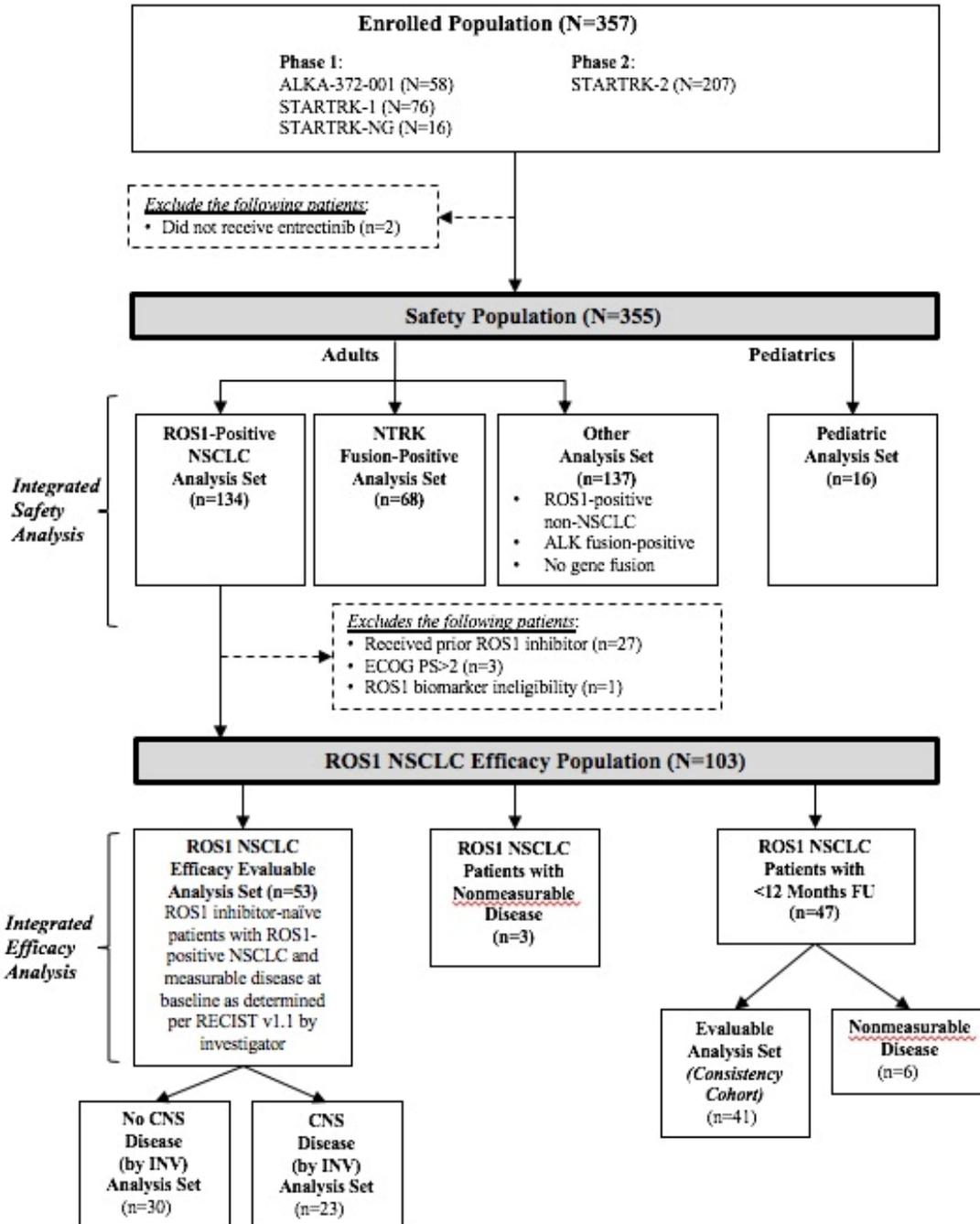
- 27 patients previously treated with crizotinib who were not expected to derive as much clinical benefit from entrectinib, as the likely mechanism of primary resistance is similar between the two molecules
- 4 patients who failed to meet eligibility criteria (1 dual oncodriver or 3 ECOG>2)

Therefore, we do not believe that the efficacy analyses for filing should include 134 patients.

In recent discussion with the EMA Rapporteur, the Rapporteur requested provision of more patients with the aim to show consistency with the primary analysis dataset. The Sponsor proposed to submit additional BICR-ORR data from 41 efficacy evaluable patients with less than 12 months of follow up from the onset of first response, for a total of 94 patients in the MAA. These data can also be provided to the Agency in the initial NDA for filing review.

The Sponsor acknowledges that the Agency would like to see more data for the As Treated population and could provide BICR-ORR from a total of 103 patients that includes an additional 47 patients (41 with measurable disease and 6 with non-measurable disease) with less than 12 months follow up in the initial NDA as a sensitivity analysis.

At the October 18, 2018 meeting, the Sponsor would like the Agency to clarify the Agency's purpose for requesting these additional data. Specifically, the Sponsor would like to get clarification that the prescribing information will reflect the efficacy evaluable population of 53 patients with greater than 12 months follow up from the onset of first response.



Discussion during the 10/18/18 Meeting: FDA requested an analysis of efficacy in all 134 patients, but agreed that sensitivity analyses excluding certain groups, as identified by Genentech, should be included in the original NDA submission. Genentech agreed to provide the data in summary analyses as requested. Genentech stated that all patients not meeting the criteria for inclusion in the “efficacy evaluable” population will be flagged for the specific deviation.

Genentech's Background to Question 2 is provided on pages 35-36 of the meeting background document:

2. *Does the Agency agree with the proposal to submit updated safety and efficacy data in the 90 Day Safety Update and that the new data would not impact the PDUFA date? Specifically, the Applicant proposes to submit:*

- *An additional 5 months of safety follow-up for patients in the original NDA dataset*
- *Updated DOR in responders in the original NDA dataset*

FDA's Response sent 10/12/18: FDA does not object to the proposal to submit updated safety and efficacy data in the 90 Day Safety Update, provided that the efficacy update also includes the updated BICR-assessed duration of response for all 134 entrectinib treated patients with *ROS1*-positive NSCLC. In general, this submission of additional safety data would not be expected to impact the PDUFA date. However, depending on the extent of the additional data and need for more extensive review there is the possibility of an extension of the PDUFA date via major amendment.

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback.

Based on the Sponsor's response to the Agency's comment to Question 1, the Sponsor proposes to submit updated DOR data for the efficacy patients in the initial submission that will be agreed upon at the October 18, 2018 meeting. The Sponsor would like to highlight that not all of the patients will have at least 12 months of follow up from the onset of first response.

In order to provide consistent updated safety data with the NTRK NDA (as the same safety dataset is applicable for both entrectinib NDAs), the same clinical cut-off date will be used for the safety update reports for both NDAs.

Discussion during the 10/18/18 Meeting: FDA prefers to receive updated DOR data for all 134 patients in the original NDA submission, as data beyond the primary efficacy evaluable population might be considered by FDA for inclusion in the labeling. However, FDA stated that if only updated DOR is provided for the 56 patients in the primary analysis population, this will be reflected in the product labeling.

Genentech's Background to Question 3 is provided on pages 36-37 of the meeting background document:

Regulatory

3. *For the proposed ROS1-positive tumor indication, does the Agency agree that the results provide substantial evidence of positive benefit-risk of entrectinib for the treatment of patients with ROS1-positive [REDACTED] ^{(b) (4)} metastatic NSCLC to support regular approval?*

FDA's Response sent 10/12/18: A determination regarding whether the available data provide substantial evidence of effectiveness and support a positive benefit-risk assessment for the treatment of patients with ROS1-positive metastatic NSCLC will be made at the time of NDA review. The proposed NDA also should contain data characterizing the natural history of patients with ROS1 fusion NSCLC tumor and justification supporting a conclusion that the reported BICR-assessed ORR and DOR provide evidence of direct clinical benefit in the indicated population, considering the natural history of the disease and available therapy.

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback. No further discussion at the meeting is needed.

Discussion during the 10/18/18 Meeting: There was no further discussion of this item during the meeting.

Genentech's Background to Question 4 is provided on pages 38-39 of the meeting background document:

4. *The Applicant plans to submit two entrectinib NDAs simultaneously, one for the ROS1-positive NSCLC indication and the other for the NTRK fusion-positive solid tumor indication. Thus, two separate Pre-NDA meeting requests are being submitted to discuss the two indications.*
- a) *Nonclinical, clinical pharmacology and companion diagnostic (CDx) questions that are common to both NDAs will be addressed at the NTRK Pre-NDA meeting. Does the Agency agree that FDA feedback on these common NDA components from the NTRK Pre-NDA meeting would also apply to the ROS1-positive NSCLC NDA?*

FDA's Response sent 10/12/18: Any comments regarding the nonclinical program and data to be submitted in support of entrectinib for the treatment of patients with NTRK-positive tumors are likely to be applicable to this indication. FDA feedback on clinical pharmacology questions for both NDAs will be provided during the October 17, 2018 meeting and will be based on the information provided in pre-NDA meeting package submitted to IND 120500.

FDA feedback on companion diagnostic assay questions for both NDAs will be provided during the October 17, 2018 meeting and will be based on the information provided in pre-NDA meeting package submitted to IND 120500. However, please note that data relevant to companion diagnostic test linked to the proposed indication for entrectinib of the treatment of patients with *ROS1*-positive (b) (4) metastatic NSCLC should be submitted to the NDA containing the clinical efficacy data for this indication.

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback. Per FDA, the Sponsor plans to seek clarification on the companion diagnostic assay for both NTRK and ROS NDAs during the October 17, 2018 meeting.

Discussion during the 10/18/18 Meeting: FDA agreed that data relevant to the companion diagnostic test, which is linked to the proposed indication for entrectinib of the treatment of patients with *ROS1*-positive (b) (4) metastatic NSCLC, should be submitted to the PMA containing the clinical efficacy data for this indication.

FDA stated that the proposal to use the total nucleic acid samples in the concordance study and for clinical bridging will be at Genentech's risk given the limited number of samples. The adequacy of the data will be a review issue for the PMA.

Genentech acknowledged FDA's feedback in the preliminary responses for the October 17, 2018 meeting for IND 120500 regarding the simulations and sensitivity analyses for the feasibility of the bridging study. As captured in Genentech's responses for the October 17, 2018 meeting, this will be further discussed at the pre-submission meeting on November 1, 2018.

- b) *Does the Agency agree that the planned NDA for ROS1-positive NSCLC can cross-reference to common sections of the NDA for NTRK fusion-positive solid tumors via a statement of cross-reference in Module 1.4.4?*

FDA's Response sent 10/12/18: The plan to cross reference the data in sections 2.3, 2.4, 2.6, 2.7.1, and Modules 3 and 4 are acceptable. The proposal to cross-reference section 2.7.2 and certain sections of Module 5 for clinical pharmacology information may not be acceptable. Clinical pharmacology data which are specific to the proposed indication being sought under this planned NDA supported by data in IND 135124 should be submitted in this NDA. Examples of such data include Exposure/Response analysis in patients with *ROS1*-positive NSCLC. Please provide further clarification regarding how clinical pharmacology data specific to each indication will be distinguished in the planned application to ensure that FDA is able to find all relevant data for each proposed indication.

Genentech's Response received via email 10/16/18: We agree to submit clinical pharmacology data specific to ROS1 in this NDA and we will provide a Reviewer's Guide to distinguish clinical pharmacology data specific to each indication.

FDA's Response sent 10/12/18: FDA referred to Genentech's response to Question 4b agreeing to provide the relevant clinical pharmacology data for the ROS1 indication in this NDA. Such data will include results from the following study: exposure-response (ER) analysis for efficacy in patients with ROS1 NSCLC, and a justification of the proposed dose for the ROS1 NSCLC indication.

- c) *The Applicant plans to request Priority Review for both NDAs. As the NDAs will have many sections in common and differences will primarily be the efficacy sections to support the different indications, does the Agency foresee that the review of both NDAs would be coordinated such that regulatory action date could be the same for both NDAs?*

FDA's Response sent 10/12/18: A determination regarding review designation will be made following submission of the NDA based upon review of Genentech's rationale supporting a request for Priority review.

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback. No further discussion is needed.

Discussion during the 10/18/18 Meeting: There was no further discussion of this item during the meeting.

- d) *The Applicant plans to request to enable rolling review of the NTRK NDA in order to allow finalization of the CMC sections. As the same CMC sections apply to both the NTRK and ROS1 NDAs, the ROS1 NDA plans to cross reference Modules 2.3 and 3 in the NTRK NDA. Does the Agency agree that the rolling submission schedule proposed in the NTRK Pre-NDA meeting package will also apply to the ROS1 NDA?*

FDA's Response sent 10/12/18: Since entrectinib has not received fast track designation nor breakthrough designation for the treatment of ROS1-positive NSCLC, Genentech is not eligible to submit an NDA under the provisions of a rolling review.

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback. No further discussion is needed.

Discussion during the 10/18/18 Meeting: There was no further discussion of this item during the meeting.

Genentech's Background to Question 5 is provided on pages 39-40 of the meeting background document:

5. *The proposed content of the NDA application is provided in Appendix 7. The Applicant does not plan to submit any minor components within 30 days after the original NDA submission. Does the Agency agree that the proposed content constitutes a complete NDA application?*

FDA's Response sent 10/12/18: FDA will evaluate whether the proposed content of section 2.3 and Module 3 meets the criteria of a complete application with respect to the Quality data during the CMC Only pre-NDA meeting scheduled for November 7, 2018 under IND 120500.

FDA will evaluate whether the proposed content of section 2.4 and Module 4 meets the criteria of a complete application with respect to the nonclinical pharmacology/toxicology data during the pre-NDA meeting scheduled for October 17, 2018 under IND 120500.

FDA will also evaluate whether the proposed content of sections 2.7.1 and 2.7.2 and Module 5 meets the criteria of a complete application with respect to the clinical pharmacology data during the pre-NDA meeting scheduled for October 17, 2018 under IND 120500 and during the meeting to be held on October 18, 2018 under IND 135124.

With regard to the clinical and statistical portion of the NDA supporting the proposed indication, the proposed content is generally acceptable provided that Genentech's responses as discussed during the meeting for Questions 1 and 3 are acceptable.

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback. No further discussion is needed.

Discussion during the 10/18/18 Meeting: There was no further discussion of this item during the meeting.

ADDITIONAL FDA COMMENTS SENT TO GENENTECH ON 10/12/18

Statistics

6. Confirm that the datasets that integrate efficacy and safety data across the studies supporting the planned NDA contain a variable that indicates the study source of each row of information.

Genentech's Response received via email 10/16/18: Genentech confirms that the integrated datasets for efficacy and safety contain a variable that indicates the study source of each row of information.

Discussion during the 10/18/18 Meeting: FDA acknowledged the responses and had no additional comments.

7. Confirm that the NDA will contain all SAS programs used to create the derived datasets for the efficacy endpoints and all SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs in the NDA submission.

Genentech's Response received via email 10/16/18: Genentech confirms that readable SAS programs and associated macros used for the efficacy endpoints and efficacy data analysis for the phase 2 study STARTRK-2 will be provided in the NDA and that the SAS programs for the phase 1 studies ALK-A, STARTRK-1, STARTRK-NG, ISS, and ISE will be provided upon request. This plan was agreed to with the Agency in an Advice/Information Request dated 17 July 2018 for IND 120500 with respect to the NDA for entrectinib for the treatment of NTRK-fusion positive solid tumors.

Discussion during the 10/18/18 Meeting: FDA acknowledged the responses and had no additional comments.

8. Confirm that the NDA will contain SAS programs for all derived datasets and analyses for all results presented in the proposed package insert.

Genentech's Response received via email 10/16/18: Genentech confirms that the NDA will contain readable SAS programs for all derived datasets and analyses for all efficacy and safety results presented in the proposed package insert.

Discussion during the 10/18/18 Meeting: FDA acknowledged the responses and had no additional comments.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

Genentech's Response received via email 10/16/18: Genentech believes a REMS is not needed, but acknowledges that the determination for a need for a REMS will be a review issue.

Genentech plans to propose in the entrectinib USPI, Warnings and Precautions for:

- Congestive Heart Failure
- QTc Interval Prolongation
- Cognitive Disorders
- (b) (4)
- Embryo-fetal toxicity

Based on the analysis of the nature, severity, and outcomes of these events the Sponsor plans to provide guidance for these events including a description of the events, monitoring, and guidance

for dose modification or discontinuation. At this time the Sponsor does not believe additional risk mitigation activities, such as a REMS, is required. Does the Agency agree?

Discussion during the 10/18/18 Meeting:

- A preliminary discussion of the content of a complete application occurred and preliminary agreements were reached regarding the non-clinical, clinical pharmacology, and clinical/statistical sections of the planned NDA. Final agreements on the content of a complete application will be reached during the November 7, 2018 CMC Only pre-NDA meeting.
- Genentech confirmed that the NDA for the proposed indication for the treatment of patients with *ROS1*-positive, (b) (4) metastatic, NSCLC will include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion on the need for a REMS was held; based on information currently available, FDA stated that a REMS will not be required in order to file the planned NDA. FDA will make a final determination regarding the need for a REMS during the review of the NDA for entrectinib for the proposed indication of the treatment of patients with *ROS1*-positive, (b) (4) metastatic NSCLC. FDA acknowledged Genentech's proposal for product labeling and recommended that justification be provided in the NDA if subsections for hepatotoxicity and interstitial lung disease (ILD) are not included in the Warnings and Precautions section of the proposed prescribing information.
- Genentech confirmed that major components of the application will be submitted with the original application submission and that the cross-referenced sections contained in the NDA for the proposed indication for the treatment of NTRK fusion-positive, (b) (4) metastatic solid tumors in adult and pediatric patients who have either progressed (b) (4), will be submitted prior to or on the same day as the NDA for entrectinib for the proposed indication of the treatment of patients with *ROS1*-positive, (b) (4) metastatic NSCLC.
- Genentech confirmed that they will submit a complete application; therefore, there were no agreements for late submission of minor application components.

As noted above, FDA will reach agreement on the contents of a complete application for the proposed NDA during the CMC pre-NDA meeting scheduled for November 7, 2018; a summary of final agreements will be reached at this meeting and will be documented in the minutes for the November 7, 2018 meeting.

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.

Because entrectinib was granted orphan designation for *ROS1*-positive NSCLC, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your NDA application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

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.”

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.				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>

ISSUES REQUIRING FURTHER DISCUSSION

As discussed above, a CMC Only meeting for entrectinib is scheduled for November 7, 2018. A summary of agreements on the content of a complete application will be reached at that meeting and documented in the meeting minutes.

ACTION ITEMS

There were no action items identified during the meeting.

ATTACHMENTS AND HANDOUTS

“Pre-NDA ROS1 Responses to Preliminary Comments_final.pdf”

**RESPONSE TO FDA REQUEST FOR ADDITIONAL INFORMATION
RECEIVED ON 12 OCTOBER 2018**

IND 135124

Entrectinib (RO7102122, RXDX-101)

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

October 16, 2018

CONFIDENTIAL

This is a Genentech, Inc. document that contains confidential information. Nothing herein is to be disclosed without written consent from Genentech, Inc.

Genentech proposes to further discuss the below questions at the Type B Pre-NDA meeting in the following sequence:

Clinical

Question 1

Does the Agency agree that the available clinical data package provides sufficient clinical evidence to characterize the benefit and risk of entrectinib in patients with ROS1-positive (b) (4) metastatic NSCLC to support a NDA filing?

FDA Response

The clinical data package intended to support an NDA filing for entrectinib for the treatment of patients with ROS1-positive metastatic NSCLC should include ORR data for all 134 entrectinib-treated patients (across ALKA-372-001, STARTRK-1, STARTRK-2) with ROS1-positive NSCLC.

The proposal to provide ORR and DOR in the population described on page 7 of the meeting package, in which Genentech states that ORR will be summarized “In 53 patients with ROS1-positive NSCLC who were followed for a minimum of 12 months from first response...” is acceptable only if Genentech also provides data from the first 56 patients with ROS1 inhibitor-naïve, ROS1-positive NSCLC-treated, in whom all responders had a follow-up duration of at least 12 months from the onset of response.

While the final wording of the indication is a review issue, FDA notes that the currently available data are (b) (4)

(b) (4) >90% of patients with ROS1-positive NSCLC enrolled to the relevant studies had metastatic disease. In addition, FDA notes that efficacy data will focus on patients who are ROS1 kinase inhibitor naïve and does not stipulate that the patients must be identified by an FDA-approved test. The final indication will consider the totality of the evidence and any tests necessary for selection of the indicated population.

Genentech Response

Genentech acknowledges the Agency’s feedback.

As previously agreed with the Agency at the Type C meeting on July 26, 2017, the efficacy analysis population should have a minimum of 12 months follow up from the onset of first response. Following this criterion, the Sponsor plans to submit data from 53 patients with measurable disease at baseline as the primary analysis population defined in the integrated SAP, as well as data from 3 additional patients with non-measurable disease to constitute the As-Treated population of 56 patients.

We would like to clarify that the 134 ROS1-positive NSCLC patients in the integrated safety population include (see updated Figure below):

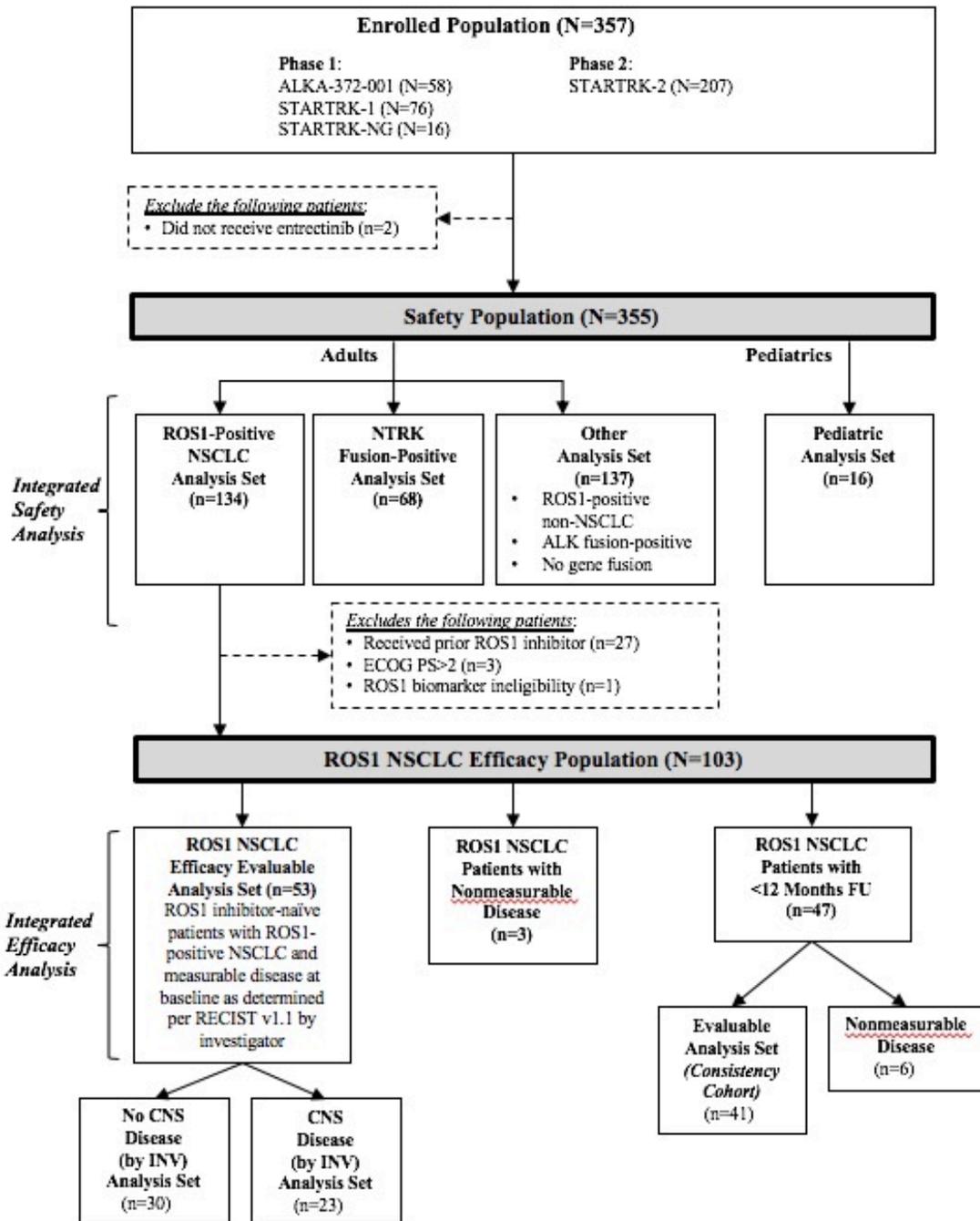
- 27 patients previously treated with crizotinib who were not expected to derive as much clinical benefit from entrectinib as the likely mechanism of primary resistance is similar between the two molecules
- 4 patients who failed to meet eligibility criteria (1 dual oncodriver or 3 ECOG>2)

Therefore, we do not believe that the efficacy analyses for filing should include 134 patients.

In recent discussion with the EMA Rapporteur, the Rapporteur requested provision of more patients with the aim to show consistency with the primary analysis dataset. The Sponsor proposed to submit additional BICR-ORR data from 41 efficacy evaluable patients with less than 12 months of follow up from the onset of first response, for a total of 94 patients in the MAA. These data can also be provided to the Agency in the initial NDA for filing review.

The Sponsor acknowledges that the Agency would like to see more data for the As Treated population and could provide BICR-ORR from a total of 103 patients that includes an additional 47 patients (41 with measurable disease and 6 with non-measurable disease) with less than 12 months follow up in the initial NDA as a sensitivity analysis.

At the October 18, 2018 meeting, the Sponsor would like the Agency to clarify the Agency's purpose for requesting these additional data. Specifically, the Sponsor would like to get clarification that the prescribing information will reflect the efficacy evaluable population of 53 patients with greater than 12 months follow up from the onset of first response.



Question 2

Does the Agency agree with the proposal to submit updated safety and efficacy data in the 90 Day Safety Update and that the new data would not impact the PDUFA date? Specifically, the Applicant proposes to submit:

- an additional 5 months of safety follow-up for patients in the original NDA dataset
- updated DOR in responders in the original NDA dataset

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FDA Response

FDA does not object to the proposal to submit updated safety and efficacy data in the 90 Day Safety Update, provided that the efficacy update also includes the updated BICR-assessed duration of response for all 134 entrectinib treated patients with ROS1-positive NSCLC. In general, this submission of additional safety data would not be expected to impact the PDUFA date. However, depending on the extent of the additional data and need for more extensive review there is the possibility of an extension of the PDUFA date via major amendment.

Genentech Response

Genentech acknowledges the Agency's feedback.

Based on the Sponsor's response to the Agency's comment to Question 1, the Sponsor proposes to submit updated DOR data for the efficacy patients in the initial submission that will be agreed upon at the October 18, 2018 meeting. The Sponsor would like to highlight that not all of the patients will have at least 12 months of follow up from the onset of first response.

In order to provide consistent updated safety data with the NTRK NDA (as the same safety dataset is applicable for both entrectinib NDAs), the same clinical cut-off date will be used for the safety update reports for both NDAs.

Regulatory

Question 3

For the proposed ROS1-positive tumor indication, does the Agency agree that the results provide substantial evidence of positive benefit-risk of entrectinib for the treatment of patients with ROS1-positive [REDACTED] (b) (4) metastatic NSCLC to support regular approval?

FDA Response

A determination regarding whether the available data provide substantial evidence of effectiveness and support a positive benefit-risk assessment for the treatment of patients with ROS1-positive metastatic NSCLC will be made at the time of NDA review. The proposed NDA also should contain data characterizing the natural history of patients with ROS1 fusion NSCLC tumor and justification supporting a conclusion that the reported BICR-assessed ORR and DOR provide evidence of direct clinical benefit in the indicated population, considering the natural history of the disease and available therapy.

Genentech Response

Genentech acknowledges the Agency's feedback. No further discussion at the meeting is needed.

Question 4

The Applicant plans to submit two entrectinib NDAs simultaneously, one for the ROS1-positive NSCLC indication and the other for the NTRK fusion-positive solid tumor indication. Thus, two separate Pre-NDA meeting requests are being submitted to discuss the two indications.

- a) Nonclinical, clinical pharmacology and companion diagnostic (CDx) questions that are common to both NDAs will be addressed at the NTRK Pre-NDA meeting. Does the Agency agree that FDA feedback on these common NDA components from the NTRK Pre-NDA meeting would also apply to the ROS1-positive NSCLC NDA?*
- b) Does the Agency agree that the planned NDA for ROS1-positive NSCLC can cross-reference to common sections of the NDA for NTRK fusion-positive solid tumors via a statement of cross-reference in Module 1.4.4?*
- c) The Applicant plans to request Priority Review for both NDAs. As the NDAs will have many sections in common and differences will primarily be the efficacy sections to support the different indications, does the Agency foresee that the review of both NDAs would be coordinated such that regulatory action date could be the same for both NDAs?*
- d) The Applicant plans to request a rolling review of the NTRK NDA in order to allow finalization of the CMC sections. As the same CMC sections apply to both the NTRK and ROS1 NDAs, the ROS1 NDA plans to cross-reference Modules 2.3 and 3 in the NTRK NDA. Does the Agency agree that the rolling submission schedule proposed in the NTRK Pre-NDA meeting package will also apply to the ROS1 NDA?*

FDA Response

- a) Any comments regarding the nonclinical program and data to be submitted in support of entrectinib for the treatment of patients with NTRK positive tumors are likely to be applicable to this indication. FDA feedback on clinical pharmacology questions for both NDAs will be provided during the October 17, 2018 meeting and will be based on the information provided in pre- NDA meeting package submitted to IND 120500.

FDA feedback on companion diagnostic assay questions for both NDAs will be provided during the October 17, 2018 meeting and will be based on the information provided in pre-NDA meeting package submitted to IND 120500. However, please note that data relevant to companion diagnostic test linked to the proposed indication for entrectinib of the treatment of patients with ROS1-positive (b) (4) metastatic NSCLC should be submitted to the NDA containing the clinical efficacy data for this indication.

- b) The plan to cross reference the data in sections 2.3, 2.4, 2.6, 2.7.1, and Modules 3 and 4 are acceptable. The proposal to cross-reference section 2.7.2 and certain sections of Module 5 for clinical pharmacology information may not be acceptable. Clinical pharmacology data which are specific to the proposed indication being sought under this planned NDA supported by data in IND

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135124 should be submitted in this NDA. Examples of such data include Exposure/Response analysis in patients with ROS1-positive NSCLC.

Please provide further clarification regarding how clinical pharmacology data specific to each indication will be distinguished in the planned application to ensure that FDA is able to find all relevant data for each proposed indication.

- c) A determination regarding review designation will be made following submission of the NDA based upon review of Genentech's rationale supporting a request for Priority review.
- d) Since entrectinib has not received fast track designation nor BTB for the treatment of ROS1-positive NSCLC, Genentech is not eligible to submit an NDA under the provisions of a rolling review.

Genentech Response

- a) Genentech acknowledges the Agency's feedback. Per FDA, the Sponsor plans to seek clarification on the companion diagnostic assay for both NTRK and ROS NDAs during the October 17, 2018 meeting.
- b) We agree to submit clin pharm data specific to ROS1 in this NDA and we will provide a Reviewer's Guide to distinguish clinical pharmacology data specific to each indication.
- c) Genentech acknowledges the Agency's feedback. No further discussion is needed.
- d) Genentech acknowledges the Agency's feedback. No further discussion is needed.

Question 5

The proposed content of the NDA application is provided in Appendix 7. The Applicant does not plan to submit any minor components within 30 days after the original NDA submission. Does the Agency agree that the proposed content constitutes a complete NDA application?

FDA Response

FDA will evaluate whether the proposed content of section 2.3 and Module 3 meets the criteria of a complete application with respect to the Quality data during the CMC Only pre-NDA meeting scheduled for November 7, 2018 under IND 120500.

FDA will evaluate whether the proposed content of section 2.4 and Module 4 meets the criteria of a complete application with respect to the nonclinical pharmacology/toxicology data during the pre-NDA meeting scheduled for October 17, 2018 under IND 120500.

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FDA will also evaluate whether the proposed content of sections 2.7.1 and 2.7.2 and Module 5 meets the criteria of a complete application with respect to the clinical pharmacology data during the pre-NDA meeting scheduled for October 17, 2018 under IND 120500 and during the meeting to be held on October 18, 2018 under IND 135124.

With regard to the clinical and statistical portion of the NDA supporting the proposed indication, the proposed content is generally acceptable provided that Genentech's responses as discussed during the meeting for Questions 1 and 3 are acceptable.

Genentech Response

Genentech acknowledges the Agency's feedback. No further discussion is needed.

Additional FDA Comments

6. Confirm that the datasets that integrate efficacy and safety data across the studies supporting the planned NDA contain a variable that indicates the study source of each row of information.
7. Confirm that the NDA will contain all SAS programs used to create the derived datasets for the efficacy endpoints and all SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs in the NDA submission.
8. Confirm that the NDA will contain SAS programs for all derived datasets and analyses for all results presented in the proposed package insert.

Genentech Response

6. Genentech confirms that the integrated datasets for efficacy and safety contain a variable that indicates the study source of each row of information.
7. Genentech confirms that readable SAS programs and associated macros used for the efficacy endpoints and efficacy data analysis for the phase 2 study STARTRK-2 will be provided in the NDA and that the SAS programs for the phase 1 studies ALK-A, STARTRK-1, STARTRK-NG, ISS, and ISE will be provided upon request. This plan was agreed to with the Agency in an Advice/Information Request dated 17 July 2018 for IND 120500 with respect to the NDA for entrectinib for the treatment of NTRK-fusion positive solid tumors.
8. Genentech confirms that the NDA will contain readable SAS programs for all derived datasets and analyses for all efficacy and safety results presented in the proposed package insert.

Discussion of the Contents of a Complete Application

As stated in our September 4, 2018 communication granting this meeting, 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 VI. Therefore, at this meeting be prepared to discuss and reach initial agreement with FDA on the content of a complete application for components other than Quality, 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. Final agreement will be reached at the November 7, 2018, CMC only pre-NDA meeting. 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.

Genentech Response

Genentech believes a REMS is not needed, but acknowledges that the determination for a need for a REMS will be a review issue.

Genentech plans to propose in the entrectinib USPI, Warnings and Precautions for:

- Congestive Heart Failure
- QTc Interval Prolongation
- Cognitive Disorders
-  (b) (4)
- Embryo-fetal toxicity

Based on the analysis of the nature, severity, and outcomes of these events the Sponsor plans to provide guidance for these events including a description of the events, monitoring, and guidance for dose modification or discontinuation. At this time the Sponsor does not believe additional risk mitigation activities, such as a REMS, is required. Does the Agency agree?

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
11/06/2018



IND 120500

MEETING MINUTES

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 Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for entrectinib.

We also refer to the meeting between representatives of your firm and the FDA on October 17, 2018. The purpose of the meeting was to obtain Agency feedback on the planned NDA submission for entrectinib for the proposed indication of the treatment of adult and pediatric patients with *NTRK* fusion-positive (b) (4) metastatic solid tumors whose cancer has progressed (b) (4).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (240) 402-6397.

Sincerely,

{See appended electronic signature page}

Kelie Reece, Ph.D.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:

Meeting Minutes
“Pre-NDA *NTRK* Responses to Preliminary Comments_final.pdf”



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: October 17, 2018, 12:00 PM – 1:00 PM
Meeting Location: White Oak Building 22, Conference Room 1313
Silver Spring, Maryland 20903

Application Number: IND 120500
Product Name: entrectinib
Proposed Indication: Treatment of patients with *NTRK* fusion-positive, (b) (4)
(b) (4) solid tumors whose cancer has progressed
(b) (4)

Sponsor Name: Genentech, Inc.

Meeting Chair: Martha Donoghue, M.D.
Meeting Recorder: Kelie Reece, Ph.D.

FDA ATTENDEES

Patricia Keegan, M.D.	Division Director, DOP2/OHOP
Martha Donoghue, M.D.	Clinical Team Leader, DOP2/OHOP
Leigh Marcus, M.D.	Clinical Reviewer, DOP2/OHOP
Pallavi Mishra-Kalyani, Ph.D.	Statistics Team Leader, DBV/OB
Whitney Helms, Ph.D.	Nonclinical Team Leader, DHOT/OHOP
Claire Myers, Ph.D.	Nonclinical Reviewer, DHOT/OHOP
Jeanne Fourie Zirkelbach, Ph.D.	Clinical Pharmacology Team Leader, DCPV/OCP
Xiling Jiang, Ph.D.	Clinical Pharmacology Reviewer, DCPV/OCP
Yuching Yang, Ph.D.	Clinical Pharmacology Reviewer, DCPV/OCP
Banu Zolnik, Ph.D.	Biopharmaceutics Team Leader, DB/BBI
Parnali Chatterjee, Ph.D.	Biopharmaceutics Reviewer, DB/BBI
Nina Ni, Ph.D.	Product Quality Team Leader, DNDPI/ONDP
Olen Stephens, Ph.D.	Product Quality Reviewer, DNDPI/ONDP
Joyce Weaver, Pharm.D.	Risk Management Analyst, DRISK/OMEPRM
Ozan Aygun, Ph.D.	Scientific Reviewer, CDRH/DMGP/MPCB
Soma Ghosh, Ph.D.	Scientific Reviewer, CDRH/DMGP/MPCB
Jincao Wu, Ph.D.	Mathematical Statistician, CDRH/DBS/DSBII
Dandan Xu, Ph.D.	Mathematical Statistician, CDRH/DBS/DSBII
Monica Hughes, M.A.	Chief, Project Manager Staff, DOP2/OHOP

Stacie Woods, Pharm.D.
Anuja Patel, M.P.H.
Kelie Reece, Ph.D.

Regulatory Health Project Manager, DOP2/OHOP
Lead Regulatory Health Project Manager, DOP2/OHOP
Regulatory Health Project Manager, DOP2/OHOP

SPONSOR ATTENDEES

Genentech

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Caitlyn Gertz, Ph.D.
Charlie Wu, Ph.D.
Mark Merchant, Ph.D.

US Regulatory Affairs
US Regulatory Affairs
Companion Diagnostics
Pharmacology

Ignitya

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Roche

Ekaterina Bassett, Ph.D.
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Todd Riehl, Pharm.D.
Brian Simmons, Pharm.D., M.S.
Chung Ying (Florence) Tao, Ph.D.
Gaurav Tyagi, BV.Sc., Ph.D.
Tim Wilson, Ph.D.
Jean-Philippe Crochard, Ph.D.
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Li Yu, Ph.D.
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Helene Pierre, Ph.D.

Sr Project Leader, Companion Diagnostics
Pediatric Clinical Development Lead
Diplom-Ingenieur Global Regulatory Lead
Technical Regulatory Lead
Biostatistics Lead
Safety Science Lead
Life Cycle Team Lead
Clinical Pharmacology Lead
Global Development Lead
Clinical Scientist
US Regulatory Partner
Nonclinical Toxicology Lead
Biomarkers Lead
Technical Regulatory Lead
Formulation Development
Nonclinical Team Lead
Medical Writing Lead
Regulatory Labeling Lead
European Regulatory Partner
Regulatory Documentation Lead
Clinical Pharmacology Scientist
Pediatric Development Regulatory Lead
Nonclinical Writing Lead

Foundation Medicine

Xiaobo Bai, Ph.D.
David Fabrizio, B.Sc.
Yali Li, Ph.D.

Sr. Regulatory Affairs Associate
Development Franchise Leader
Lead Statistician

Christine Vietz, Ph.D.

VP, Regulatory Affairs

BACKGROUND

This application will be subject to “the Program”. The objective of the pre-New Drug Application (NDA) meeting to be held on October 17, 2018, is to obtain agreement between Genentech, Inc. (Genentech) and the FDA on the content and presentations of data to support the filing of the planned NDA for the following proposed indication with a breakthrough designation (BTD).

Genentech’s Proposed Indication

Genentech is proposing submission of an NDA for the following indication:

Entrectinib is indicated for the treatment of NTRK fusion-positive, (b) (4) metastatic solid tumors in adult and pediatric patients who have either progressed (b) (4).

The pre-meeting package for this October 17, 2018 interdisciplinary pre-NDA meeting, received on September 17, 2018, states that Genentech plans to file two NDAs for entrectinib: one for the treatment of adults with *ROS1*-positive non-small cell lung cancer (NSCLC), in which clinical development occurred under IND 135124, and one for the treatment of adult and pediatric patients with *NTRK* fusion-positive solid tumors, in which clinical development occurred under IND 120500. The pre-meeting package further states that entrectinib will be supplied as an immediate-release hydroxypropyl methylcellulose capsule available in 100 mg and 200 mg strengths. Entrectinib received orphan designation for the “treatment of *NTRK* fusion-positive solid tumors” on July 5, 2017. Entrectinib received breakthrough therapy designation (BTD) for the treatment of *NTRK* fusion-positive locally advanced or metastatic solid tumors in adult and pediatric patients who have either progressed following prior therapies or who have no acceptable standard therapies on May 12, 2017.

The Chemistry, Manufacturing and Controls (CMC) only pre-NDA meeting has been scheduled for November 7, 2018 to reach agreement on the content and format of the CMC components of both planned NDAs. At this meeting, Genentech and FDA will capture the agreements regarding the content and format of a completed application for each NDA under the PDUFA VI program.

A separate interdisciplinary pre-NDA meeting has been scheduled for October 18, 2018 under IND 135124 for the NDA that will support the proposed indication for entrectinib “for the treatment of *ROS1*-positive, (b) (4) metastatic NSCLC.” BTD has not been granted for entrectinib for this indication.

Regulatory

On February 27, 2014, Ignyta submitted IND 120500 for the initiation of clinical studies with entrectinib (RXDX-101) in the United States. Ignyta acquired RXDX-101 from Nerviano Medical Sciences (NMS), who initiated the first-in-human dose escalation trial, Study ALK-372-001, in Italy in October 2012. IND 120500 was allowed to proceed on March 28, 2014.

On January 29, 2015, FDA met with Ignyta to discuss the overall design of two studies, RXDX-101-03 “STARTRK 3,” a randomized, multicenter, active-comparator study and RXDX-101-02 “STARTRK 2,” a multicenter, single-arm study, to support traditional approval of entrectinib for the treatment of patients with advanced ROS1-positive and advanced neurotrophic tropomyosin receptor kinase 1/2/3 (*NTRK1/2/3*) fusion-positive NSCLC and accelerated approval of entrectinib for the treatment of patients with advanced *NTRK*^{(b) (4)} fusion-positive NSCLC.

Following the January 29, 2015 meeting, the design of Protocol RXDX-101-03 was re-titled, “A Phase 1/1b, Open-Label, Dose-Escalation and Expansion Study of Entrectinib (RXDX-101) in Children and Adolescents with Recurrent or Refractory Solid Tumors and Primary CNS Tumors,” and revised to be a dose-finding and activity-estimating trial in adults and pediatric patients across multiple disease-specific cohorts. Activity-estimating cohorts include (1) children and adolescents with relapsed or refractory primary central nervous system (CNS) tumors, (2) children and adolescents with relapsed or refractory neuroblastoma, and (3) children and adolescents with relapsed or refractory non-neuroblastoma, extracranial solid tumors harboring *TRK1/2/3*, *ROS* proto-oncogene 1 (*ROS1*), or anaplastic lymphoma kinase (*ALK*) fusion proteins.

On September 22, 2015, FDA met with Ignyta to discuss Protocol RXDX-101-02 entitled, “An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients with Locally Advanced or Metastatic Solid Tumors that Harbor *NTRK1/2/3*, *ROS1*, or *ALK* Gene Rearrangements,” and to discuss Ignyta’s overall clinical development program.

On August 30, 2016, an Investigational Device Exemption for the planned companion diagnostic (CDx) test, Trailblaze Pharos™, the proposed companion diagnostic test for selection of patients with either *TRKA*-positive, *TRKB*-positive, *TRKC*-positive, *ROS1*-positive, or *ALK*-positive cancers for treatment with entrectinib, was approved.

On November 10, 2016, the Center for Devices and Radiological Health (CDRH) granted Expedited Access Pathway designation to the Trailblaze Pharos CDx assay, the proposed companion diagnostic assay for selection of patients for whom entrectinib is indicated. Subsequently, Roche and Ignyta partnered with Foundation Medicine Inc. (FMI) and plan to file a supplement premarketing approval application for the F1CDx as the companion diagnostic test for entrectinib, to select for patients with *NTRK* fusion-positive solid tumors or *ROS1* fusion-positive NSCLC. This was noted in the Final Written Responses issued June 26, 2018, in response to the Type B meeting request submitted by Ignyta to IND 120500 on April 25, 2018.

On November 17, 2016, Ignyta submitted a Type C Guidance meeting request to discuss the proposed clinical pharmacology program intended to support the filing of planned NDA for

entrectinib. Following a virtual discussion via electronic mail, meeting minutes were issued on March 2, 2017.

On December 22, 2016, Ignyta submitted a Proposed Pediatric Study Request, and on April 20, 2017, FDA issued a Pediatric Written Request. Ignyta requested an amendment to the Written Request on May 3, 2017, and FDA issued a Revised Pediatric Written Request on May 31, 2017. The primary objective of Study 1 (RXDX-101-03 [STARTRK-NG]) is to determine the maximum tolerated dose or “recommended phase 2 dose RP2D” of entrectinib in pediatric patients (children and adolescents) with relapsed or refractory solid tumors.

On March 31, 2017, FDA issued an Advice/Information Request letter, in response to questions posed in the February 22, 2017 amendment containing an *NTRK1/2/3* integrated statistical analysis plan (SAP) and *ROS1* NSCLC integrated SAP. In that communication, FDA advised Ignyta that the data necessary to support the filing of a marketing application for the treatment of the proposed population (*ROS1* fusion-positive NSCLC) should be discussed in a meeting with clinical review staff from the Thoracic Malignancies team in the Division of Oncology Products 2. Subsequently, on May 3, 2017, Ignyta submitted new IND 135124 for the development program supporting the proposed indication of the treatment of patients with *ROS1* fusion-positive, (b) (4) metastatic NSCLC, along with a request for 30-day waiver. A waiver of the 30-day review period for the original IND submission was granted on May 12, 2017.

On May 12, 2017, Ignyta was granted BTM for entrectinib for “the treatment of *NTRK* fusion-positive, locally advanced or metastatic solid tumors in adult and pediatric patients who have either progressed following prior therapies or who have no acceptable standard therapies.” On August 30, 2017, Ignyta submitted an Amended Agreed iPSP for the following indications:

- *TRK* fusion-positive, (b) (4) metastatic solid tumors in adult and pediatric patients who have either progressed (b) (4)
- *ROS1* fusion-positive, (b) (4) metastatic NSCLC

On September 7, 2017, an initial comprehensive multidisciplinary BTM meeting was held to discuss the development plan for entrectinib for the treatment of *NTRK* fusion-positive solid tumors. FDA and Ignyta discussed the proposal for a proposed NDA relying on evidence of safety and efficacy in a pooled population enrolled in Studies RXDX-101-02 (STARTRK-2), ALKA-372-001, RXDX-101-01, (STARTRK-1), and RXDX-101-03 (STARTRK-NG), with safety data from at least 300 patients treated with at least 1 dose of entrectinib. FDA advised Ignyta to submit a detailed SAP explaining how the analysis population for efficacy will be constructed, including justification for atypical approaches, and describing how the timing of final data cut-off for the efficacy analysis will be determined. FDA also requested to review Ignyta’s blinded independent central review (BICR) charter.

On December 15, 2017, a BTD meeting was held to seek agreement on the detailed SAP, BICR Charter, and the study data standardization plan for the pooled analysis of data across clinical studies.

On April 18, 2018, Ignyta requested a BTD meeting to seek FDA feedback on whether a shift to co-develop the FoundationOne CDx™ (instead of Trailblaze Pharos) as the CDx for entrectinib is acceptable for supporting the overall benefit-risk assessment for the entrectinib NDA.

On June 12, 2018, Ignyta transferred sponsorship of IND 120500, and all rights and responsibilities related to the IND application to Genentech.

On August 8, 2018 FDA notified Genentech that the information required for the complete transfer of the orphan drug application (#17-5871) had been submitted.

On August 17, 2018, Genentech requested a meeting to discuss the nonclinical, clinical pharmacology, and clinical data package to support an NDA submission in December 2018 for entrectinib for the treatment of patients *NTRK* fusion-positive solid tumors. The meeting package was received on September 17, 2018. FDA sent Preliminary Comments to Genentech on October 12, 2018.

Orphan Drug Designation

Ignyta received orphan drug designation for entrectinib for the following indications:

- Neuroblastoma (designation granted on December 22, 2014)
- Treatment of TrkA-positive, TrkB-positive, TrkC-positive, *ROS1*-positive, or *ALK*-positive NSCLC (designation granted on February 3, 2015; modified designation granted on May 6, 2015)
- Treatment of TrkA-positive, TrkB-positive, TrkC-positive, *ROS1*-positive, or *ALK*-positive CRC (designation granted on February 12, 2015)
- *NTRK* fusion-positive solid tumors (designation granted on July 5, 2017)

CMC

Genentech indicated that the drug product formulation, F06, is the intended commercial product. Formulation F06 is an immediate-release hydroxypropyl methylcellulose capsule available in 100 mg and 200 mg strengths. The two strengths are manufactured (b) (4). The formulations use USP/NF compendial excipients and none of the excipients are novel. The drug product does not contain overages or overfills.

Nonclinical

Entrectinib is a pan-TRK, ROS1, and ALK tyrosine kinase inhibitor. Based on information from the meeting package, Genentech has conducted repeat dose toxicology studies of up to 13 weeks in duration in dogs and rats, a full genotoxicity battery, a phototoxicity study, and several pharmacology studies including safety pharmacology studies for CNS, cardiovascular, and respiratory toxicity. An assessment of embryofetal toxicity was conducted in pregnant rats, and Genentech does not plan an additional study as the results were positive for embryofetal defects. In addition, Genentech conducted a 13-week study in juvenile rats to characterize the toxicity in developing animals.

Clinical Pharmacology

Per Genentech, exposure of entrectinib increased in a dose-proportional manner from 100 to 800 mg/m²/day (F1 fasted) and from 200 to 800 mg/day (F1 fed), and reached steady-state within a week of dosing in cancer patients. Saturable absorption was observed at dose levels higher than 800 mg/m²/d for F1 formulation in the fasted state. In vivo, entrectinib is metabolized primarily by CYP3A4 (~76%) to the active metabolite M5. The minor contributions from several other CYPs and UGT1A4 were estimated at <25% in total. Following a single dose of [¹⁴C]entrectinib, the mean total recovery was 86.0%. The majority of radioactivity was recovered in feces (82.9%) compared to urine (3.06%), and the oral bioavailability of entrectinib in humans is estimated to be at least 50% based on total radioactivity recovered in urine and as metabolites in feces. The estimated terminal half-lives of entrectinib and M5 are 19.2 hours and 37.8 hours, respectively. Clinical pharmacokinetic (PK) studies have been conducted in both healthy subjects and cancer patients to assess drug-drug interaction (DDI) liability by CYP3A perpetrators and proton pump inhibitors, and the inhibition potential of entrectinib toward CYP3A4, and P-glycoprotein. Clinical PK studies have also been conducted to evaluate the relative bioavailability for different formulations.

Clinical

Genentech intends to utilize safety and efficacy data from the below studies (see Table 1), and PK data from these and other clinical pharmacology studies in healthy volunteers, to support an NDA for entrectinib for the treatment of *NTRK* fusion-positive, (b) (4) metastatic solid tumors in adult and pediatric patients who have either progressed (b) (4) (b) (4).

Table 1: Clinical Studies to Support Efficacy in Entrectinib NDA

Protocol No.	Study Design	Patient Population	Entrectinib Regimen
RXDX-101-02 (STARTRK-2) Japan, US, EU, Australia, and Asia Pacific	Phase II, global, multicenter, open-label, basket study	Patients (≥ 18 years of age) with advanced or metastatic solid tumors that harbor an <i>NTRK1/2/3</i> , <i>ROS1</i> , or <i>ALK</i> gene rearrangement (fusion), excluding <i>ALK</i> - positive	Orally, once daily 600 mg on 28-day (ie, 4-week) cycles
ALKA Italy	First-in-human, multicenter, open-label, ascending-dose study with dose escalation according to a standard 3+3 scheme	Advanced/metastatic solid tumors, including patients with <i>TRKA/B/C</i> , <i>ROS1</i> , or <i>ALK</i> molecular alterations	<u>Schedule A</u> : once daily (fasted) 4-days on, 3-days off schedule $\times 3$ weeks followed by 7-day rest <u>Schedule B</u> : continuous once daily (fed) <u>Schedule C</u> : once daily (fed) in a continuous 4-days on, 3-days off schedule
RXDX-101-01 (STARTRK-1) US and South Korea	Phase I, multicenter, open-label, ascending-dose study with dose escalation according to a standard 3+3 scheme	Solid tumors with a <i>NTRK1/2/3</i> , <i>ROS1</i> , or <i>ALK</i> molecular alterations	Continuous once daily (fed) on 28-day (ie, 4-week) cycles
RXDX-101-03 (STARTRK-NG) US	5-part, Phase I/Ib, open-label, dose escalation and expansion study	Children and adolescents (2-22 years of age) with recurrent or refractory solid tumors and primary brain tumors. Parts B (gene fusion) and D enroll patients with cancers that harbor <i>NTRK1/2/3</i> , <i>ROS1</i> , or <i>ALK</i> gene fusion.	Orally, once daily Dosing nomogram based on BSA, ranging from 250 mg/m ² to 750 mg/m ²

Source: Modified from Appendix 3 of the Meeting Package, pg. 86

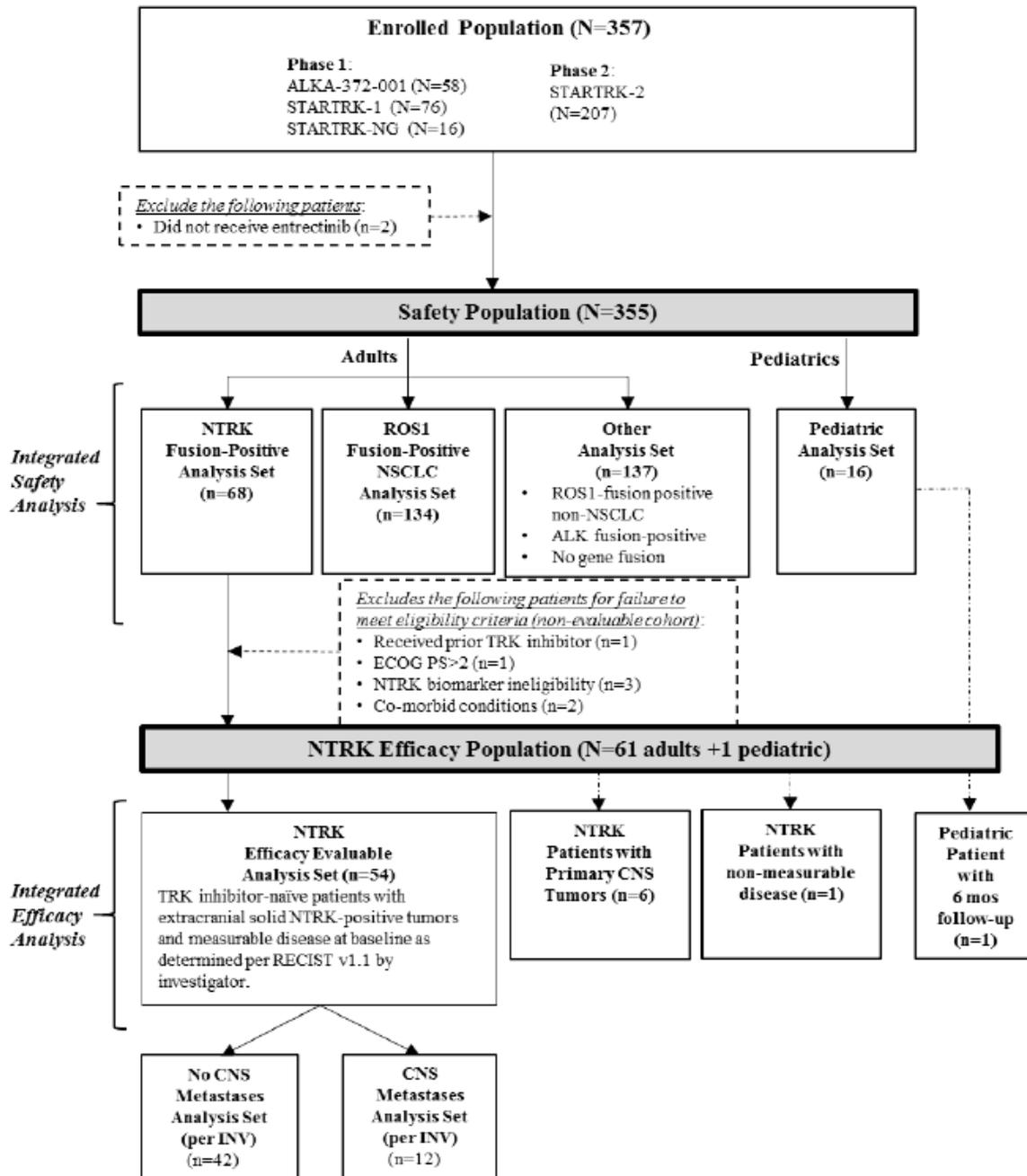
Results

The proposed NDA will be supported by pooled data pooled derived from patients enrolled in ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG who had measurable disease at baseline as assessed by the investigator, and had received at least 1 dose of entrectinib (Table 2, Figure 1). An integrated analysis of safety and efficacy was conducted across all four studies based on a clinical cutoff date of July 31, 2018.

Table 2: Patient Populations Supporting the Proposed NDA

N	Safety N=355	Efficacy N=54
ALKA	57	1
STARTRK-1	76	2
STARTRK-2	206	51
STARTRK-NG (pediatrics)	16	NA

Figure 1: Proposed Patient Populations and Analyses Sets for Integrated Analysis Supporting the NDA



Source: Figure 1 of the Meeting Package, pg. 32

Safety

In the pre-meeting package, Genentech stated that the majority of adverse events (AEs) were NCI-CTCAE Grade 1-2 and non-serious; however, in all adult patients to receive study drug, 50 (73.5%) experienced a Grade 3 or above toxicity, while 8 (50.0%) experienced a Grade 3 or above toxicity in the pediatric study. AEs leading to discontinuation occurred in 13% of adult patients and 6% of pediatric patients. AE leading to dose reduction occurred in 41% of adult patients and 25% of pediatric patients. AE leading to death occurred in 9% of adult patients (all Grade 5 events were assessed by the investigator as not related to entrectinib) and none of pediatric patients. The AE that occurred with the highest incidence ($\geq 20\%$) by preferred term were: constipation, dysgeusia, fatigue, dizziness, diarrhea, nausea, dyspnea, edema peripheral, anemia, weight increased, vomiting, cough, blood creatinine increased, pyrexia, arthralgia, myalgia, and paresthesia. Serious AE occurred in 47% of adult patients and 13% of pediatric patients; 6% of adult patients experienced hypoxia and/or pneumonia and 1 (6%) pediatric patient experienced a pleural effusion.

Efficacy

The primary efficacy analysis for the proposed NDA submission is based on 54 patients in the *NTRK* Efficacy-Evaluable Analysis Set pooled from studies ALKA, STARTRK-1 and STARTRK-2 who were enrolled on or before November 30, 2017. The clinical cutoff date for the efficacy and safety analyses was May 31, 2018 which ensured there would be at least 6 months of follow-up for all the patients enrolled into entrectinib studies up to November 30, 2017.

Of the entrectinib-treated patients, 68 patients whose solid tumors were *NTRK* fusion-positive by local nucleic-acid based diagnostic testing met the criteria for the requested 6 months minimum follow-up. Among these patients, eight were excluded from the efficacy evaluable population for the following reasons:

- prior TRK tyrosine kinase inhibitor treatment (n=1),
- biomarker ineligibility (n=3),
- clinical ineligibility (n=3; ECOG >2 [n=1], presence of pericardial effusion [n=1], peripheral neuropathy >Grade 2 [n=1]), and
- non-measurable disease at baseline (n=1).

Additionally, patients with primary brain tumors (n=6) were excluded from the pooled analysis, as these patients are not most accurately assessed for response by RECIST v1.1, but rather were assessed in the trial using RANO criteria, as is common for CNS primary tumors in clinical trials.

The procedures employed for patient selection and confirmation of eligible *NTRK* fusions for inclusion of patients in the efficacy analysis set, included:

- confirmation of use of a CLIA-certified or equivalently accredited nucleic acid-base local test
- adequate specimen nucleic acid sufficient for producing a reliable test result

- the presence of an *NTRK* fusion known to result in oncogenic driver activity, and
- the lack of co-occurrence with other strong oncodriver mutations likely to confer resistance.

The primary endpoints are objective response rate (ORR) and duration of response (DOR) as assessed by BICR. The meeting package stated that the ORR was 57.4% (95% CI: [43.2%, 70.8%]) and there were 4 patients with a complete response (7%) (Table 3). Responses were observed across 10 tumor types (see Table 4). The number of confirmed responders with observed (not Kaplan-Meier estimated) DOR of ≥ 6 months, ≥ 9 months, ≥ 12 months, ≥ 18 months is 54.8% (17 of 31), 38.7% (12 of 31), 29.0% (9 of 31), 9.7% (3 of 31), respectively.

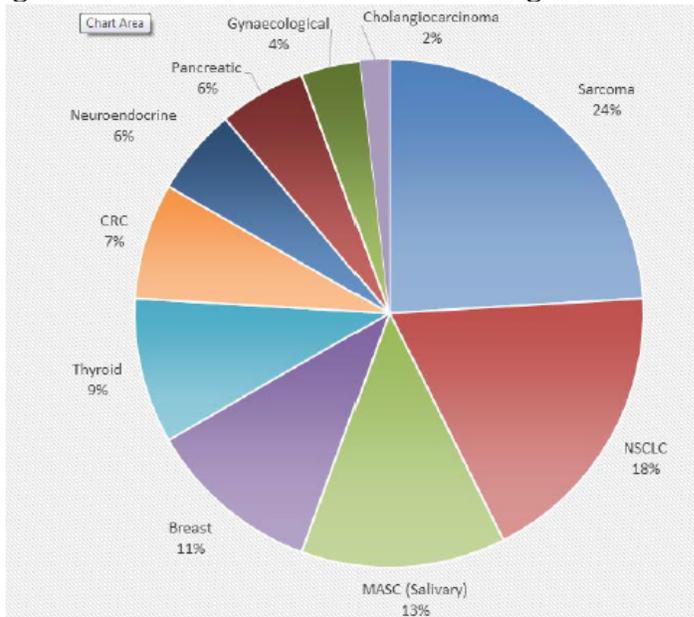
Table 3: Efficacy in *NTRK*-fusion Solid Tumors

	ALKA (N=1)	ST-01 (N=2)	ST-02 (N=51)	Total (N=54)
Responders	0	2 (100.0%)	29 (56.9%)	31 (57.4%)
95% CI (%)	NA	NA	(42.25, 70.65)	(43.2, 70.8)
Complete Response	0	0	4 (7.8%)	4 (7.4%)
Partial Response	0	2 (100.0%)	25 (49.0%)	27 (50.0%)
Stable Disease	0	0	10 (19.6%)	10 (18.5%)
Progressive Disease	1 (100.0%)	0	3 (5.9%)	4 (7.4%)
Non – CR/PD	0	0	3 (5.9%)	3 (5.6%)
Missing or Unevaluable	0	0	6 (11.8%)	6 (11.1%)

*NA=not applicable (confidence intervals not calculated with fewer than 3 responses)

Source: Modified from Table 5 of the Meeting Package, pg. 35

Figure 2: Distribution of Tumor Histologies in the Efficacy Population



Source: Figure 2 of the Meeting Package, pg. 34

Table 4: Efficacy by Tumor Type

Tumor Types	N	Responders n (%)
Breast	6	5 (83.3%)
CRC	4	1 (25%)
MASC	7	6 (85.7%)
NSCLC	10	7 (70%)
Neuroendocrine	3	1 (33.3%)
Other*	3	2 (66.7%)
Pancreatic	3	2 (66.7%)
Sarcoma	13	6 (46.2%)
Thyroid	5	1 (20%)

Other: 1 ovarian, 1 endometrial, 1 cholangiocarcinoma

Source: Figure 6 of the Meeting Package, pg. 37

Table 5: Intracranial Responses (BICR assessment) in Patients with CNS Metastases at Baseline

Patients with CNS Metastases at Baseline as assessed by BICR	All patients N=11	Patients with Measurable Disease N=7
Numbers of patients with intracranial response	6	4
Intracranial ORR% (95% CI)*	54.5% (23.4, 83.3)	57.1% (18.4, 90.1)
Complete Response	3 (27.3%)	1 (14.3%)
Partial Response	3 (27.3%)	3 (42.9%)
Median duration of CNS response, months (95% CI)	NE (5.0, NE)	NE (5.0, NE)
Median PFS, months (95% CI)	14.3 (5.1, NE)	NE (2.8 NE)

BICR, blinded independent central review; CNS, central nervous system; IC-ORR, intracranial objective response rate; NE, not estimable.

IC-ORR derived using RANO-BM criteria applied only to CNS lesions.

*Confidence Intervals (CI) calculated using the Clopper-Pearson method.

CCOD: 31 May 2018.

Source: Table 8 of the Meeting Package, pg. 39

Companion Diagnostic

Genentech intends to use FoundationOne CDx (F1CDx) supplemental premarket approval (sPMA) submission plan, as the companion diagnostic for entrectinib. For the dose expansion part of STARTRK-2 (gene fusions mandatory for inclusion), patients could be enrolled either by the Ignyta NGS Pharos test (*NTRK*, *ROS1*, or *ALK* gene fusions only) or by any other nucleic acid-based diagnostic testing method that relied on direct assessment of gene rearrangements and was performed by a CLIA-certified or equivalently-accredited diagnostic laboratory.

Patients with alterations of *NTRK* gene other than gene fusions were permitted to enroll in the dose-finding studies. As described in Table 6 below, 29 patients had other *NTRK* molecular alterations, including 8 “without a known alteration of *NTRK*.” No objective responses were observed in any of these patients.

Table 6: Selected molecular abnormalities across trials

	ALKA	STARTRK-1	TOTAL
TRK Molecular Alterations, n (%)	10	19	29
Amplification/overexpression	6	5	11
Other mutations*	4	6	10
Unknown#	0	8	8

*Other mutations: deletions and single point mutations, including *NTRK* R686C, *NTRK* R326G, and others not specified

#Unknown: data not available or not otherwise specified.

Source: Meeting Package, pg. 180

DISCUSSION

GENERAL COMMENTS

FDA will not be able to reach agreements with Genentech on the contents of a complete application for an NDA for entrectinib for the treatment of *NTRK* fusion-positive, (b) (4) (b) (4) metastatic solid tumors in adult and pediatric patients (b) (4) (b) (4) who have either progressed (b) (4) (b) (4) (IND 120500) and entrectinib for *ROS1*-positive, (b) (4) (b) (4) metastatic NSCLC (IND 135124) under the PDUFA VI program, because the pre-NDA meeting for discussion of quality components has not been held. We acknowledge that a separate clinical pre-NDA meeting for *ROS1*-positive, (b) (4) metastatic NSCLC is scheduled for October 18, 2018 and that a pre-NDA CMC Only meeting to discuss quality components for both NDAs is scheduled for November 7, 2018. During the November 7, 2018 meeting, FDA and Genentech will need to reach agreement on the CMC, Clinical, Nonclinical, and Clinical Pharmacology information necessary to allow each NDA to be considered complete, and to reach agreement on the submission of late components for each NDA, if any are planned.

Clinical/Statistics

1. *Does the Agency agree that the available clinical data package provides sufficient clinical evidence to characterize the benefit and risk of entrectinib in adult and pediatric patients with *NTRK* fusion-positive (b) (4) metastatic solid tumors to support an NDA filing?*

FDA's Response sent 10/12/18: FDA agrees that the summary level efficacy results of ORR and DOR appear sufficient to support the filing of an NDA seeking accelerated approval for the proposed indication for entrectinib for the treatment of adult and pediatric patients with *NTRK* fusion-positive (b) (4) metastatic solid tumors.

Please confirm that, as discussed during the December 15, 2017 Type B BTD/Other meeting, Genentech will include efficacy analyses for all patients whose tumor harbors an *NTRK* fusion or other alteration (regardless of the presence or absence of any other mutations/co-drivers) who received at least one dose of entrectinib and inclusive of patients with non-measurable disease at baseline in the NDA submission. In the NDA submission, also include efficacy results for patients with primary CNS disease, and an analysis of efficacy by *NTRK*-fusion partner for all patients receiving at least one dose of entrectinib.

As also discussed during the December 15, 2017 meeting, FDA will determine the most appropriate population for evaluation of efficacy during review of the NDA, irrespective of the efficacy population prespecified in the statistical analysis plan.

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback and agrees to include the following efficacy analyses in the NDA:

- for all patients whose tumor harbors an NTRK fusion or other alteration (regardless of the presence or absence of any other mutations/co-drivers) who received at least one dose of entrectinib and inclusive of patients with nonmeasurable disease at baseline in the NDA submission.
- for patients with primary CNS disease
- by NTRK-fusion partner for all patients receiving at least one dose of entrectinib

The Sponsor would like the Agency to clarify the request for efficacy analyses in the patients whose tumor harbors a non-fusion NTRK alteration (regardless of the presence or absence of any other mutations/co-drivers). Per Table 6 in FDA's Preliminary Comments, the 29 patients in this population include point mutations, insertions, deletions, and amplifications. Prior data have been published showing the lack of efficacy (Drilon A, Cancer Discovery 2017) in these patients with non-fusion NTRK alterations; thus, these data are not planned for inclusion in the NDA.

Two patients with NTRK-fusion positive tumors with co-occurring oncodrivers and 1 patient with an out-of-frame NTRK gene fusion will be listed in the efficacy nonevaluable population as shown in Figure 1 of the meeting package.

Efficacy data in 6 patients with primary CNS tumors as evaluated by RANO criteria will be provided in the NDA as a separate analysis from the integrated RECIST-based efficacy analyses.

There was a large diversity of fusion partners among the efficacy evaluable patient population, with most fusion partners occurring in 1-2 patients. A line listing of BOR and DOR for one patient per row will be provided in the NDA and will include a column for fusion partner. As these data will not be included in the prescribing information, datasets for this analysis will not be separately provided for this table.

In summary, efficacy analyses of all the requested patients will be provided with the exception of 29 patients with non-fusion NTRK alterations.

Discussion during the 10/17/18 Meeting: Per FDA's request, Genentech stated that data for the 29 patients enrolled without clear evidence of NTRK fusion positivity in Phase 1 trials (ALKA-372-001, and STARTRK-1) and patients in the non-evaluable cohort of STARTRK-2 will be included in the datasets with a flag identifying such patients. Genentech agreed to provide the analyses in the subgroup of patients with primary CNS tumors and datasets to allow a summary analysis of response by NTRK fusion partner in the original NDA submission. FDA stated that this was acceptable.

2. *Does the Agency agree with the proposal to submit updated safety and efficacy data in the 90 Day Safety Update and that the new data would not impact the PDUFA date? Specifically, the Applicant proposes to submit:*

- *an additional 5 months of safety follow-up for patients in the original NDA dataset*
- *updated DOR in responders in the original NDA dataset*
- *PK, safety and efficacy data from additional pediatric patients than were submitted in the initial application.*

FDA's Response sent 10/12/18: No, FDA requests that Genentech update the safety and efficacy data at Day 60 (rather than Day 90) in order to permit sufficient time for FDA review. Efficacy data included in the Day 60 update should be limited to the efficacy population included in the original NDA submission. The Day 60 safety and efficacy update should also include updated datasets and text for the integrated summaries of safety and efficacy. In addition, an addendum to the clinical study report for each study contributing to efficacy also should be included with the updated pooled efficacy data to ensure that the study reports reflect these updated data. In this amendment to the NDA, provide a single dataset summarizing demographic information and updated tumor response data for each patient (1 row per patient) in the efficacy dataset as reflected in the summary tables to be provided, and a single updated safety dataset containing all safety information for each patient included in the safety analysis as described in the summary tables.

Although FDA does not anticipate that the contents of the Day 60 update will constitute a major amendment that would impact the PDUFA date, such a determination cannot be made until the new data are available for review.

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback.

The Sponsor would like to clarify whether the Agency agrees with the scope of the safety update report. To reiterate, in accordance with the agreement from the WRO Type B meeting on June 22, 2018, we are planning to provide:

- an additional 5 months of safety follow-up for patients in the original NDA dataset
- updated DOR in responders in the original NDA dataset

As requested by the Agency, no update to the ORR will be needed. The Sponsor is planning to update the DOR for the responders in a supplemental report that integrates all three studies. The patient-level response listing, including demographics, will be refreshed for the supplemental report.

The 3 patients contributing to the efficacy evaluable population from the ALKA and STARTRK-1 had already discontinued the study at the time of the initial CSR. Therefore, updated DOR will only be contributed by STARTRK-2 patients.

In the pooled efficacy analysis, data will be shown by individual study and overall. Therefore, the Sponsor does not plan to update any CSRs because the data, including pooled datasets, will be provided in the submission.

The Sponsor has additionally proposed to submit updated pediatric data including:

PK, safety and efficacy data from additional pediatric patients than were submitted in the initial application.

These data would be provided as a supplemental report and would include an additional 10 patients for safety, including a subset of 4 patients for efficacy with at least 6 months of follow up from first response. The report would present analyses of the total pediatric population comprised of 26 patients for safety (16 patients in the original NDA and 10 additional patients) and 5 patients for efficacy (1 patient in the original NDA and 4 additional patients). The purpose of these data is to strengthen the pediatric data package. Does the Agency agree with this proposal?

Regarding the Agency's request for submission of the safety update report at Day 60, the Sponsor will evaluate feasibility and would like to come to a final agreement with the Agency before NDA submission.

Discussion during the 10/17/18 Meeting: Genentech clarified that they will provide updated DOR data for the 54 patients in the primary efficacy population. If one or more patient among this group of 54 exhibits a late response (i.e., during followup), this should be identified descriptively. In lieu of addenda to clinical study reports, Genentech will provide updates to the SCS and SCE.

With regards to the pediatric data, Genentech clarified that all pediatric patients were dosed with the F1 formulation and received intact capsules. The age range for the 16 patients for whom PK data are available is from 2 to 17 years. Genentech proposes to use modelling to bridge PK data in children from the F1 to F06 formulation. Genentech confirmed that the F06 capsule should not be opened; therefore, the dosage form in pediatric patients would be limited to those children who can swallow intact capsules. Genentech continues to develop an age-appropriate formulation that may be introduced into the clinic in 2019. FDA stated that the proposed data package may not support a dosing recommendation in pediatric patients but agrees that pediatric data should be submitted in the original NDA. Whether additional data may be accepted for review after submission of the original NDA may be contingent upon a better understanding of the proposed pediatric data package and timing of submission. Genentech agreed to provide a more detailed description of the data package as an amendment to the IND subsequent to the meeting, but prior to the November 7, 2018 CMC Only meeting.

Regulatory

3. *For the proposed NTRK fusion-positive tumor indication, does the Agency agree that the results demonstrate positive benefit-risk to support an accelerated approval in the*

proposed indication and that conversion to regular approval may be based on durable ORR from an additional 50 patients followed for a minimum of 6 months and additional follow up from the patients in the initial NDA?

FDA's Response sent 10/12/18: Because the proposed treatment effect of entrectinib is based on a surrogate endpoint that is reasonably likely to predict clinical benefit and because limited data will be submitted in the NDA for certain tumor types, FDA considers the accelerated approval pathway appropriate for the proposed NDA. If entrectinib is approved, the indication, including qualifications regarding prior therapy and the potential exclusion of primary CNS, will be determined during the review of the NDA.

During the review of the NDA, FDA will also consider the data necessary to support regular approval (e.g., additional follow-up and broader clinical experience), as described in a post-marketing requirement (PMR). With regard to the PMR, FDA cannot determine the extent of the data package that will be needed to verify clinical benefit until after the data included in the original NDA submission are reviewed. FDA will discuss post-marketing requirements and commitments with Genentech during the NDA review period, according to 21st Century Review timelines for new molecular entity NDAs. Additionally, the proposed NDA should contain data characterizing the natural history of patients with NTRK fusion solid tumors and justification supporting a conclusion that the reported BICR-assessed ORR and DOR provide evidence of direct clinical benefit in the indicated population, considering the natural history of the disease and available therapy.

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback. No further discussion is needed at the meeting.

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

4. *Under the auspices of the BTD designation, the Applicant would like to request rolling review for the NTRK NDA in order to allow finalization of the CMC sections. Does the Agency agree with the proposal?*

FDA's Response sent 10/12/18: The plan to request rolling review of the proposed NDA is acceptable. FDA notes that agreements regarding the data content of the CMC modules will be discussed during the CMC Only pre-NDA meeting scheduled for November 7, 2018. Upon receipt of the rolling review request containing the schedule for submission of complete components of the NDA, FDA will discuss the acceptability of the proposed schedule. The request for rolling review should be submitted as soon as possible, but no later than November 1, 2018.

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback. No further discussion is needed at the meeting.

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

5. *The proposed content of the NDA application is provided in Appendix 6. The Applicant may need to submit eCRFs from some healthy volunteer clinical pharmacology studies within 30 days after the original NDA submission. Does the Agency agree with the proposed content of the complete NDA and that some eCRFs may be submitted within 30 days after the original NDA submission if they are not available at the time of submission?*

FDA's Response sent 10/12/18: FDA does not object to the submission of eCRFs from the healthy volunteer clinical pharmacology studies within 30 days after the original NDA submission as a late component. Regarding Module 5, Section 5.3.5.2, please submit both ADaM and SDTM datasets.

Genentech's Response received via email 10/16/18: We will be submitting the patient eCRFs for all the studies.

As per Genentech's communication to the agency on July 6, 2018 - All of the studies which are part of submission started prior to December 17, 2016 and will be placed as per the Module 5 eCTD structure in the legacy folder (non-CDISC) in accordance with the FDA guidance document "Providing Regulatory Submissions in Electronic Format - Standardized Study Data" (FDA 2014). In compliance with FDA's Guidance on Technical Rejection Criteria for Study Data (revised June 22, 2017), Genentech acknowledges that a Trial Summary dataset (TS.xpt) and Demographics (DM.xpt) will be submitted for each study even if the study started prior to December 17, 2016

Discussion during the 10/17/18 Meeting: FDA requested, and Genentech agreed to provide, the reviewer guide for datasets to clarify the deviations between the legacy datasets and the STDM/ADaM in the original NDA submission.

Clinical Pharmacology

6. *Does the Agency agree that the overall clinical pharmacology program, including the DDI strategy, is sufficient to support registration of entrectinib?*

FDA's Response sent 10/12/18: The proposed clinical pharmacology package appears to be acceptable for the proposed NDA. Genentech proposes to use the physiologically based pharmacokinetic (PBPK) approach to evaluate the impact of moderate and weak CYP3A inhibitors/inducers and CYP3A sensitive substrates. The acceptability of PBPK modeling and all other components of the clinical pharmacology package will be determined at the time of review of the planned NDA submission.

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback. No further discussion is needed at the meeting.

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

7. *Does the Agency agree with the proposed content, structure and format of the datasets for clinical pharmacology studies?*

FDA's Response sent 10/12/18: Yes, FDA generally agrees with the proposed content, structure, and format of the datasets for the clinical pharmacology studies. However, a final determination will be made prior to filing of the planned NDA submission.

For the population PK analysis, please also submit dataset and analysis codes for exposure-response analyses for efficacy and safety. For PBPK analysis, the PBPK modeling report should describe in detail the development of the PBPK model and any assumptions being made. Model files used to generate the final PBPK simulations (e.g., drug model files and workspace files) should be submitted. Software-specific files such as parameter estimation data files, simulation outputs, sensitivity analysis and observed clinical data should be submitted as MS Excel files. Refer to the following FDA guidance for additional information entitled, "*Physiologically Based Pharmacokinetic Analyses-Format and Content. Guidance for Industry,*" (August 2018) available at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm531207.pdf>

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback. No further discussion is needed at the meeting.

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

8. *Does the Agency agree with the proposed clinical Modeling and Simulation analysis plan for entrectinib?*

FDA's Response sent 10/12/18: Yes, FDA generally agrees with the proposed clinical modeling and simulation analysis plan for entrectinib. However, a final determination will be made at the time of review of the planned NDA submission. Tumor size modeling may be submitted as the PK/PD analysis along with the population PK analysis. Please also submit exposure-efficacy analyses for primary and major secondary clinical efficacy endpoints for each specific indication. Please also submit exposure-safety analyses for adverse events of special interest (e.g., neurotoxicity, hepatotoxicity).

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback and confirms that exposure-efficacy analyses for primary clinical efficacy endpoints for each specific indication will be submitted. Could the Agency clarify which major secondary endpoints are requested?

For exposure-safety analyses for selected AEs (i.e. neurological toxicity, liver dysfunction, hematologic toxicity, and pneumonitis), there are insufficient patients with

these AEs to build a model. Therefore, exposure of the identified patients will be tabulated. Exposure QTc will be presented in the PopPK report.

Discussion during the 10/17/18 Meeting: FDA clarified that the exposure-response analyses should look at the relationship between exposure and duration of response as well as exposure and ORR.

9. *Does the Agency agree with the proposed strategy to provide an estimated pediatric dose recommendation with the commercial formulation (F06) and that submission of updated data with the 90 Day Safety Update Report will not delay the PDUFA action date?*

FDA's Response sent 10/12/18: FDA is unable to answer this question due to insufficient information about the proposed dosing regimen in the current submission. The proposed timing of submission of the bridging study may not permit adequate time for review during the initial NDA review cycle if it is not included in the original NDA submission.

Due to limited clinical pharmacology data provided in the meeting package, FDA is unable to determine whether the formulation bridging, the allometric scaling in children > 4 years old, and the PBPK modeling for younger children would be sufficient to support a dosage recommendation for the commercial formulation (F06) that is safe and effective in pediatric patients. Per current practice, PBPK modeling and simulation in children should be verified with sufficient clinical data. PBPK predictions cannot be used prospectively to support pediatric dose recommendations in the absence of clinical data.

Please also see FDA's Additional Clinical Comment 13.

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback.

The Sponsor would like to clarify that pediatric patients in the STARTRK-NG clinical trial have been dosed with F1 formulation, not suitable for commercial use. F06 will be the commercial formulation for patients who can swallow capsules.

At the time of the initial meeting package submission, the PopPK model and extrapolation analyses were ongoing and the recommended pediatric dose with F06 could not be provided.

Since then, comprehensive modeling analyses have been completed and demonstrated that the systemic exposure seen in pediatric patients is comparable to the observed and estimated exposure in adults, based on the following:

- The PopPK model was built with clinical data using F2A formulation.
- Bioequivalence was demonstrated between F2A/F06.
- Thus, PopPK results can justify the use of F06 in pediatric patients who are able to swallow:

- The pharmacokinetics (PKs) of entrectinib and M5 are comparable in adults and children based on NCA and PopPK approaches.
- The PopPK characterized the PK of entrectinib and M5 in both patient population (adults and children)
- The PopPK has been used to predict the dose in pediatrics to match the adult target exposure taking into account the difference between F2A/F06 and F1.
- The estimated pediatric dose with F06 based on PopPK modeling is 300 mg/m².
- Different modeling approaches (PopPK and PBPK-GastroPlus – where maturation is being taken into account) resulted in the same estimated dose of 300 mg/m² in pediatric patients able to swallow, increasing the confidence and robustness of the estimation.
- The current estimated pediatric dose BSA-adjusted gives an exposure (predicted AUC_t at steady state) equivalent to the one predicted and observed in adults receiving a 600 mg QD flat dose (~ 300 mg/m²).
- Based on the exposure/safety relationship analyses conducted in adults – no exposure safety relationship has been found, indicating a wide therapeutic window.
- F06 at the 300 mg/m² dose will be introduced into the pediatric clinical trial STARTRK-NG by the end of 2018.

In addition, the ongoing rBA study between F1/F06 should provide reassurance of the proposed estimated dose.

In conclusion, based on the current available information, the Sponsor believes that the current estimated dose in pediatrics with F06 is sufficient to ensure clinical response.

Does the Agency agree that the information provided is sufficient to support the recommended pediatric dosing with F06?

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

Nonclinical

10. *Does the Agency agree with the toxicology data package to support the NDA and that no additional studies are required?*

FDA's Response sent 10/12/18: Yes, the toxicology data package appears sufficient to support the submission of the proposed NDA.

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback. No further discussion is needed at the meeting.

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

Companion Diagnostic

11. *Do CDER and CDRH agree that this analysis plan will support co-filing of F1CDx sPMA for the CDx claim for selection of patients whose tumors harbor NTRK or ROS1 rearrangements for whom entrectinib is indicated?*

FDA's Response sent 10/12/18: There is insufficient information for FDA to determine whether the proposed analysis plan will support filing the F1CDx sPMA for the CDx claims for selection of patients whose tumors harbor *NTRK* or *ROS1* rearrangements for whom entrectinib is indicated. FDA acknowledges that the pre-submission from FMI was received under pre-submission number Q181647; a meeting between the device sponsor (FMI) and CDRH is scheduled to take place on November 1, 2018. CDRH will provide pre-meeting written feedback to the pre-submission questions to FMI by October 26, 2018, as per the pre-submission process.

Based on the limited information provided in the meeting package, it appears that there could be a very small number of efficacy-evaluable patients available for the proposed clinical bridging study, leading to considerable amount of uncertainty in the bridging study results. Given the low prevalence of the *NTRK* and *ROS1* fusions, the positive predictive value ($p(\text{representative LDT (Trailblaze Pharos)} + |F1CDx+)$) could be very low even when negative percent agreement (NPA) ($p(\text{CDx-} | \text{representative LDT (Trailblaze Pharos) -})$) is high and therefore the intent-to-treat population with F1CDx positive results will be dominated by (representative LDT (Trailblaze Pharos)-, F1CDx+) patients who were excluded from the trial with no clinical outcomes. Ideally the estimated NPA and its confidence interval should be very close to 100% for the feasibility of the bridging study. FDA strongly recommends that Genentech perform the above simulations for sensitivity analyses to assess the feasibility of the bridging study and if feasible, determine the required number of samples, especially negative samples to target an adequate NPA for the proposed bridging study.

As the device will be evaluated based on the totality of the data from the bridging study including concordance study between representative LDT (Trailblaze Pharos) and F1CDx, an appropriate positive percent agreement (PPA, including CI) is also required no matter whether the bridging efficacy analysis is feasible or not. Genentech may procure positive samples in addition to the clinical trial samples to achieve the desired PPA.

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback. Per FDA, feedback for the companion diagnostic questions is applicable for both the *NTRK* and *ROS1* NDAs. We would like to request the following feedback:

We would like to confirm with CDRH that using TNA (total nucleic acid) samples in the concordance study and clinical bridging is acceptable to support the planned sPMA, and that the TNA will be tested with F1CDx as described in the TNA feasibility study (refer to Pre-Submission Q181647 attachment 3, "QSR-DEV-RPT-025-01 QSR Development Report for Feasibility Evaluation of Processing Total Nucleic Acid (TNA) in the F1CDxAssay").

The Sponsors would like to clarify that we plan to discuss details of the requested simulations for feasibility of the proposed bridging study at the CDRH Pre-Submission meeting on Nov 1. We also plan to provide the complete clinical validation for F1CDx including imputation and sensitivity analyses in the final sPMA submission for both NTRK and ROS1. Does the Agency agree with this approach?

Furthermore, we would like to seek clarification on FDA's feedback on Question4a for ROS1 meeting package. The Agency stated, "data relevant to companion diagnostic test linked to the proposed indication for entrectinib of the treatment of patients with ROS1-positive (b) (4) metastatic NSCLC should be submitted to the NDA containing the clinical efficacy data for this indication". Clinical and analytical validation data supporting F1CDx as the companion diagnostic for the proposed ROS1 indication for entrectinib will be included in the planned sPMA submission. The same clinical validation report can be submitted to the NDAs concurrently with the sPMA submission. Does the FDA agree with this approach?

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

12. *In case CDRH requires more or different analyses impacting availability timing of the sPMA data package, does CDER agree that entrectinib NDAs may be filed without contemporaneous filing of F1CDx sPMA?*

FDA's Response sent 10/12/18: FDA will not determine whether to file the proposed NDA until after the NDA is submitted; however, because entrectinib is intended to treat a serious and life-threatening disease for which no satisfactory alternative treatment exists and the benefit from the use of entrectinib is likely to outweigh the risk from the lack of an approved or cleared IVD companion diagnostic device, FDA will consider filing the entrectinib NDA for the proposed indication if contemporaneous filing of the F1CDx sPMA is not possible.

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback. No further discussion is needed at the meeting.

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

ADDITIONAL FDA COMMENTS SENT TO GENENTECH ON 10/12/18

Clinical

13. The meeting package contains insufficient information for FDA to determine whether the proposed use of the F06 commercial formulation is appropriate for pediatric patients. The doses achievable using the commercial formulation (F06) strengths of 100 mg and 200 mg may not provide the optimal entrectinib exposure in younger pediatric patients. Furthermore, no information has been provided regarding clinical experience with dosing of pediatric patients under the intended directions for use to be described in the package insert. Please characterize the data available from clinical experience in clinical trials, included safety (including medication errors) and PK data that support this proposed dose and preparation for administration of the commercial product in pediatric patients. As soon as possible, please provide information regarding the proposed pediatric dosage regimen and available data to support the proposed pediatric dosage regimen

Genentech's Response received via email 10/16/18: Genentech acknowledges the Agency's feedback and refers the Agency to the response to Question 9 for the justification for the dose and exposure.

At the time of the initial NDA for entrectinib, only F06 formulation will be commercially available for adult and pediatric patients who can swallow intact capsules. (b) (4)

(b) (4)

Therefore, the F06 capsule formulation is specified not to be opened and coadministered with food or liquid.

The F1 formulation is not suitable for commercial use and has only been used in the STARTRK-NG and ALKA-372-001 (Phase 1, Italy) trials. In the STARTRK-NG trial, F1 has been used both for pediatric patients who are able to swallow capsules and in at least 6 pediatric patients who are unable to swallow capsules.

(b) (4)

All the arguments to support implementation of F06 in pediatric patients able to swallow capsules are outlined in Question 9.

Could the Agency clarify the timing of the following request "As soon as possible, please provide information regarding the proposed pediatric dosage regimen and available data to support the proposed pediatric dosage regimen"? Specifically, does the Agency want this information to be submitted before NDA submission?

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

14. As soon as possible, please provide information regarding the status of development of the pediatric formulation of entrectinib.

Genentech's Response received via email 10/16/18: For the final age-appropriate formulation(s), the Sponsor is currently evaluating solubility enhancing, multiparticulate solid oral formulation options, including mini-tablets, granules, and pellets. Following formulation development, one or more prototype formulations will be evaluated in a relative bioavailability study in 2019, prior to introduction into study STARTRK-NG by December 2019. The palatability challenge of these formulation prototypes is planned to be addressed (b) (4). Formulation taste acceptance will be confirmed in a taste panel assessment. (b) (4)

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

15. In the original NDA submission, provide a draft Instructions for Use document for caregivers who are expected to prepare and administer entrectinib to pediatric patients.

Genentech's Response received via email 10/16/18: As detailed in the Sponsor's response under Question 13, the F06 capsule formulation is specified not to be opened. At the time of the initial NDA, only the entrectinib F06 formulation will be commercially available for adult and pediatric patients who can swallow intact capsules. As such, the label/USPI will not contain instructions specifically for caregivers who are expected to prepare and administer entrectinib to pediatric patients.

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

Clinical Pharmacology

FDA recommends the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry entitled, "*Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format,*" available at: <https://go.usa.gov/xn4qB>. Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

16. Address the following questions in the Summary of Clinical Pharmacology:

- a. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
- b. What are the exposure-response relationships for efficacy, safety and biomarkers?
- c. What is the effect of entrectinib on the QT/QTc interval?
- d. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
- e. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
- f. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

17. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

18. Provide final study report for each clinical pharmacology trial. Present the PK parameter data as geometric mean with coefficient of variation (and mean \pm standard deviation) and median with minimum and maximum values as appropriate.

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

19. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the PK datasets should be consistent with the numbers used in the clinical datasets.
 - a. Provide all concentration-time and derived PK parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a

define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

- b. Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

20. Submit the following for the population PK analysis reports:

- a. Standard model diagnostic plots
- b. Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
- c. Model parameter names and units in tables.
- d. Summary of the report describing the clinical application of modeling results. Refer to the following pharmacometric data and models submission guidelines, entitled, “*Model/Data Format*,” available at:
<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

21. Submit the following information and data to support the population PK analysis:

- a. SAS transport files (*.xpt) for all datasets used for model development and validation
- b. A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
- c. Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

22. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry, available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> for population PK,
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf> for exposure-response relationships, and
<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm> for pharmacometric data and models submission guidelines.

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

23. Include the following items in the submitted your QT study report:
- a. Study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
 - b. Study report
 - c. Statistical analysis plan
 - d. Clinical study protocol
 - e. Investigator's Brochure
 - f. A completed Highlights of Clinical Pharmacology and Cardiac Safety Table
 - g. Annotated CRF
 - h. A data definition file which describes the contents of the electronic data sets
 - i. Electronic data sets as SAS.xpt transport files (in CDISC SDTM and ADAM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses. Please make sure that the ECG raw data set includes at least the following: Subject ID, treatment, period, ECG date, ECG time (down to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g., QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI), Lead, and ECG ID (link to waveform files, if applicable).
 - j. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
 - k. Adverse Event analysis using the MedDRA SMQ “Torsade de pointes/QT Prolongation” and include the preferred term “Seizure” by treatment and dose level.
 - l. Narrative summaries and case report forms for any
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure
 - vi. Adverse events resulting in the subject discontinuing from the study

Genentech's Response received via email 10/16/18: The Sponsor plans to provide an analysis of adverse events identified using the MedDRA SMQ "Torsade de pointes/QT Prolongation" and also separately, an analysis of adverse events with the MedDRA Preferred Term of "Seizure" within the Summary of Clinical Safety. The current QT substudy has been conducted as part of the STARTRK-2 study with all patients dosed at the RP2D of 600mg daily. Therefore, an analysis by dose level is not possible.

The Sponsor had previously agreed with the Agency on narrative categories in a follow up communication to the Type C WRO meeting provided on 16 July 2018 to include:

- AEs leading to Deaths
- AE leading to discontinuation
- Serious adverse events (SAEs)
- Non-serious adverse events of \geq Grade 3 in severity, specifically for:
 - neurological toxicity
 - liver dysfunction
 - hematologic toxicity
 - prolonged QTc
 - pneumonitis requiring dose modification

Based on this previous agreement, the Sponsor will provide narratives for any SAEs of ventricular tachycardia or fibrillation, syncope, and seizures. The Sponsor will also provide an analysis of these adverse events (serious and non-serious) within the Summary of Clinical Safety.

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

24. Submit all related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com).

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

25. FDA is also interested in the effects of the test substance on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.

Discussion during the 10/17/18 Meeting: There was no further discussion of this item during the meeting.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- A preliminary discussion of the content of a complete application occurred and preliminary agreements were reached regarding the non-clinical, clinical pharmacology, and clinical/statistical sections of the planned NDA. Final agreements

on the content of a complete application will be reached during the November 7, 2018 CMC Only pre-NDA meeting.

- Genentech agreed that the NDA will include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion on the need for a REMS was held; based on information currently available, FDA stated that a REMS will not be required in order to file the planned NDA. FDA will make a final determination for the need for a REMS during the review of the NDA for the proposed indication cited above.
- Genentech confirmed that major components of the application are expected to be submitted with the original application. Genentech proposed, and FDA agreed, that the following minor application component may be submitted within 30 calendar days after submission of the original application:
 - eCRF from healthy volunteer clinical pharmacology studies

Prominently identify each submission containing your late minor component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY

As noted above, FDA will reach agreement on the contents of a complete application for the proposed NDA during the CMC pre-NDA meeting scheduled for November 7, 2018; a summary of final agreements will be reached at this meeting and will be documented in the minutes for the November 7, 2018 meeting.

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.

Because entrectinib was granted orphan drug designation for *NTRK* fusion-positive solid tumors by FDA's Office of Orphan Products Development on July 5, 2017, you are exempt from PREA requirements for this proposed indication. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD

submissions) of your NDA application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

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."

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.				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This

information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

ISSUES REQUIRING FURTHER DISCUSSION

As discussed above, a CMC Only meeting for entrectinib is scheduled for November 7, 2018. A summary of agreements on the content of a complete application will be reached at that meeting and documented in the meeting minutes.

ACTION ITEMS

Action Item/Description	Owner	Due Date
Genentech agreed to provide a more detailed description of the proposed data package to support approval for use in pediatric patients.	Genentech	Prior to the November 7, 2018 CMC Only meeting.
Proposed schedule for rolling NDA submission	Genentech	By November 1, 2018

ATTACHMENTS AND HANDOUTS

“Pre-NDA NTRK Responses to Preliminary Comments_final.pdf”

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
11/05/2018

**RESPONSE TO FDA REQUEST FOR ADDITIONAL INFORMATION
RECEIVED ON 12 OCTOBER 2018**

IND 120500

Entrectinib (RO7102122, RXDX-101)

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

October 16, 2018

CONFIDENTIAL

This is a Genentech, Inc. document that contains confidential information. Nothing herein is to be disclosed without written consent from Genentech, Inc.

Genentech proposes to further discuss the below questions at the Type B Pre-NDA meeting in the following sequence:

Clinical/Statistical Questions

Question 1

Does the Agency agree that the available clinical data package provides sufficient clinical evidence to characterize the benefit and risk of entrectinib in adult and pediatric patients with NTRK fusion-positive (b) (4) metastatic solid tumors to support NDA filing?

FDA Response

FDA agrees that the summary level efficacy results of ORR and DOR appear sufficient to support the filing of an NDA seeking accelerated approval for the proposed indication for entrectinib for the treatment of adult and pediatric patients with NTRK fusion-positive (b) (4) metastatic solid tumors.

Please confirm that, as discussed during the December 15, 2017 Type B BTD/Other meeting, Genentech will include efficacy analyses for all patients whose tumor harbors an NTRK fusion or other alteration (regardless of the presence or absence of any other mutations/co-drivers) who received at least one dose of entrectinib and inclusive of patients with non-measurable disease at baseline in the NDA submission. In the NDA submission, also include efficacy results for patients with primary CNS disease, and an analysis of efficacy by NTRK-fusion partner for all patients receiving at least one dose of entrectinib.

As also discussed during the December 15, 2017 meeting, FDA will determine the most appropriate population for evaluation of efficacy during review of the NDA, irrespective of the efficacy population prespecified in the statistical analysis plan.

Genentech Response

Genentech acknowledges the Agency's feedback and agrees to include the following efficacy analyses in the NDA:

- for all patients whose tumor harbors an NTRK fusion or other alteration (regardless of the presence or absence of any other mutations/co-drivers) who received at least one dose of entrectinib and inclusive of patients with non-measurable disease at baseline in the NDA submission.
- for patients with primary CNS disease
- by NTRK-fusion partner for all patients receiving at least one dose of entrectinib?

The Sponsor would like the Agency to clarify the request for efficacy analyses in the patients whose tumor harbors a non-fusion NTRK alteration (regardless of the presence or absence of any other mutations/co-drivers). Per Table 6 in FDA's Preliminary Comments, the 29 patients in this population include point mutations, insertions, deletions, and amplifications. Prior data have been published showing the lack of

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efficacy (Drilon A, Cancer Discovery 2017) in these patients with non-fusion NTRK alterations; thus, these data are not planned for inclusion in the NDA.

Two patients with NTRK-fusion positive tumors with co-occurring oncodrivers and 1 patient with an out-of-frame NTRK gene fusion will be listed in the efficacy non-evaluatable population as shown in Figure 1 of the meeting package.

Efficacy data in 6 patients with primary CNS tumors as evaluated by RANO criteria will be provided in the NDA as a separate analysis from the integrated RECIST-based efficacy analyses.

There was a large diversity of fusion partners among the efficacy evaluable patient population, with most fusion partners occurring in 1-2 patients. A line listing of BOR and DOR for one patient per row will be provided in the NDA and will include a column for fusion partner. As these data will not be included in the prescribing information, datasets for this analysis will not be separately provided for this table.

In summary, efficacy analyses of all the requested patients will be provided with the exception of 29 patients with non-fusion NTRK alterations.

Question 2

Does the Agency agree with the proposal to submit updated safety and efficacy data in the 90 Day Safety Update and that the new data would not impact the PDUFA date? Specifically, the Applicant proposes to submit:

- *an additional 5 months of safety follow-up for patients in the original NDA dataset*
- *updated DOR in responders in the original NDA dataset*
- *PK, safety and efficacy data from additional pediatric patients than were submitted in the initial application.*

FDA Response

No, FDA requests that Genentech update the safety and efficacy data at Day 60 (rather than Day 90) in order to permit sufficient time for FDA review. Efficacy data included in the Day 60 update should be limited to the efficacy population included in the original NDA submission. The Day 60 safety and efficacy update should also include updated datasets and text for the integrated summaries of safety and efficacy. In addition, an addendum to the clinical study report for each study contributing to efficacy also should be included with the updated pooled efficacy data to ensure that the study reports reflect these updated data. In this amendment to the NDA, provide a single dataset summarizing demographic information and updated tumor response data for each patient (1 row per patient) in the efficacy dataset as reflected in the summary tables to be provided, and a single updated safety dataset containing all safety information for each patient included in the safety analysis as described in the summary tables.

Although FDA does not anticipate that the contents of the Day 60 update will constitute a major amendment that would impact the PDUFA date, such a determination cannot be made until the new data are available for review.

Genentech Response

Genentech acknowledges the Agency's feedback.

The Sponsor would like to clarify whether the Agency agrees with the scope of the safety update report. To reiterate, in accordance with the agreement from the WRO Type B meeting on June 22, 2018, we are planning to provide:

- an additional 5 months of safety follow-up for patients in the original NDA dataset
- updated DOR in responders in the original NDA dataset

As requested by the Agency, no update to the ORR will be needed. The Sponsor is planning to update the DOR for the responders in a supplemental report that integrates all three studies. The patient-level response listing, including demographics, will be refreshed for the supplemental report.

The 3 patients contributing to the efficacy evaluable population from the ALKA and STARTRK-1 had already discontinued the study at the time of the initial CSR. Therefore, updated DOR will only be contributed by STARTRK-2 patients.

In the pooled efficacy analysis, data will be shown by individual study and overall. Therefore, the Sponsor does not plan to update any CSRs because the data, including pooled datasets, will be provided in the submission.

The Sponsor has additionally proposed to submit updated pediatric data including:

- PK, safety and efficacy data from additional pediatric patients than were submitted in the initial application.

These data would be provided as a supplemental report and would include an additional 10 patients for safety, including a subset of 4 patients for efficacy with at least 6 months of follow up from first response. The report would present analyses of the total pediatric population comprised of 26 patients for safety (16 patients in the original NDA and 10 additional patients) and 5 patients for efficacy (1 patient in the original NDA and 4 additional patients). The purpose of these data is to strengthen the pediatric data package. Does the Agency agree with this proposal?

Regarding the Agency's request for submission of the safety update report at Day 60, the Sponsor will evaluate feasibility and would like to come to a final agreement with the Agency before NDA submission.

Administrative/Regulatory Questions

Question 3

For the proposed NTRK fusion-positive tumor indication, does the Agency agree that the results demonstrate positive benefit-risk to support an accelerated approval in the proposed indication and that conversion to regular approval may be based on durable ORR from an additional 50 patients followed for a minimum of 6 months and additional follow up from the patients in the initial NDA?

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FDA Response

Because the proposed treatment effect of entrectinib is based on a surrogate endpoint that is reasonably likely to predict clinical benefit and because limited data will be submitted in the NDA for certain tumor types, FDA considers the accelerated approval pathway appropriate for the proposed NDA. If entrectinib is approved, the indication, including qualifications regarding prior therapy and the potential exclusion of primary CNS, will be determined during the review of the NDA.

During the review of the NDA, FDA will also consider the data necessary to support regular approval (e.g., additional follow-up and broader clinical experience), as described in a post-marketing requirement (PMR). With regard to the PMR, FDA cannot determine the extent of the data package that will be needed to verify clinical benefit until after the data included in the original NDA submission are reviewed. FDA will discuss post-marketing requirements and commitments with Genentech during the NDA review period, according to 21st Century Review timelines for new molecular entity NDAs.

Additionally, the proposed NDA should contain data characterizing the natural history of patients with NTRK fusion solid tumors and justification supporting a conclusion that the reported BICR-assessed ORR and DOR provide evidence of direct clinical benefit in the indicated population, considering the natural history of the disease and available therapy.

Genentech Response

Genentech acknowledges the Agency's feedback. No further discussion is needed at the meeting.

Question 4

Under the auspices of the BTD designation, the Applicant would like to request rolling review for the NTRK NDA in order to allow finalization of the CMC sections. Does the Agency agree with the proposal?

FDA Response

The plan to request rolling review of the proposed NDA is acceptable. FDA notes that agreements regarding the data content of the CMC modules will be discussed during the CMC-only pre-NDA meeting scheduled for November 7, 2018. Upon receipt of the request containing the schedule for submission of complete components of the NDA, FDA will discuss the acceptability of the proposed schedule. The request for rolling review should be submitted as soon as possible, but no later than November 1, 2018.

Genentech Response

Genentech acknowledges the Agency's feedback. No further discussion is needed at the meeting.

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Question 5

The proposed content of the NDA application is provided in Appendix 6. The Applicant may need to submit eCRFs from some healthy volunteer clinical pharmacology studies within 30 days after the original NDA submission. Does the Agency agree with the proposed content of the complete NDA and that some are not available at the time of submission?

FDA Response

FDA does not object to the submission of eCRFs from the healthy volunteer clinical pharmacology studies within 30 days after the original NDA submission as a late component. Regarding Module 5, Section 5.3.5.2, please submit both ADaM and SDTM datasets.

Genentech Response

We will be submitting the patient eCRFs for all the studies.

As per Genentech's communication to the agency on July 6, 2018 - All of the studies which are part of submission started prior to December 17, 2016 and will be placed as per the Module 5 eCTD structure in the legacy folder (non-CDISC) in accordance with the FDA guidance document "Providing Regulatory Submissions in Electronic Format - Standardized Study Data" (FDA 2014). In compliance with FDA's Guidance on Technical Rejection Criteria for Study Data (revised June 22, 2017), Genentech acknowledges that a Trial Summary dataset (TS.xpt) and Demographics (DM.xpt) will be submitted for each study even if the study started prior to December 17, 2016.

Clinical Pharmacology Questions

Question 6

Does the Agency agree that the overall clinical pharmacology program, including the DDI strategy, is sufficient to support registration of entrectinib?

FDA Response

The proposed clinical pharmacology package appears to be acceptable for the proposed NDA. Genentech proposes to use the physiologically based pharmacokinetic (PBPK) approach to evaluate the impact of moderate and weak CYP3A inhibitors/inducers and CYP3A sensitive substrates. The acceptability of PBPK modeling and all other components of the clinical pharmacology package will be determined at the time of review of the planned NDA submission.

Genentech Response

Genentech acknowledges the Agency's feedback. No discussion is needed at the meeting.

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Question 7

Does the Agency agree with the proposed content, structure and format of the datasets for clinical pharmacology studies?

FDA Response

Yes, FDA generally agrees with the proposed content, structure, and format of the datasets for the clinical pharmacology studies. However, a final determination will be made prior to filing of the planned NDA submission.

For the population PK analysis, please also submit dataset and analysis codes for exposure-response analyses for efficacy and safety. For PBPK analysis, the PBPK modeling report should describe in detail the development of the PBPK model and any assumptions being made. Model files used to generate the final PBPK simulations (e.g., drug model files and workspace files) should be submitted. Software-specific files such as parameter estimation data files, simulation outputs, sensitivity analysis and observed clinical data should be submitted as MS Excel files. Refer to the following FDA guidance for additional information entitled, “Physiologically Based Pharmacokinetic Analyses-Format and Content. Guidance for Industry,” (August 2018) available at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm531207.pdf>.

Genentech Response

Genentech acknowledges the Agency’s feedback. No discussion is needed at the meeting.

Question 8

Does the Agency agree with the proposed clinical Modeling and Simulation analysis plan for entrectinib?

FDA Response

Yes, FDA generally agrees with the proposed clinical modeling and simulation analysis plan for entrectinib. However, a final determination will be made at the time of review of the planned NDA submission. Tumor size modeling may be submitted as the PK/PD analysis along with the population PK analysis. Please also submit exposure-efficacy analyses for primary and major secondary clinical efficacy endpoints for each specific indication. Please also submit exposure-safety analyses for adverse events of special interest (e.g., neurotoxicity, hepatotoxicity).

Genentech Response

Genentech acknowledges the Agency's feedback and confirms that exposure-efficacy analyses for primary clinical efficacy endpoints for each specific indication will be submitted. Could the Agency clarify which major secondary endpoints are requested?

For exposure-safety analyses for selected AEs (i.e. neurological toxicity, liver dysfunction, hematologic toxicity, and pneumonitis), there are insufficient patients with these AEs to build a model. Therefore, exposure of the identified patients will be tabulated. Exposure QTc will be presented in the PopPK report.

Question 9

Does the Agency agree with the proposed strategy to provide an estimated pediatric dose recommendation with the commercial formulation (F06)?

FDA Response

FDA is unable to answer this question due to insufficient information about the proposed dosing regimen in the current submission. The proposed timing of submission of the bridging study may not permit adequate time for review during the initial NDA review cycle if it is not included in the original NDA submission.

Due to limited clinical pharmacology data provided in the meeting package, FDA is unable to determine whether the formulation bridging, the allometric scaling in children > 4 years old, and the PBPK modeling for younger children would be sufficient to support a dosage recommendations for the commercial formulation (F06) that is safe and effective in pediatric patients. Per current practice, PBPK modeling and simulation in children should be verified with sufficient clinical data. PBPK predictions cannot be used prospectively to support pediatric dose recommendations in the absence of clinical data.

Please also see FDA's Additional Clinical Comment 13.

Genentech Response

Genentech acknowledges the Agency's feedback.

The Sponsor would like to clarify that pediatric patients in the STARTRK-NG clinical trial have been dosed with F1 formulation, not suitable for commercial use. F06 will be the commercial formulation for patients who can swallow capsules.

At the time of the initial PMP submission, the PopPK model and extrapolation analyses were ongoing and the recommended pediatric dose with F06 could not be provided.

Since then, comprehensive modeling analyses have been completed and demonstrated that the systemic exposure seen in pediatric patients is comparable to the observed and estimated exposure in adults, based on the following:

- The PopPK model was built with clinical data using F2A formulation.
- Bioequivalence was demonstrated between F2A/F06.

- Thus, PopPK results can justify the use of F06 in pediatric patients who are able to swallow:
 - The pharmacokinetics of entrectinib and M5 are comparable in adults and children based on NCA and PopPK approaches.
 - The PopPK characterized the PK of entrectinib and M5 in both patient population (adults and children)
 - The PopPK has been used to predict the dose in pediatrics to match the adult target exposure taking into account the difference between F2A/F06 and F1.
 - The estimated pediatric dose with F06 based on PopPK modeling is 300 mg/m².
 - Different modeling approaches (PopPK and PBPK-GastroPlus – where maturation is being taken into account) resulted in the same estimated dose of 300 mg/m² in pediatric patients able to swallow, increasing the confidence and robustness of the estimation.
 - The current estimated pediatric dose BSA-adjusted gives an exposure (predicted AUC_t at steady state) equivalent to the one predicted and observed in adults receiving a 600 mg QD flat dose (~ 300 mg/m²).
 - Based on the exposure/safety relationship analyses conducted in adults – no exposure safety relationship has been found, indicating a wide therapeutic window.
 - F06 at the 300mg/m² dose will be introduced into the pediatric clinical trial STARTRK-NG by the end of 2018.

In addition, the ongoing rBA study between F1/F06 should provide reassurance of the proposed estimated dose.

In conclusion, based on the current available information, the Sponsor believes that the current estimated dose in pediatrics with F06 is sufficient to ensure clinical response.

Does the Agency agree that the information provided is sufficient to support the recommended pediatric dosing with F06?

Could the Agency clarify the timing of the following request “As soon as possible, please provide information regarding the proposed pediatric dosage regimen and available data to support the proposed pediatric dosage regimen”? Specifically, does the Agency want this information to be submitted before NDA submission?

Non Clinical Questions

Question 10

Does the Agency agree with the toxicology data package to support the NDA and that no additional studies are required?

FDA Response

Yes, the toxicology data package appears sufficient to support the submission of the proposed NDA.

Genentech Response

Genentech acknowledges the Agency's feedback. No discussion is needed at the meeting.

Companion Diagnostic Questions

Foundation Medicine, Inc. (FMI) requested a Pre-Submission meeting for the F1CDx sPMA with CDRH in October, to coordinate with the entrectinib Pre-NDA meetings. FMI's Pre-Submission meeting package submitted to CDRH includes comprehensive analytical and clinical validation plans for the F1CDx sPMA to support co-filing of F1CDx as the companion diagnostic for entrectinib. The analysis reports will be included in the F1CDx sPMA.

Question 11

Do CDER and CDRH agree that this analysis plan will support co-filing of F1CDx sPMA for the CDx claim for selection of patients whose tumors harbor NTRK or ROS1 rearrangements for whom entrectinib is indicated?

FDA Response

There is insufficient information for FDA to determine whether the proposed analysis plan will support filing the F1CDx sPMA for the CDx claims for selection of patients whose tumors harbor NTRK or ROS1 rearrangements for whom entrectinib is indicated. FDA acknowledges that the pre-submission from FMI was received under pre-submission number Q181647; a meeting between the device sponsor (FMI) and CDRH is scheduled to take place on November 1, 2018. CDRH will provide pre-meeting written feedback to the pre-submission questions to FMI by October 26, 2018, as per the pre-submission process.

Based on the limited information provided in the meeting package, it appears that there could be a very small number of efficacy-evaluable patients available for the proposed clinical bridging study, leading to considerable amount of uncertainty in the bridging study results. Given the low prevalence of the NTRK and ROS1 fusions, the positive predictive value (p(representative LDT (Trailblaze Pharos) +|F1CDx+)) could be very low even when negative percent agreement (NPA) (p(CDx-| representative LDT (Trailblaze Pharos) -)) is high and therefore the intent-to-treat population with F1CDx positive results will be dominated by (representative LDT (Trailblaze Pharos)-,F1CDx+) patients who were excluded from the trial with no clinical outcomes. Ideally the estimated NPA and its confidence interval should be very close to 100% for the feasibility of the bridging study. FDA strongly recommends that Genentech perform the above simulations for sensitivity analyses to assess the feasibility of the bridging study and if feasible,

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determine the required number of samples, especially negative samples to target an adequate NPA for the proposed bridging study.

As the device will be evaluated based on the totality of the data from the bridging study including concordance study between representative LDT (Trailblaze Pharos) and F1CDx, an appropriate positive percent agreement (PPA, including CI) is also required no matter whether the bridging efficacy analysis is feasible or not. Genentech may procure positive samples in addition to the clinical trial samples to achieve the desired PPA.

Genentech Response

Genentech acknowledges the Agency's feedback. Per FDA, feedback for the companion diagnostic questions is applicable for both the NTRK and ROS1 NDAs. We would like to request the following feedback:

We would like to confirm with CDRH that using TNA (total nucleic acid) samples in the concordance study and clinical bridging is acceptable to support the planned sPMA, and that the TNA will be tested with F1CDx as described in the TNA feasibility study (refer to Pre-Submission Q181647 attachment 3, "QSR-DEV-RPT-025-01 QSR Development Report for Feasibility Evaluation of Processing Total Nucleic Acid (TNA) in the F1CDx Assay").

The Sponsors would like to clarify that we plan to discuss details of the requested simulations for feasibility of the proposed bridging study at the CDRH Pre-Submission meeting on Nov 1. We also plan to provide the complete clinical validation for F1CDx including imputation and sensitivity analyses in the final sPMA submission for both NTRK and ROS1. Does the Agency agree with this approach?

Furthermore, we would like to seek clarification on FDA's feedback on Question 4a for ROS1 meeting package. The Agency stated, "data relevant to companion diagnostic test linked to the proposed indication for entrectinib of the treatment of patients with ROS1-positive (b) (4) metastatic NSCLC should be submitted to the NDA containing the clinical efficacy data for this indication". Clinical and analytical validation data supporting F1CDx as the companion diagnostic for the proposed ROS1 indication for entrectinib will be included in the planned sPMA submission. The same clinical validation report can be submitted to the NDAs concurrently with the sPMA submission. Does the FDA agree with this approach?

Question 12

In case CDRH requires more or different analyses impacting availability timing of the sPMA data package, does CDER agree that entrectinib NDAs may be filed without contemporaneous filing of F1CDx sPMA?

FDA Response

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FDA will not determine whether to file the proposed NDA until after the NDA is submitted; however, because entrectinib is intended to treat a serious and life threatening disease for which no satisfactory alternative treatment exists and the benefit from the use of entrectinib is likely to outweigh the risk from the lack of an approved or cleared IVD companion diagnostic device, FDA will consider filing the entrectinib NDA for the proposed indication if contemporaneous filing of the F1CDx sPMA is not possible.

Genentech Response

Genentech acknowledges the Agency's feedback. No discussion is needed at the meeting.

Additional FDA Comments

Clinical

13. The meeting package contains insufficient information for FDA to determine whether the proposed use of the F06 commercial formulation is appropriate for pediatric patients. The doses achievable using the commercial formulation (F06) strengths of 100 mg and 200 mg may not provide the optimal entrectinib exposure in younger pediatric patients. Furthermore, no information has been provided regarding clinical experience with dosing of pediatric patients under the intended directions for use to be described in the package insert. Please characterize the data available from clinical experience in clinical trials, included safety (including medication errors) and pharmacokinetic data that support this proposed dose and preparation for administration of the commercial product in pediatric patients. As soon as possible, please provide information regarding the proposed pediatric dosage regimen and available data to support the proposed pediatric dosage regimen.
14. As soon as possible, please provide information regarding the status of development of the pediatric formulation of entrectinib.
15. In the original NDA submission, provide a draft Instructions for Use document for caregivers who are expected to prepare and administer entrectinib to pediatric patients.

Genentech Response for FDA Comment 13

Genentech acknowledges the Agency's feedback and refers the Agency to the response to Question 9 for the justification for the dose and exposure.

At the time of the initial NDA for entrectinib, only F06 formulation will be commercially available for adult and pediatric patients who can swallow intact capsules. (b) (4)

(b) (4)

(b) (4) Therefore, the F06 capsule formulation is specified not to be opened and coadministered with food or liquid.

The F1 formulation is not suitable for commercial use and has only been used in the STARTRK-NG and ALKA-372-001 (Phase 1, Italy) trials. In the STARTRK-NG trial, F1 has been used both for pediatric patients who are able to swallow capsules and in at least 6 pediatric patients who are unable to swallow capsules.



All the arguments to support implementation of F06 in pediatric patients able to swallow capsules are outlined in Question 9.

Could the Agency clarify the timing of the following request “As soon as possible, please provide information regarding the proposed pediatric dosage regimen and available data to support the proposed pediatric dosage regimen”? Specifically, does the Agency want this information to be submitted before NDA submission?

Genentech Response for FDA Comment 14

For the final age-appropriate formulation(s), the Sponsor is currently evaluating solubility enhancing, multiparticulate solid oral formulation options, including mini-tablets, granules, and pellets. Following formulation development, one or more prototype formulations will be evaluated in a relative bioavailability study in 2019, prior to introduction into study STARTRK-NG by December 2019. The palatability challenge of these formulation prototypes is planned to be addressed (b) (4)

(b) (4). Formulation taste acceptance will be confirmed in a taste panel assessment. (b) (4)



Genentech Response for FDA Comment 15

As detailed in the Sponsor’s response under Question 13, the F06 capsule formulation is specified not to be opened. At the tie of the initial NDA, only the entrectinib F06 formulation will be commercially available for adult and pediatric patients who can swallow intact capsules. As such, the label/USPI will not contain instructions specifically for caregivers who are expected to prepare and administer entrectinib to pediatric patients.

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Clinical Pharmacology

FDA's Comment

23. Include the following items in the submitted your QT study report:

- k. Adverse Event analysis using the MedDRA SMQ “Torsade de pointes/QT Prolongation” and include the preferred term “Seizure” by treatment and dose level.
- l. Narrative summaries and case report forms for any
 - a. Deaths
 - b. Serious adverse events
 - c. Episodes of ventricular tachycardia or fibrillation
 - d. Episodes of syncope
 - e. Episodes of seizure
 - f. Adverse events resulting in the subject discontinuing from the study

Genentech Response

- k. The Sponsor plans to provide an analysis of adverse events identified using the MedDRA SMQ “Torsade de pointes/QT Prolongation” and also separately, an analysis of adverse events with the MedDRA Preferred Term of “Seizure” within the Summary of Clinical Safety. The current QT substudy has been conducted as part of the STARTRK-2 study with all patients dosed at the RP2D of 600mg daily. Therefore an analysis by dose level is not possible.
- l. The Sponsor had previously agreed with the Agency on narrative categories in a follow up communication to the Type C WRO meeting provided on 16 July 2018 to include:
 - AEs leading to Deaths
 - AE leading to discontinuation
 - Serious adverse events (SAEs)

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- Non-serious adverse events of \geq Grade 3 in severity, specifically for:
 - neurological toxicity
 - liver dysfunction
 - hematologic toxicity
 - prolonged QTc
 - pneumonitis requiring dose modification

Based on this previous agreement, the Sponsor will provide narratives for any SAEs of ventricular tachycardia or fibrillation, syncope, and seizures. The Sponsor will also provide an analysis of these adverse events (serious and non-serious) within the Summary of Clinical Safety.

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
11/05/2018



IND 120500

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

Ignyta, Inc.
Attention: Sunni Churchill
Senior Director, Regulatory Affairs
4545 Towne Centre Court
San Diego, CA 92121

Dear Ms. Churchill:

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 March 30, 2017, request for Breakthrough Therapy designation with your proposed indication of entrectinib for the treatment of NTRK fusion-positive, locally advanced or metastatic solid tumors in adult and pediatric patients, (b) (4), who have either progressed following prior therapies or who have no available standard therapies. We are revising the indication to entrectinib for the treatment of NTRK fusion-positive, locally advanced or metastatic solid tumors in adult and pediatric patients who have either progressed following prior therapies or who have no acceptable standard therapies, and have determined that this revised indication meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation with the revised indication noted above. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of entrectinib for the treatment of NTRK fusion-positive, locally advanced or metastatic solid tumors in adult and pediatric patients who have either progressed following prior therapies or who have no acceptable standard therapies to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.¹

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy- Designated Drugs and Biologics*, Attachment 1, for potential topics for discussion at this initial Breakthrough Therapy meeting². Please refer to the *Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants*³ for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

If the Breakthrough Therapy designation for entrectinib for the treatment of NTRK fusion-positive, locally advanced or metastatic solid tumors in adult and pediatric patients who have either progressed following prior therapies or who have no acceptable standard therapies is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, call Claire Myers, Ph.D., Regulatory Project Manager, at (240) 402-6612.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

²

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>

³ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

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

/s/

PATRICIA KEEGAN
05/12/2017

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 <u>60</u> 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 and pediatric patients, including those (b)(4) 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-threatening¹? 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 therapy²/ 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- γ , 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

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	<i>NTRK1</i>	<i>NTRK2</i>	<i>NTRK3</i>
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 to consult CDRH for advice in the development of a companion diagnostic.

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 designation³.**

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).

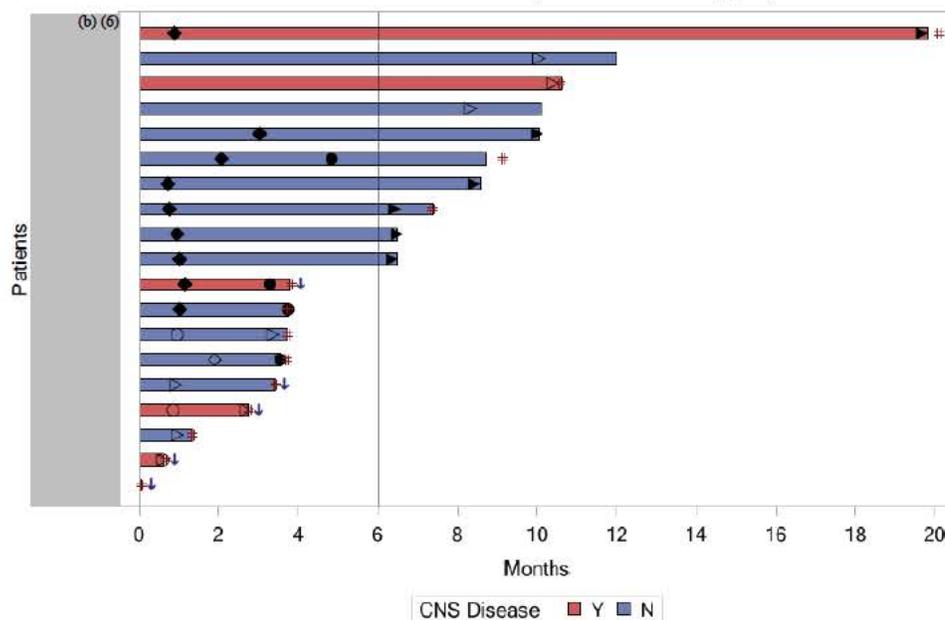
Nine of the 19 evaluable patients are partial responders (per independent review) = **ORR 47.4% (95% CI: 24.5%, 71.1%)**, and there are no patients with a complete response (CR). Clinical activity in patients with CNS disease consists of 2 out of 6 (33%) patients (1 stable disease and 1 partial response). **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) 46/M/1/Y	NSCLC	4	<i>SQSTM1-NTRK1</i>	PR	PR	18.82	18.82*	19.84	N	CNS CR
2	ST-1 57/M/0/Y	PBT	0	<i>BCAN-NTRK1</i>	SD	SD	NA	NA	10.39	N	Lesions [60% 3D-vol assessment ^a
3	ST-1 42/F/1/N	MASC	4	<i>ETV6-NTRK3</i>	PR	PR	4.64	2.80	8.72	N	
4	ST-2/ (b) (6) 75/F/1/N	Ovarian	4	<i>ETV6-NTRK3</i>	SD	SD*	NA	NA	12.01	Y	BICR non-measurable at baseline
5	ST-2/ 28/M/1/N	NET	1	<i>ETV6-NTRK3</i>	PD	SD	NA	NA	10.10	Y	
6	ST-2/ 48/M/1/N	MASC	2	<i>ETV6-NTRK3</i>	PR	PR	5.66*	5.66*	7.37	N	
7	ST-2/ 67/F/1/N	Uterine	2	<i>ETV6-NTRK3</i>	SD	PR	NA	6.97*	10.03	Y	
8	ST-2/ 47/F/1/N	STS	2	<i>IPM3-NTRK1</i>	PR	PR	7.73*	7.73*	8.39	Y	
9	ST-2/ 56/F/1/N	mCRC	1	<i>ETV6-NTRK3</i>	PD	PD	NA	NA	3.72	N	
10	ALKA (b) (6) 75/F/1/N	mCRC	3	<i>LMNA-NTRK1</i>	PR	PD	2.63	NA	3.56	N	BICR missing Cycle 1 scan
11	ST-2/ (b) (6) 56/M/1/N	STS	3	<i>PEAR1-NTRK1</i>	uSD	uSD	NA	NA	3.42	N	
12	ST-2/ 48/M/0/N	STS	0	<i>IPM3-NTRK1</i>	PR	PR	2.76	2.76	3.72	N	
13	ST-2/ 36/F/2/N	Breast	4	<i>ETV6-NTRK3</i>	PR	PR	5.56*	5.56*	6.48	Y	
14	ST-2/ 46/M/1/Y	Gastric	4	<i>MDM4-NTRK1</i>	PD	PD	NA	NA	2.76	N	
15	ST-2/ 65/F/0/N	NSCLC	1	<i>ETV6-NTRK3</i>	PR	PR	6.05*	5.36*	6.48	Y	
16	ST-2/ 73/M/2/N	NSCLC	3	<i>ETV6-NTRK3</i>	uSD	uSD	NA	NA	1.35	N	Squamous NSCLC
17	ST-2/ 52/F/3/Y	PBT	1	<i>unK-NTRK1</i>	PD	PD	NA	NA	0.59	N	ECOG 3 at baseline
18	ST-2/ 57/F/3/Y	MASC	3	<i>ETV6-NTRK3</i>	ND	ND	NA	NA	0.07	N	ECOG 3 at baseline
Pediatric Population											
19	ICU (b) (6) 18mo/M/4/Y	IF	2	<i>ETV6-NTRK3</i>	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
NTRK1/2/3 BICR Duration of Response and Time on Study (N=19)



◆ = 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 the development of a diagnostic test.

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



IND 120500

MEETING MINUTES

Ignyta Operations, Inc.
Attention: Patti O'Sullivan
Regulatory Affairs Consultant
11095 Flintkote Avenue, Suite D
San Diego, CA 92121

Dear Ms. O'Sullivan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for entrectinib (RXDX-101).

We also refer to the meeting between representatives of your firm and the FDA on January 29, 2015. The purpose of the meeting was to discuss the overall design of your two proposed studies (RXDX-101-03 "STARTRK 3, a randomized, multicenter, active-comparator study and RXDX-101-02 "STARTRK 2, a multicenter, single-arm study) to support traditional approval for treatment of patients with advanced ROS1-positive and advanced NTRK^{(b) (4)}-positive ^{(b) (4)} NSCLC and accelerated approval, respectively, of RXDX-101 for the treatment of patients with advanced NTRK^{(b) (4)}-positive ^{(b) (4)} NSCLC.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-6612.

Sincerely,

{See appended electronic signature page}

Claire Myers, Ph.D.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Meeting Minutes
Ignyta Slide Presentation
Ignyta Responses to FDA Preliminary Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2/Pre-Phase 3

Meeting Date and Time: Thursday January 29, 2015, 2:30-3:30 PM EST
Meeting Location: FDA, White Oak Building 22, Room 1313

Application Number: IND 120500
Product Name: Entrectinib (RXDX-101)
Proposed Indication: NTRK ^{(b) (4)}-positive and ROS1-positive ^{(b) (4)} metastatic non-small cell lung cancer (NSCLC), as detected by an FDA-approved test

Sponsor/Applicant Name: Ignyta Operations, Inc.

Meeting Chair: Gideon Blumenthal, M.D.
Meeting Recorder: Claire Myers, Ph.D.

FDA ATTENDEES

Patricia Keegan, M.D., Division Director, DOP2
Luckson Mathieu, M.D., Clinical Reviewer, DOP2
Gideon Blumenthal M.D., Clinical Team Leader, DOP2
Claire Myers, Ph.D., Regulatory Project Manager, DOP2
Karen Boyd, M.S., Senior Regulatory Project Manager, DOP2
Stephanie Aungst, Ph.D., Pharmacology/Toxicology Reviewer, DHOT
Whitney Helms, Ph.D., Pharmacology/Toxicology Team Leader, DHOT
Olen Stephens, Ph.D., CMC Branch Chief, ONDQA
Laura Fernandes, Ph.D., Statistical Reviewer, DBV
Shenghui Tang, Ph.D., Statistical Team Leader, DBV
Sriram Subramaniam, Ph.D., Clinical Pharmacology Reviewer, DCPV
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader, DCPV
Prakash Jha, Lead Reviewer, OIR/CDRH
Reena Philip, Division Director, OIR/CDRH
Martin Mendoza, Ph.D., Health Programs Coordinator, OC/OMH

SPONSOR ATTENDEES

Jonathan Lim, M.D., Chairman and CEO
Adrian Senderowicz, M.D., Chief Medical Officer
Robert Wild, PhD, CSO and SVP, Research
Zachary Hornby, Chief Operating Officer and Entrectinib Program Leader
Patti O'Sullivan, Entrectinib Regulatory Lead
Jason Christiansen, Ph.D., Senior Director, Diagnostic Assay Development
(b) (4) Clinical Consultant
Larry Roi, Statistician
Jay Yang, Statistician

1.0 BACKGROUND

On November 10, 2014, Ignyta submitted a Type B meeting request to discuss the development of entrectinib (RXDX-101) and the overall design of their two studies (a randomized, parallel cohort, active-comparator (docetaxel) study and a single-arm, multicenter study) to support approval of entrectinib for the treatment of patients with advanced ROS1-positive and advanced NTRK (b) (4) -positive (b) (4) NSCLC. Preliminary comments were sent to Ignyta on January 27, 2015.

Brief Regulatory History

On December 4, 2013, Ignyta, Inc. (Ignyta) submitted a pre-IND meeting request to discuss the development of entrectinib and on February 3, 2014, FDA issued responses to these questions in a written response only (WRO) format. On February 27, 2014, Ignyta submitted an Investigational New Drug Application (IND) to evaluate entrectinib in patients with locally advanced or metastatic solid tumors (IND 120500), and this study was allowed to proceed on March 28, 2014.

Ignyta states that a request for orphan drug designation was submitted to the Office of Orphan Products Development on November 14, 2014 for entrectinib for the treatment of TrkA/B/C-positive, ROS1-positive, and ALK-positive NSCLC and TrkA/B/C-positive, ROS1-positive (and ALK-positive colorectal cancer (CRC)) and is still pending review.

Chemistry, Manufacturing and Controls (CMC)

Entrectinib is currently available as 50, 100, and 200 mg oral capsules. The capsules are dose proportional, formulated with compendial excipients (b) (4) (b) (4) in a hard (b) (4) capsule without overages. The capsules are packaged in (b) (4) High Density Polyethylene (HDPE) bottles closed with twist-off (b) (4) caps. (b) (4).

Nonclinical

Entrectinib is an orally-available adenosine triphosphate competitive inhibitor of the tyrosine kinases TrkA, TrkB, TrkC, ROS1, and ALK, with IC₅₀ values in the nanomolar range. In the current meeting package, nonclinical information is limited to pharmacology data on entrectinib; however, in the meeting request dated November 10, 2014, Ignyta states that following the

determination of the clinical dosing schedule, they plan to conduct 13-week, repeat-dose toxicology studies in dogs and rats in parallel with the clinical registration studies described in the current meeting package.

Clinical

Ignya is proposing to pursue registration to conduct the following studies in support for accelerated and full approval of entrectinib in the treatment of ROS1-positive and TrkA/B/C-positive patients with (b) (4) metastatic NSCLC.

1. RXDX-101-02 “STARTRK 2”—a multicenter, single-arm, open-label study of entrectinib in any line, crizotinib-naïve ROS1 or TrkA/B/C rearranged advanced NSCLC patients in the US and Europe. Patients will be screened by a 2-step diagnostic assay; IHC followed by next generation sequencing (NGS) conducted in Ignya’s central lab to detect ROS1 and TrkA/B/C fusions.
2. RXDX-101-03 “STARTRK 3”—a multicenter, international, randomized, open-label study comparing entrectinib versus docetaxel in second line ROS1 or TrkA/B/C rearranged advanced NSCLC patients primarily outside of the US.
3. Supportive Studies:
 - a. ALKA-372-001—This on-going, first-in-human (FIH), dose escalation, open-label study of entrectinib in adult patients with locally advanced or metastatic solid tumors with identified molecular alterations of TrkA, ROS1, and ALK was initiated in October 2012 in Italy. Per Ignya, 31/40 patients have been enrolled in one of the three dose schedules (A: 4 days on/3 days off for 3 weeks in fasted condition, B: daily treatment for 28 days in fed conditions, and C: 4 days on/3 days off (4 week cycle) in fed condition). Ignya reports that 6 of the first 25 patients treated with entrectinib in ALK-372-001 have had complete or partial responses by RECIST criteria and an additional 2 patients have had stable disease for 11 and 18 treatment cycles as shown in Figure 19 from the December 28, 2014 Meeting Package.

Figure 19 ALKA-372-001: TrkA, ROS1 and ALK Patients Exhibiting Clinical Antitumor Activity

Tumor type (Alteration)	Dose (mg/m ²)	Treatment Cycles / Months												Best Response
		2	4	6	8	10	12	14	16	18	20	22	24	
Neuroblastoma (ALK)	200→400→800→1200 (A)													PR
NSCLC (ALK)	1200→800 (A)													PR
NSCLC (ROS1)	1200 (A)													PR
NSCLC (ROS1)	400 (C)													PR
CRC (TrkA)	1600 (A)													PR
NSCLC (ROS1)	400 (C)													CR
NSCLC (ROS1)	400 (B)													PR

CR = complete response; PR = partial response

Schedule A = 4-day on, 3-day off dosing for 3 weeks, followed by 7-day rest

Schedule B = continuous once daily dosing

Schedule C = continuous 4-day on, 3-day off dosing

Timing of CR

Timing of PR

Ignyta reports that the safety data for the first 25 patients enrolled in ALKA-372-001 revealed no dose-limiting toxicity (DLT). The most frequently reported adverse events have been nausea (68%), paresthesia (56%), asthenia (52%), vomiting (40%), abdominal pain (32%) and diarrhea, back pain, and myalgia (26%). The incidence of adverse events that were Grade 3 or 4 in severity are shown in Table 11 from the December 28, 2014 Meeting Package.

Table 11 Preliminary^a Treatment-Emergent Adverse Events Considered CTCAE Grade 3 or 4 in Severity in Study ALKA-372-001 as of 22 December 2014

Adverse Event	Schedule A (100-1600 mg/m ² /day) (N=19)	Schedule B (200-400 mg/m ² /day) (N=6)	Schedule C (400-800 mg/m ² /day) (N=6)	Total (N=31)
Any Grade 3 or 4 AE	6 (32%)	2 (33%)	1 (17%)	9 (29%)
Gastrointestinal Disorders				
Ascites	G3: N = 1 (5%)	0	0	G3: N = 1 (3%)
Intestinal obstruction	0	0	G3: N = 1 (17%)	G3: N = 1 (3%)
General Disorders and Administrative Site Conditions				
Asthenia ^b	G3: N = 1 (5%)	0	0	G3: N = 1 (3%)
General physical health deterioration	G3: N = 1 (5%)	0	0	G3: N = 1 (3%)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	G3: N = 2 (11%)	0	0	G3: N = 2 (6%)
Pneumonia	G3: N = 1 (5%)	0	0	G3: N = 1 (3%)
Metabolism and Nutrition Disorders				
Lipase increased	G3: N = 1 (5%) G4: N = 1 (5%)	G3: N = 1 (17%)	0	G3: N = 2 (6%) G4: N = 1 (3%)
Cardiovascular System Disorders				
Myocardial infarction	0	G3: N = 1 (33%)	0	G3: N = 1 (3%)
Blood and Lymphatic System Disorders				
Anemia	Grade 3: 1 (5%)	G3: N = 1 (17%)	0	G3: N = 2 (6%)
Psychiatric Disorders				
Confusional state	Grade 3: 1 (5%)	0	0	G3: N = 1 (3%)

Schedule A = 4-day on, 3-day off dosing for 3 weeks, followed by 7-day rest

Schedule B = continuous once daily dosing

Schedule C = continuous 4-day on, 3-day off dosing

- a. The adverse events listed were captured in the safety database as of 22 December 2014. The data has not been audited and is subject to change
- b. The case of severe asthenia was considered to be related to entrectinib and resolved when the entrectinib dose was reduced from 1200 to 800 mg/m²/day
- b. RXDX-101-01—This on-going, multi-center, international, dose escalation/dose expansion, open-label study evaluating entrectinib when administered on a continuous daily basis in adult patients with locally advanced or metastatic solid tumors with identified molecular alterations of TrkA/B/C, ROS1, and ALK was initiated on July 2014 after being deemed safe to proceed by the FDA. Per Ignyta, 10 of 140 planned patients have been enrolled and received entrectinib according to schedule B in the ALKA-372-001 study. Dose escalation will occur according to the standard 3+3 scheme until the recommended Phase 2 dose (RP2D) is determined. Ignyta plans to enroll patients in six dose expansion cohorts according to differentiated by molecular alteration and irrespective of tumor histology. According to the Ignyta, the following 6 expansion cohorts are planned with approximately 20 patients enrolled per cohort:
- (1) TrkA mutation-positive,
 - (2) TrkB mutation-positive,
 - (3) TrkC mutation-positive,
 - (4) ROS1 mutation-positive,
 - (5) ALK mutation-positive (treatment-naïve to ALK inhibitors), and

(6) ALK mutation-positive (received at least one prior ALK inhibitor).

Ignyta anticipates at least 60 patients would have been treated with entrectinib for several months before initiation of registration studies.

Clinical Pharmacology:

The briefing package is limited to preliminary activity, safety, and pharmacokinetic results of ongoing Phase 1 dose-escalation studies (ALKA-372-001 and RXDX-101-01) in patients with TrkA, ROS1, or ALK molecular alterations. Ignyta stated that once the optimal dose regimen is selected for entrectinib, the proposed clinical studies will be initiated. Based on the preliminary results, Ignyta reported that entrectinib is well tolerated between 100 mg/m² and 1,600 mg/m² when administered on an intermittent schedule of 4 days on, 3 days off, followed by a 7-day rest, under fasted or fed conditions. With food, PK exposure increased within 2-fold range and, according to Ignyta, reduced the incidence of gastrointestinal disorders compared to the fasted state. The mean elimination half-life following multiple dosing under the fed state was reported to be 17 to 32 days. *In vitro* results (from version 5 of the Investigator's Brochure) suggest that entrectinib is metabolized by CYP3A4, 2C19, 2C8, and 2C9, and has a potential for inhibition of CYP2C9, 2D6, and 3A4, and for the induction of CYP1A1, 2B6, and 3A4. Ignyta has not performed any PK drug-interaction studies. Furthermore, the QT prolongation potential of entrectinib in patients has not been assessed.

RXDX-101-02:

Ignyta proposes to conduct Study RXDX-101-02, entitled "A Phase 2, Multicenter, Open-Label Study of RXDX-101 in Adult Patients with Locally Advanced or Metastatic NSCLC that is Positive for ROS1, TrkA, TrkB, or TrkC Fusions." This "STARTRK-2" study is intended to support a request for accelerated approval of entrectinib for the proposed indication of treatment of patients with NSCLC with ROS1 (b) (4).

Ignyta will place eligible patients into 1 of 2 biomarker groups (ROS1 or Trk A/B/C group). According to Ignyta, the planned sample size is 75 patients for each two biomarker groups and all patients in the study will receive entrectinib orally according to the dose regimen and schedule yet to be selected (either once or twice daily on either a daily basis or on a continuous schedule of 4 days on treatment and 3 days off treatment) in repeated 4-week cycles, in a fed state. Patients will have radiological tumor assessment performed at the end of Cycle 1, then approximately every 8 weeks thereafter. All radiological images will be transmitted to an independent central radiology laboratory for assessment. Treatment may continue until the patient experiences disease progression, as determined by independent central radiology review; withdraws consent; or experiences unacceptable toxicity.

The primary objective of this study is objective response rate (ORR) as defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) according to RECIST v1.1, as assessed by an independent radiology review. Secondary objectives are duration of response, time to response, disease control rate, disease control rate, progression-free response, overall survival, and intracranial tumor response for patients with brain metastases using Response Assessment in Neuro-Oncology (RANO) criteria. According to Ignyta, an ORR

of 15% is considered to be uninteresting for further study in a given biomarker group, while an ORR of $\geq 32\%$ is considered interesting for further exploration. The statistical null hypothesis that the ORR is less than or equal to 0.15 versus the alternative hypothesis that the ORR is greater than or equal to 0.15 will be tested and according to Ignyta with 70 evaluable patients in a biomarker group and the true response rate equal to 0.32, there is approximately 90% power to reject the null hypothesis that the ORR is less than or equal to 0.15 versus that alternative hypothesis that it is greater than 0.15 with a one-sided $\alpha=0.025$ using a single stage design. Ignyta plans to reject the null hypothesis if greater than or equal to 17 objective responses are observed among the 70 evaluable patients per group. According to Ignyta, a response evaluable population is defined as those patients who have received at least one dose of the study drug and who are assessed by an independent radiology review as having measurable disease at baseline and one subsequent radiology evaluation while on treatment.

RXDX-101-03:

Ignyta proposes to conduct Study RXDX-101-03, entitled “ A Phase 3, Multicenter, International, Open-Label, Randomized , Active Comparator study of RXDX-101 or Docetaxel in Previously-Treated Adult Patients with Locally Advanced or Metastatic NSCLC that are Positive for ROS1, TrkA, TrkB, or TrkC Fusions (STARTRK-3),” to verify of the clinical benefit of entrectinib in patients receiving second-line therapy for ROS1 rearrangement-positive NSCLC and for Trk A/B/C rearrangement-positive NSCLC. Similarly to STARTRK-2, Ignyta will enroll patients who are eligible based on molecular confirmation of ROS1 rearrangement or Trk A/B/C rearrangement into one of two study cohort based on the molecular test. According to Ignyta, the planned sample size is 300 patients in each cohort. Patients randomized to receive investigational drug in each cohort will receive entrectinib orally according a dose and schedule yet to be selected; entrectinib will be administered in the fed state. Patients in each cohort randomized to control will receive docetaxel, $75\text{mg}/\text{m}^2$ IV will be administered on Day 1 of each 21-day cycle. Within each genetically-defined cohort, patients will be randomized (1:1) to entrectinib or docetaxel via an independent interactive voice response system (IVRS) using a randomized block design. Randomization will be stratified by ECOG performance status (0-1 vs. 2), presence of brain metastases, and previous treatment with an EGFR tyrosine kinase inhibitor.

Patients will have radiological tumor assessment performed at the end of Cycle 1, then approximately every 6 weeks thereafter. All radiological images will be transmitted to an independent central radiology laboratory for assessment. Treatment may continue until patient experiences disease progression, as determined by independent central radiology review; withdraws consent; or experiences unacceptable toxicity. Patients on the chemotherapy arm in each biomarker group will be allowed to cross over to entrectinib once progression has been confirmed by independent central review.

According to Ignyta, the primary objective of this study is to demonstrate that entrectinib is superior to the second line chemotherapeutic agent docetaxel in prolonging progression-free survival (PFS) in previously-treated adult patients with locally advanced or metastatic NSCLC who either harbor a fusion resulting in gene rearrangement in protein ROS1, NTRK1, NTRK2, or NTRK3. The primary analysis for each cohort will be a one-sided log rank test stratified for baseline stratification factors, comparing PFS in patients randomized to entrectinib to those

randomized to docetaxel. Ignyta proposed that an interim analysis of PFS will be conducted by the independent Data Monitoring Committee (DMC) when at least 200 evaluable patients have been randomized in that cohort, with the intention of supporting accelerated approval (ORR analysis) for that cohort, or if highly significant findings are observed in PFS, Ignyta will submit an application seeking traditional approval. According to Ignyta, if the interim analysis of PFS is not statistically significant, the final analysis for PFS will be performed when approximately 166 PFS events have occurred in each cohort. This study required one-sided alpha-level is 0.0245 if the interim analysis is based on 83 PFS events. The PFS results will be summarized using Kaplan-Meier method; the median event time for each treatment arm and corresponding two-sided 95% confidence interval for the median will also be provided, according to Ignyta. An unstratified log-rank test (one-sided, $\alpha = 0.025$) and Cox regression model will also be used as secondary analyses for PFS.

Companion Diagnostic

Ignyta, Inc. is proposing to pursue registration for entrectinib for the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) that is ROS1-positive as detected by an FDA-approved test. In parallel, Ignyta is also proposing to pursue registration for entrectinib for the treatment of patients with (b) (4) metastatic NSCLC (b) (4) (b) (4) as detected by an FDA-approved test.

The sponsor intends to enroll patients based on a two-step diagnostic assay, conducted in Ignyta's central laboratory, as follows:

1. First, an initial "multiplex" immunohistochemistry (IHC) screening test to detect increased protein expression of ROS1/TrkA/B/C.
2. Then, next generation sequence (NGS) testing will be performed on IHC-positive tumor samples to confirm the specific presence or absence of target gene rearrangements.

The results of NGS testing will be used to determine enrollment eligibility and assignment to a specific treatment arm.

According to Ignyta, a pre-Submission meeting was held with CDRH on July 25, 2014 to discuss the assays to be used in the six expansion cohorts of RXDX-101-01, described above.

2. DISCUSSION

Clinical

1. Does FDA agree that Study RXDX-101-02, with supporting data from Studies RXDX-101-01, ALKA-372-001 and RXDX-101-03, is adequate in design and size to support an NDA and full approval of entrectinib for the treatment of patients with NTRK (b) (4)-positive NSCLC?

FDA Response

The overall clinical development strategy for patients with NTRK (b) (4) positive NSCLC appears acceptable, given that there are no drugs approved for this patient population; however, FDA notes minimal exploration of entrectinib in this patient population to date. In addition, FDA notes that Ignyta plans to pool safety and efficacy data obtained in patients who are treatment-naïve with the safety and efficacy data obtained in patients who have previously received platinum-doublet therapy for advanced NSCLC in Study RXDX-101-02. In a proposed NDA seeking accelerated approval for treatment of NTRK (b) (4)-positive NSCLC, Ignyta must provide evidence that safety and efficacy are similar, regardless of the prior line of therapy. Alternatively, consider studying front-line and second-line patients in separate cohorts.

In a proposed NDA seeking accelerated approval for treatment of NTRK (b) (4) (b) (4)-positive NSCLC, Ignyta must also provide evidence that this is a serious and life-threatening disease for which there is no satisfactory alternative therapy. For example, Ignyta could provide prognostic information on this subset of NSCLC and data on response rates to available standard therapies (e.g., platinum doublet and docetaxel).

- a. Does FDA agree that all patients with NTRK1, NTRK2, and NTRK3 rearrangements should be enrolled and can be combined for purposes of efficacy and safety analyses?

FDA Response

FDA does not object to enrolling patients with NTRK1, NTRK2, or NTRK3 rearrangements. In a proposed NDA seeking accelerated approval for treatment of NTRK (b) (4)-positive NSCLC, Ignyta must provide available nonclinical and clinical information to justify why these rearrangements are biologically similar such that pooling of efficacy and safety analyses is scientifically valid.

- b. Does FDA agree that overall objective response rate, based on independent radiology review committee assessment, is an appropriate endpoint for demonstrating clinical benefit in patients with NTRK1/2/3-rearranged NSCLC and supports approval? Specifically, would a response rate of $\geq 40\%$ with a median duration of ≥ 6 months be considered a clinically meaningful benefit in the proposed patient population?

FDA Response

Whether a response rate of 40% with a median durability of at least six months is clinically meaningful would depend on the overall risk-benefit profile of the drug and the totality of the clinical data. In addition, Ignyta would need to provide evidence that entrectinib is superior to available therapy for treatment of this population.

- c. Are the secondary endpoints in RXDX-101-02 acceptable?

FDA Response

PFS and overall survival (OS) are difficult to interpret in a single-arm study, and, therefore, would not be considered to provide substantial evidence of effectiveness. These endpoints would be considered exploratory and would not be included in product labeling or promotional claims.

- d. Are the selected patient populations in RXDX-101-02 acceptable?

FDA Response

The selected patient populations in RXDX-101-102 appear generally acceptable; however, there is insufficient information in the briefing materials on the definition of “docetaxel-eligible.” Please define the term “docetaxel-eligible.”

- e. Is the sample size of 75 patients in the NTRK1/2/3 biomarker group acceptable?

FDA Response

The sample size of 75 patients based on an assumed response rate of 40% to exclude a response rate of less than 20% as the lower limit of the 95% confidence interval is acceptable, provided that this is superior to the response rate that could be achieved with first-line platinum doublet therapy or with second-line docetaxel therapy. However, note that the response rate of 40% will be reviewed in the context of the totality of the clinical data, the overall risk-benefit profile of the drug, and results reported with available therapy.

- f. While RXDX-101-02 is designed to treat patients with NTRK1/2/3 gene rearrangements, it is likely that there will be an uneven distribution of patients enrolled across the 3 genotypes. Is there a minimum number of patients for each genotype that would be needed to provide sufficient evidence of a benefit trend and, if so, what is that minimum number?

FDA Response

FDA is unable to provide a minimum number of patients to enroll for each NTRK rearrangement subtype. Please note that the indication may be restricted to the population actually studied. If a given genotype is underrepresented in study RXDX-101-102, Ignyta should provide available nonclinical and clinical data in the planned NDA to justify why the safety and efficacy results can be extrapolated to the underrepresented genotype.

Ignyta's Response to Question 1 (received via email on January 28, 2015)

Clarifying Question 1:

Ignyta appreciates FDA's feedback on the acceptability of the overall clinical development strategy in support of accelerated approval for patients with NTRK (b) (4) positive NSCLC. *In light of the significant challenges of conducting a randomized controlled trial in this ultra-rare NTRK1/2/3-positive NSCLC subset, Ignyta seeks further clarification from FDA regarding what additional requirements, if any, beyond Study RXDX-101-02, would be necessary to obtain Full Approval of entrectinib for patients with NTRK (b) (4) positive NSCLC.*

Clarifying Question 2:

Ignyta notes FDA's response "In a proposed NDA seeking accelerated approval for treatment of NTRK (b) (4) positive NSCLC, Ignyta must also provide evidence that this is a serious and life-threatening disease for which there is no satisfactory alternative therapy. For example, Ignyta could provide prognostic information on this subset of NSCLC and data on response rates to available standard therapies (e.g., platinum doublet and docetaxel)." *Ignyta seeks clarification of what information could be used to satisfy this request for "prognostic information on this subset of NSCLC and data on response rates to available standard therapies."* To satisfy this request, at the time of submission, Ignyta intends to provide the following: (a) Summary of the totality of literature on the prognostic and treatment outcomes for this NTRK rearranged subset of NSCLC and (b) a descriptive summary of the natural history of the NTRK rearranged patients who fail screening for Study RXDX-101-02. Does FDA concur that this would satisfy FDA's request?

Discussion during the meeting

In response to the clarifying questions, FDA stated that Ignyta would need to make a compelling argument that the magnitude and durability of the observed responses are evidence of direct clinical benefit and that this result would be unlikely to be achieved with available therapy, in order to support a request for traditional approval for the TRK-positive population. At this time, FDA cannot state whether a randomized trial would be required to verify clinical benefit and recommended that Ignyta provide interim or final data of the single arm trial in this patient population in a request for further discussion of this issue. Information providing context on the natural history of this subgroup would also be required at the time of this discussion. Such data could include prospectively-evaluated patients who do not enter the RXDX-101-02 trial, published literature, and data from registries (national or international).

FDA recommended that RXDX-101-02 could be improved by evaluating patients who are chemotherapy-naïve in a separate cohort from those who are receiving second-line or greater therapy. Ignyta proposed to study at least 75 patients with TRK-positive NSCLC, of whom approximately 25 are anticipated to be treatment-naïve and 50 are anticipated to have received prior therapy in these cohorts.

FDA stated that a presubmission/risk determination meeting with CDRH should be held prior to enrollment of patients who are treatment-naïve.

With regards to the ROS1 arm of RXDX-101-02, Ignyta clarified that patients with severe liver dysfunction or neuropathy would be considered docetaxel-ineligible. Ignyta proposed to study at least 75 patients with ROS1-positive NSCLC, of whom approximately 25 are anticipated to be treatment-naïve and 50 are anticipated to have received prior crizotinib therapy.

2. Does FDA agree that Study RXDX-101-03 is adequate in design and size to support full approval of entrectinib for the treatment of patients with second-line, ROS1-positive NSCLC?

FDA Response

No, FDA does not agree with a control arm of docetaxel in crizotinib-naïve patients with ROS1-positive NSCLC. Please see FDA's response to Question 2d.

Discussion during the meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this question at the meeting.

- a. Does FDA agree that progression-free survival (PFS), based on independent radiology review committee assessment, is an appropriate endpoint for demonstrating clinical benefit in patients with ROS1-positive NSCLC?

FDA Response

A demonstration of a clinically meaningful improvement in PFS, based on independent radiology review committee assessment, with an acceptable risk-benefit profile may confer clinical benefit in patients with ROS1-positive NSCLC; however, see response to Question 2d and 2e.

Discussion during the meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this question at the meeting.

- b. Are the secondary endpoints acceptable?

FDA Response

Yes, the secondary endpoints appear to be acceptable; however, see response to Question 2.

Discussion during the meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this question at the meeting.

- c. Does FDA agree with the proposed patient population, as stipulated by the study

eligibility criteria?

FDA Response

The proposed population as stipulated by the study eligibility criteria appears acceptable. Please provide detailed criteria identifying patients who are “eligible” for docetaxel treatment.

Discussion during the meeting:

Ignyta acknowledged FDA’s response; there was no further discussion of this question at the meeting.

- d. Is the active comparator, docetaxel, acceptable?

FDA Response

No, docetaxel is not an acceptable comparator given the ORR of 72% (95% CI 58 to 84) with a median duration of response of 17.6 months with crizotinib as reported by Shaw et al (NEJM 2014; 371, 1963-1971)

Ignyta’s Response to Question 2d (received via email on January 28, 2015)

Due to the rare incidence of ROS1-positive NSCLC (1-3%; Gerber et al., 2014), in order for RXDX-101-03 to be able to enroll sufficient patients to demonstrate a statistically significant effect to a comparator, the study will be need to be conducted in many regions (Ignyta plans to include approximately 200 clinical sites in 20+ countries around the world). Docetaxel was selected as the active comparator in RXDX-101-03 because it is approved, readily available, and is standard of care for the treatment of second-line NSCLC in these regions. Patients randomized to docetaxel will have the opportunity to receive entrectinib once they have failed docetaxel to address ethical concerns.

While it is possible that crizotinib could be approved in the US prior to the initiation of Study RXDX-101-03, it is unlikely that approval will be granted and payers will reimburse the cost of crizotinib in other countries for the treatment of ROS1-positive NSCLC in a similar timeframe as the US. Thus, crizotinib is an inappropriate comparator for an international study and without access to sufficient number of sites outside of the US, the conduct of Study RXDX-101-03 would not be feasible.

Given that i) the selected active comparator must be widely used around the world to treat the intended patient population; ii) docetaxel has demonstrated a benefit in overall survival in second-line NSCLC; and iii) the selection of crizotinib as an active comparator would limit study enrollment to the US, which would greatly hamper accrual; Ignyta maintains that docetaxel is an adequate comparator in Study RXDX-101-03.

Discussion during the meeting

FDA acknowledged the comments made by Ignyta, noting that some health plans in the U.S. do not cover the cost of crizotinib for patients with ROS1-positive NSCLC; however, FDA felt that equipoise would not be present in the U.S., given the availability of off-label crizotinib. FDA noted that a trial conducted predominantly outside of the U.S. for which the consent form provided available information on the risk and benefits of crizotinib as described in the published literature could be acceptable to support regulatory approval in the U.S., provided that extrapolation of the ex-U.S. data to the U.S. population was supported. FDA agreed to review the proposal for interim analysis of overall response rate for termination of randomization, to be contained in the final protocol and in the statistical analysis plan.

- e. Is the sample size of 300 patients in RXDX-101-03 acceptable?

FDA Response

The sample size of 300 patients in the cohort of patients with ALK rearrangement-positive NSCLC is acceptable. However, the improvement in median PFS of 2.5 months may not be sufficient to demonstrate clinical benefit; this would be evaluated in the context of the totality of the entire data. Please note that filing of a marketing application with PFS as the primary endpoint would require demonstration of a large magnitude of treatment effect on PFS that is statistically robust, is clinically meaningful, and that demonstrates an acceptable benefit-risk assessment.

Discussion during the meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this question at the meeting.

- f. Does FDA agree that statistically significant and clinically beneficial results from RXDX-101-03 and RXDX-101-02 in ROS1-positive NSCLC patients would support an indication statement of "Entrectinib is indicated for the treatment of patients with locally advanced or metastatic NSCLC that is ROS1-positive as detected by an FDA-approved test"?

FDA Response

No; see response to Question 2d.

Discussion during the meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this question at the meeting.

- g. Does FDA agree with the interim analysis plan for PFS, and that statistically significant and clinically beneficial results based on PFS from the proposed interim analyses in Study RXDX-101-03 would be adequate to support full

approval of entrectinib in the treatment of patients with ROS1-positive advanced NSCLC with the same indication statement provided in Question 2f)?

FDA Response

No, FDA does not recommend an interim analysis for PFS. Given that the interim analysis would be based on only 83 events, an interim efficacy PFS analysis may not provide an accurate or reproducible estimate of the treatment effect size due to inadequate follow-up, missing assessments, disagreements between radiological reviewers and/or disagreements between investigator and independent assessments. Therefore, FDA recommends against performing the interim efficacy PFS analysis.

Discussion during the meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this question at the meeting.

3. A master protocol design is planned for the proposed RXDX-101-02 study due to the ultra-rare frequency of NTRK1/2/3 and ROS1 gene rearrangements in NSCLC. Under the umbrella of the master protocol, patients with advanced NSCLC who are naïve to crizotinib and other Trk and ROS1 inhibitors will be centrally tested for the presence of either NTRK1/2/3 or ROS1 gene rearrangements. All efficacy and safety analyses are to be performed within the confines of each biomarker group. Does FDA agree that the data from the NTRK1/2/3 and ROS1 biomarker groups within a master protocol could be used to support independent registration packages and indications for NTRK (b) (4) NSCLC and/or ROS1 (b) (4) NSCLC, respectively?

FDA Response

In general, the FDA does not object to master protocol designs; however, a detailed protocol should be provided for FDA review and feedback.

Discussion during the Meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this question at the meeting.

4. Entrectinib has demonstrated significant antitumor effects in heavily pre-treated patients with ROS1-rearranged NSCLC. Based on these exciting clinical responses, 3-4 additional ROS1 rearranged NSCLC patients are likely to be enrolled in the ongoing entrectinib clinical studies over the next 2 months. Ignyta is interested in pursuing breakthrough therapy designation in this patient population and is interested in understanding how many more objective responses would be needed in this patient population to warrant submission of a request for breakthrough therapy designation. Can the FDA comment on when it would be appropriate to submit such a request?

FDA Response

Breakthrough Therapy Designation is intended to facilitate expedited drug development for drugs in which preliminary clinical evidence indicated the drug may demonstrate

substantial improvement over existing therapies on one or more clinically meaningful endpoints. FDA recommends that an informal discussion via teleconference be held before formal submission of the data intended to support the request. FDA recommends that at least 20 patients be treated at the recommended Phase 2 dose with a suitable fraction (e.g., 50%) of patients having suitable information on durability of response (e.g., 6 months of follow-up prior to initiating the informal discussion).

Discussion during the Meeting:

Ignya acknowledged FDA's response; there was no further discussion of this question at the meeting.

5. Given the safety profile observed so far (for durations of up to 23 months), the seriousness of NSCLC, the unmet medical need of patients with NTRK1/2/3 or ROS1 rearranged NSCLC, and the size of the proposed registration studies, does FDA agree that exposure of at least 60 patients to entrectinib for several months, with an acceptable safety profile, should be sufficient to assess the safety of entrectinib for determination of whether it is safe to initiate registration studies with entrectinib?

FDA Response

Ignya's strategy to assess the safety of entrectinib for suitability to initiate studies intended to support marketing approval, based on exposure of at least 60 patients over several months, appears to be inadequate. Ignya should have confidence in the recommended Phase 2 dose prior to embarking on Studies RXDX-101-02 and RXDX-101-03.

Discussion during the Meeting:

Ignya acknowledged FDA's response; there was no further discussion of this question at the meeting.

Companion Diagnostic

6. Ignya proposes to utilize a 2-step IHC, NGS assay in its central laboratory in San Diego to support the profiling of patients for NTRK1/2/3 and ROS1 gene rearrangements for enrollment into either RXDX-101-03 or RXDX-101-02. The results of both trials would be used to support companion diagnostic approval of a lab-based testing service under a PMA, for identifying NSCLC patients eligible for entrectinib therapy. Does FDA concur with this approach?

FDA Response

FDA concurs.

Discussion during the Meeting:

Ignya acknowledged FDA's response; there was no further discussion of this question at the meeting.

7. Ignyta believes that positive first-step IHC results can arise from a broad range of factors that may be biological or technical in nature as the result of low specificity. Thus, the intent-to-treat (ITT) patient population should comprise only patients who are identified as positive for NTRK1/2/3 or ROS1 rearrangements as identified by NGS. Does FDA concur with this proposed selection criterion?

FDA Response

FDA concurs. Please note that the companion diagnostic device will be a 2-step assay, i.e., a multiplex immunohistochemistry (IHC) screening test reflexed to NGS.

Discussion during the Meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this question at the meeting.

Additional Comments: Nonclinical

8. FDA notes that 13-week toxicology studies should be submitted to the Agency in the planned NDA and no later than initiation of Phase 3 clinical trial, whichever is earlier, as described in the ICH Guidance for Industry: S9 Nonclinical Evaluation for Anticancer Pharmaceuticals available at: <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm085389.pdf>. Ignyta should initiate 13-week studies as early as feasible to support further clinical development. FDA notes that use of daily schedule in animal studies would support either the continuous or 4 day on/3 day off clinical dosing schedule. Other nonclinical studies required at the time of an NDA submission include embryofetal toxicity studies in two species, and genotoxicity studies (including Ames test, and in vitro and in vivo tests for micronuclei and chromosomal aberrations).

Discussion during the Meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this item at the meeting.

Additional Comments: Clinical Pharmacology

With regards to the proposed protocol synopses for Studies RXDX-101-02 and RXDX-101-03:

9. The protocol synopses for the proposed Studies RXDX-101-02 and RXDX-101-03 have not proposed the dose and dosing regimen of entrectinib. Dose selection of entrectinib should be optimized before starting registration trials. Pool available pharmacology, pharmacokinetic (PK), pharmacodynamics (PD), activity, and safety data during the development of entrectinib in order to conduct an integrated dose-response and exposure-response (ER) analyses and evaluate the frequency of dose reductions and interruptions and time to these dose modifications to support dose selection.

Discussion during the Meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this item at the meeting.

10. Assess the effect of body size (such as body weight and body surface area) on PK and PD of entrectinib to determine a better dosing approach (body size-based or fixed dosing) that minimizes inter-patient variability for the registration trial(s).

Discussion during the Meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this item at the meeting.

11. Include specified time points for PK sampling in the protocols for the proposed Studies RXDX-101-02 and RXDX-101-03. The extent of PK and PD sampling for the current protocols should be based on adequate characterization of PK and PD of entrectinib and allow for population PK and exploratory ER analyses.

Discussion during the Meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this item at the meeting.

12. Include additional ECG monitoring around C_{max} and provide the times of ECG monitoring relative to study drug administration in the protocols for Studies RXDX-101-02 and RDX-101-03.

Discussion during the Meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this item at the meeting.

General Comments:

13. Conduct population PK analyses to evaluate the effect of intrinsic and extrinsic factors on the PK of entrectinib and its active metabolites, if any in humans. Refer to the FDA Guidance for Industry entitled "Population Pharmacokinetics" found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf>.

Discussion during the Meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this item at the meeting.

14. Explore the ER relationships for entrectinib and its active metabolite(s), if any for measures of effectiveness, toxicity, and PD biomarkers. Refer to the FDA Guidance for Industry entitled "Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications" found at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>.

Discussion during the Meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this item at the meeting.

15. Validate the analytical methods used to determine the concentrations of entrectinib and its metabolite(s). Refer to the FDA Guidance for Industry entitled "Bioanalytical Method Validation" found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf>.

Discussion during the Meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this item at the meeting.

16. Evaluate the in vitro ability of entrectinib and its major metabolites to act as substrates, inhibitors of cytochrome P450 enzymes (including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A) or inducers of cytochrome P450 enzymes (including CYP1A2, 2B6, 3A), transporters, and conjugating enzymes early in entrectinib development. Provide as appropriate the calculated R values or ratios of the mean steady-state concentrations to the 50% maximal inhibitory concentration (IC₅₀) or the enzyme inhibition constant K_i to determine the need for drug interaction studies. Conduct mechanism based drug-drug interaction studies. Refer to the FDA draft Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations" found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>.

Discussion during the Meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this item at the meeting.

17. Identify the pathways by which entrectinib and its active metabolites are eliminated to determine the need to assess the effect of organ impairment on their systemic exposures. Refer to the FDA draft Guidances for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf> and "Pharmacokinetics in Patients with Impaired Hepatic Function : Study Design, Data Analysis, and Impact on Dosing and Labeling" found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf>.

Discussion during the Meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this item at the meeting.

18. Conduct a 'thorough QT' study to evaluate entrectinib for its QT prolongation potential. Alternative proposals to the 'thorough QT' study including ECG collection at baseline, around the anticipated maximal and steady-state plasma concentrations (C_{max} and C_{ss}) with time matched pharmacokinetic sampling in a dedicated study or a substudy of a clinical trial may be appropriate if entrectinib cannot be administered to healthy subjects. Submit a QT evaluation plan to the IND for FDA review and comment. Conduct an adequate assessment early in the drug development to rule out the QT prolongation potential of entrectinib and to avoid the need for conducting intensive ECG monitoring in the future clinical trials. Refer to the FDA Guidance for Industry entitled "E14 Clinical Evaluation of QT/QTc Interval Prolongation" found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf>.

Discussion during the Meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this item at the meeting.

19. Determine bioavailability of entrectinib in humans per the FDA Guidance for Industry entitled "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations" found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf>.

Discussion during the Meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this item at the meeting.

20. Conduct a study to assess the effect of pH-elevating agents (e.g., proton pump inhibitors, H2 antagonists and antacids) on the absorption of entrectinib if entrectinib demonstrates pH dependent solubility and becomes poorly soluble as gastrointestinal pH increases. The study may be conducted in a gated manner, first assessing the effect of a proton pump inhibitor (PPI) on the exposure of entrectinib. In the event that concomitant administration of a PPI has a large impact on the drug exposure, an H2 antagonist and an antacid should be subsequently evaluated.

Discussion during the Meeting:

Ignyta acknowledged FDA's response; there was no further discussion of this item at the meeting.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting and no less than 210 days prior to an NDA or BLA submission. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies 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 PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP 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* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S.

conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ATTACHMENTS AND HANDOUTS

Ignyta presented slides 1-7 from their “Ignyta Intro Slides” file, and a handout entitled, “Ignyta Responses to FDA Preliminary Comments,” at the meeting.

Entrectinib Type B Meeting Agenda

(29 January 2015)

Item	Time Allocated
Introductions	5 minutes
Question 1	40 minutes
Question 2/2d	10 minutes
Conclusions	5 minutes

1.1 Clinical

1. Does FDA agree that Study RXDX-101-02, with supporting data from Studies RXDX-101-01, ALKA-372-001 and RXDX-101-03, is adequate in design and size to support an NDA and full approval of entrectinib for the treatment of patients with NTRK^{(b) (4)}-positive NSCLC?

Background

Ignyta aims to seek registration for entrectinib in NTRK^{(b) (4)}-positive NSCLC, a high unmet need subset of NSCLC with no treatment options approved or in Phase 2 development or later. Because of the extremely low frequency of patients with NTRK1/2/3-positive NSCLC, Ignyta has significant reservations regarding the feasibility of executing a randomized controlled trial within an acceptable timeframe and is interested in consulting with the FDA on whether a more feasible clinical program could be considered acceptable for these ultra-rare NTRK1/2/3 rearranged NSCLC patients with a life-threatening condition that represents an unmet medical need.

In designing the clinical development program for entrectinib, Ignyta has encountered significant challenges with the prospect of conducting a randomized controlled trial in this ultra-rare NTRK1/2/3-positive NSCLC subset and would like to work with FDA to identify a practical path to bring a treatment option to patients with NTRK rearranged NSCLC:

- i. Extremely low prevalence population (current data: 0.31%)
- ii. Very high molecular profiling volume required (24,000 tested yields 75 biomarker positive)
- iii. Complex testing methodology: multiple potential fusion partners => requires NGS characterization (IHC or FISH alone insufficient)
- iv. Low enrollment yields (~30%), even for marker positive patients (10 biomarker positive patients yield 3 enrolled patients)

i. Extremely low prevalence population

NTRK rearranged NSCLC is an extremely low prevalence population and is difficult to detect. For example, in a comprehensive analysis of currently available data sources, only 12 NTRK1 fusions and 1 NTRK2 fusion have been found in 4,243 lung cancer samples, implying a frequency of 0.31% (see Table 1).

Table 1 Frequency of NTRK Rearrangements in NSCLC

Data Source	NTRK Fusion+	Total Samples	%
Publications ^{a,b}	10	956	1.05%
Collaborators	0	114	0.00%
Foundation Medicine ^c	3	3,173	0.09%
Total	13	4,243	0.31%

- a. Stransky N., Ceremi E, Schelm S, Kim JL, Lengauer C (2014). The landscape of kinase fusions in cancer. Nature Communications; 5(4846)
- b. Doebele R (2014) Analysis of NTRK1 gene fusion incidence in an unselected cohort of non-small cell lung cancer patients. ASCO Annual Meeting (Abstract 8048)
- c. Database query executed on FMI panel version T5a in June-July 2014

Furthermore, an NTRK rearrangement incidence of 0.3 – 1.0% of NSCLC indicates an incident population of approximately 600 – 2,000 new patients in the US each year. While this patient population may be comparable in size to other orphan populations (e.g., cystic fibrosis, Gaucher’s disease, Fabry’s disease) where RCTs have been conducted, a critical distinction is that these other orphan populations are phenotypically distinct, are usually subject to patient registries and are generally treated at a small number of centers of excellence. NTRK rearranged NSCLC patients, on the other hand, are a phenotypically indistinguishable subset of NSCLC (>200K new cases per year), are not currently part of a patient registry and are treated in a distributed manner by community oncologists, making these patients much more difficult to identify, capture and treat in a systematic fashion.

ii. Very high molecular profiling volume required

The ultra-low frequency of NTRK fusions implies extremely high molecular testing volume, even for studies with relatively low sample sizes.

- Assuming 100% enrollment yield of marker positive patients, screening of >24,000 patients would be required just to yield 75 enrolled ($75/24,000 = 0.31\%$); *such a screening volume is unprecedented, and this is just for a modest-sized single arm study*
- However, many lung cancer patients have insufficient tissue for any molecular characterization (particularly post EGFR/KRAS/ALK testing) => *screening 24,000 patients will be challenging in and of itself*

iii. Complex testing methodology: multiple potential fusion partners => requires NGS characterization (IHC or FISH alone insufficient)

In the table above, 9 of the published NTRK fusions have a reported fusion partner, and each of the 9 fusion partners is different; therefore, NGS (on RNA) is required for detection of emerging fusions. Four of the fusions detected were not FISH positive.

iv. Low enrollment yields (~30%), even for marker positive patients

Further exacerbating the ultra-rare frequency and other challenges cited, many patients with NTRK rearrangements will not ultimately enroll into any clinical study for the following reasons:

- 71% of patients screened positive for a biomarker fail to enroll into a clinical trial (Liu et al. 2014)
- Inclusion criteria failure

- Concomitant Meds
- Performance Status
- Active brain disease
- Deterioration during time of testing
- According to verbal communications with international PI's, 30-50% of NSCLC patients who progress on 1L chemotherapy are not in sufficient condition to be eligible for a 2L treatment study

Alternative regulatory frameworks for practical trial designs in ultra-low frequency indications clearly are needed. FDA has indicated that it may be time to reintroduce the use of ORR as a primary endpoint and the utility of single-arm studies, albeit with some external control, to support initial full approval for targeted therapies directed at a small subset of oncology patients. For example, at the 12 December 2014 “*Developing and Using Precision Therapies in the ‘Omics’ Era: Generating and Interpreting Evidence for Rare Subsets*” Meeting held by the FDA, Janet Woodcock acknowledged alternative design and sample size requirements to support approval in low prevalence, high unmet need populations where traditional RCTs may be unethical and/or impractical. Furthermore, in the Issue Brief white paper entitled “The Role of Non-Randomized Trials for the Evaluation of Oncology Drugs” (Armstrong et al., 2014), FDA officials state that there are situations where randomized trials may not be feasible or ethical. It also cites prior precedents where full approval has been granted for single-arm studies.

Ignyta believes that for the reasons identified above, the development of a drug to treat patients with NTRK1/2/3 gene rearrangements is such a situation, and warrants evaluating whether more efficient and feasible trial designs, such as a single-arm study, could be appropriate.

Ignyta Clarifying Question 1

Ignyta appreciates FDA’s feedback on the acceptability of the overall clinical development strategy in support of accelerated approval for patients with NTRK^{(b) (4)} positive NSCLC. ***In light of the significant challenges of conducting a randomized controlled trial in this ultra-rare NTRK1/2/3-positive NSCLC subset, Ignyta seeks further clarification from FDA regarding what additional requirements, if any, beyond Study RXDX-101-02, would be necessary to obtain Full Approval of entrectinib for patients with NTRK^{(b) (4)} positive NSCLC.***

Ignyta Clarifying Question 2

Ignyta notes FDA’s response “In a proposed NDA seeking accelerated approval for treatment of NTRK^{(b) (4)} positive NSCLC, Ignyta must also provide evidence that this is a serious and life-threatening disease for which there is no satisfactory alternative therapy. For example, Ignyta could provide prognostic information on this subset of NSCLC and data on response rates to available standard therapies (e.g., platinum doublet and docetaxel).” ***Ignyta seeks clarification of what information could be used to satisfy this request for “prognostic information on this subset of NSCLC and data on response rates to available standard therapies.”*** To satisfy this request, at the time of submission, Ignyta intends to provide the following: (a) Summary of the totality of literature on the prognostic and treatment outcomes for this NTRK rearranged subset of NSCLC and (b) a descriptive summary of the natural history of the NTRK rearranged patients who fail screening for Study RXDX-101-02. Does FDA concur that this would satisfy FDA’s request?

2. Does FDA agree that Study RXDX-101-03 is adequate in design and size to support full approval of entrectinib for the treatment of patients with second-line ROS1-positive NSCLC?

d) Is the active comparator, docetaxel, acceptable?

Due to the rare incidence of ROS1-positive NSCLC (1-3%; Gerber et al., 2014), in order for RXDX-101-03 to be able to enroll sufficient patients to demonstrate a statistically significant effect to a comparator, the study will need to be conducted in many regions (Ignyta plans to include approximately 200 clinical sites in 20+ countries around the world). Docetaxel was selected as the active comparator in RXDX-101-03 because it is approved, readily available, and is standard of care for the treatment of second-line NSCLC in these regions. Patients randomized to docetaxel will have the opportunity to receive entrectinib once they have failed docetaxel to address ethical concerns.

While it is possible that crizotinib could be approved in the US prior to the initiation of Study RXDX-101-03, it is unlikely that approval will be granted and payers will reimburse the cost of crizotinib in other countries for the treatment of ROS1-positive NSCLC in a similar timeframe as the US. Thus, crizotinib is an inappropriate comparator for an international study and without access to sufficient number of sites outside of the US, the conduct of Study RXDX-101-03 would not be feasible.

Given that i) the selected active comparator must be widely used around the world to treat the intended patient population; ii) docetaxel has demonstrated a benefit in overall survival in second-line NSCLC; and iii) the selection of crizotinib as an active comparator would limit study enrollment to the US, which would greatly hamper accrual; Ignyta maintains that docetaxel is an adequate comparator in Study RXDX-101-03.

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CLAIRE E MYERS
02/17/2015