CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210861Orig1s000
211710Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 121211

MEETING MINUTES

Loxo Oncology, Inc.
Attention: Katie Cairati, M.S.
Executive Director, Global Regulatory Affairs
701 Gateway Boulevard
Suite 420
South San Francisco, CA 94080

Dear Ms. Cairati:

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

We also refer to the teleconference between representatives of your firm and the FDA on November 17, 2017. The purpose of the meeting was to discuss the adequacy of the safety and efficacy data obtained in three, single-arm studies (LOXO-TRK-14001, LOXO-TRK-15002, and LOXO-TRK-15003) to support your planned New Drug Application (NDA) for larotrectinib and to obtain FDA feedback regarding the content and format of the planned NDA.

A copy of the official minutes of the teleconference 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 (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
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
Meeting Date and Time:	November 17, 2017; 12:00 PM – 1:00 PM, EST
Meeting Location:	White Oak Building 22, Conference Room 1415
Application Number:	IND 121211
Product Name:	larotrectinib
Indication:	Treatment of unresectable or metastatic solid tumors with NTRK-fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments
Sponsor/Applicant Name:	Loxo Oncology, Inc.
Meeting Chair:	Martha Donoghue
Meeting Recorder:	Idara Udoh

FDA ATTENDEES

Patricia Keegan, Director, Division of Oncology Products 2 (DOP2)
Martha Donoghue, Clinical Team Leader, DOP2
Leigh Marcus, Clinical Reviewer, DOP2
Whitney Helms, Nonclinical Team Leader, Division of Hematology, Oncology, Toxicology (DHOT)
Idara Udoh, Senior Regulatory Health Project Manager, DOP2
Stacie Woods, Regulatory Health Project Manager, DOP2
Kwadwo Korsah, Regulatory Health Project Manager, DOP2
Ruby Leong, Clinical Pharmacology Reviewer, DCPV
Nina Ni, CMC Team Leader, Office of Pharmaceutical Quality (OPQ)
Olen Stephens, CMC Drug Product Reviewer, OPQ
Xiaoping Jiang, Biometrics Reviewer, Division of Biometrics (DB)
Reena Philip, Director, Division of Molecular Genetics and Pathology (DMPG), Center for Devices and Radiological Health (CDRH)
Sharon Liang, Regulatory Scientist, DMPG, CDRH
Debra Lewis, Deputy Director, Office of Orphan Product Development (OOPD)
Carla Epps, Medical Officer, OOPD
Larry Bauer, Regulatory Scientist, OND Rare Diseases Program
Carolyn McCloskey, Epidemiologist, Office of Surveillance and Epidemiology

Jeongmi Kim, Contractor, Division of Oncology Products 1

LOXO ONCOLOGY ATTENDEES

Joshua Bilenker, M.D., Chief Executive Officer
Jacob Van Naarden, Chief Business Officer
Nisha Nanda, Ph.D., Senior Vice President, Development Strategy
Katie Cairati, M.S., Executive Director, Global Regulatory Affairs
Lars Holzhausen, Ph.D., Manager, Regulatory Affairs
Cindy Rocha, Director, Project Management
(b) (4) Regulatory Affairs Consultant
Nora Ku, M.D., Senior Medical Director
Michael Cox, Pharm.D., Senior Medical Director, Clinical Development and Medical Affairs
Hope Qamoos, Associate Director, Clinical Scientist
(b) (4) Pharmacology Consultant
(b) (4) Biostatistics Consultant
Brian Tuch, Senior Vice President, Regulatory Strategy
Deepika Jalota, Senior Vice President, Regulatory Strategy, Bayer

MEETING PURPOSE

On September 18, 2017, Loxo Oncology, Inc. ("Loxo") requested a Type B, pre-NDA meeting to discuss the adequacy of the safety and efficacy data obtained in three, single-arm studies (LOXO-TRK-14001, LOXO-TRK-15002, and LOXO-TRK-15003) to support their planned New Drug Application (NDA) for larotrectinib and to obtain FDA feedback regarding the content and format of the planned NDA.

FDA granted the meeting on September 29, 2017, and the briefing package for this meeting was received on October 20, 2017. FDA sent Preliminary Comments to Loxo on November 14, 2017.

BACKGROUND

Regulatory History

- *On February 28, 2014*, IND 121211 was submitted to the Division of Oncology Products 2 (DOP2) for the evaluation of larotrectinib for the treatment of patients with solid tumors. The IND contained Protocol LOXO-TRK-14001 entitled "A Phase 1a/1b Study of the Oral TRK Inhibitor LOXO-101 in Subjects with Adult Solid Tumors," and was allowed to proceed on May 28, 2014.

- *On June 29, 2015*, Loxo submitted Protocol LOXO-TRK-15002, entitled "A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects with NTRK Fusion-Positive Tumors." Study LOXO-TRK-15002 is an open-label, multicenter trial enrolling

patients with tumors harboring an NTRK1, NTRK2, or NTRK3 gene fusion. FDA issued an Information Request on July 21, 2015 seeking clarification regarding dose modification, sample size, and eligibility criteria in the study. Loxo provided a revised protocol LOXO-TRK-15002 on August 17, 2015 addressing FDA recommendations.

- *On August 21, 2015*, Loxo submitted a meeting request to discuss and obtain clinical guidance regarding the development of larotrectinib in pediatric patients with advanced solid tumors, including primary central nervous system (CNS) tumors. The meeting was granted but later cancelled upon Loxo's request because FDA's October 21, 2015 preliminary responses were considered clear and complete.

- *On August 31, 2015*, larotrectinib was granted orphan drug designation for the treatment of soft tissue sarcoma.

- *On February 23, 2016*, a Type B meeting was held via teleconference to discuss clinical study, LOXO-TRK-15002, and seek FDA input regarding the larotrectinib development program, including the planned efficacy analyses intended to demonstrate the clinical benefit of larotrectinib in adult patients with cancers harboring NTRK fusions. During the meeting, FDA recommended that Loxo expand the eligibility criteria for Study LOXO-TRK-15002 to permit enrollment of patients with tumors harboring an NTRK mutation. FDA agreed that Loxo could amend the protocol to enroll patients as young as 12 years of age and did not object to the enrollment of patients with ECOG performance status 3 into the trial. Additionally, FDA recommended that Loxo consider providing expanded access to larotrectinib for patients unable to enroll in the ongoing clinical trials and that data from expanded access protocols could provide data to support clinical development of larotrectinib. In response to this advice, Loxo subsequently submitted the following six single patient protocols for the treatment of patients with cancers harboring an NTRK gene fusion to IND 121211:

  – LOXO-TRK-16004, for treatment of a patient with soft tissue liposarcoma (received April 25, 2016)

  – LOXO-TRK-16005, for treatment of a patient with metastatic breast cancer (received July 26, 2016)

  – LOXO-TRK-16006, for treatment of a patient with an advanced primary CNS malignancy (received August 1, 2016)

  – LOXO-TRK-16008, for treatment of an adult patient with secondary acute myelogenous leukemia (received September 29, 2016). A subsequent protocol amendment provided for use of the liquid formulation of larotrectinib as an alternative to capsules due to the patient's difficulty swallowing (received October 11, 2016)

- LOXO-TRK-17018, for treatment of a patient with locally advanced recurrent secretory breast cancer (received May 4, 2017)

- LOXO-TRK-17019, for treatment of a patient with recurrent breast cancer (received May 16, 2017).

- *On April 4, 2016*, Loxo submitted a meeting request to obtain FDA input regarding the nonclinical and clinical pharmacology development programs for larotrectinib. The meeting was granted but later cancelled upon Loxo's request following receipt of FDA's June 1, 2016, Preliminary Meeting Comments document. As conveyed in FDA's June 1, 2016, response to Question #11, a separate Advice/Information Request letter was issued to provide FDA feedback regarding Loxo's plan to study the effects of larotrectinib on cardiac electrophysiology.

- *On May 12, 2016*, Loxo submitted a Breakthrough Therapy Designation (BTD) request for the treatment of advanced solid tumors with NTRK fusions. On July 11, 2016, FDA granted BTD designation to larotrectinib for the treatment of unresectable or metastatic solid tumors with NTRK fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments.

- *On June 16, 2016*, larotrectinib was granted rare pediatric disease designation for the treatment of infantile sarcoma.

- *On November 9, 2016*, Type B Breakthrough Therapy-Initial Comprehensive Multidisciplinary meeting was held between FDA and Loxo to discuss the overall development program for larotrectinib and plan future interactions with FDA. During the meeting, FDA recommended that Loxo pre-specify the number of patients upon which efficacy analysis will be based (i.e. 55 patients) and stated that any additional patient data will be considered supportive. Loxo agreed to submit an independent radiology review charter for FDA review and concurrence prior to initiating the central review process. On January 26, 2017, the draft review charter, entitled "Rationale for and Summary of Key Elements of a Proposed Combined Review Charter for Larotrectinib" was received, and FDA issued an Advice/Information Request letter on May 12, 2017, addressing Loxo's questions.

- *On January 9, 2017*, Loxo submitted an Initial Pediatric Study Plan (iPSP) describing a plan for seeking a partial waiver for development of larotrectinib in pediatric patients 0 to <1 month of age. FDA issued a Written Response letter with additional feedback on the iPSP, and on April 20, 2017 Loxo submitted its agreed iPSP. FDA issued an Initial Agreement letter on May 18, 2017.

- *On March 8, 2017*, Loxo submitted a request for review of the proposed proprietary name "(b) (4)". On June 5, 2017, FDA issued a Proprietary Name Request Unacceptable

letter because the proposed name may be confused with another currently marketed drug (Trokendi XR).

- *On May 9, 2017*, larotrectinib was granted orphan drug designation for treatment of solid tumors with NTRK-fusion proteins.

- *On June 19, 2017*, Loxo submitted a letter to the Office of Orphan Products Development. In this letter, Loxo expressed intent to seek "first approval for larotrectinib simultaneously in an adult and pediatric indication ('solid tumors with NTRK-fusion proteins'), which encompasses the original rare pediatric disease designation ('infantile fibrosarcoma')". Loxo also provided the following justification for why larotrectinib may qualify for a rare pediatric disease priority review voucher:

  – According to Loxo, the development of larotrectinib was inspired by the observation of NTRK-fusion proteins in childhood cancers

  – Loxo maintains that the proposed tissue-agnostic indication for pediatric and adult patients with solid tumors with NTRK-fusion proteins is not a different indication from infantile fibrosarcoma (since the tissue agnostic indication and rare pediatric disease of infantile fibrosarcoma have the same underlying pathophysiology)

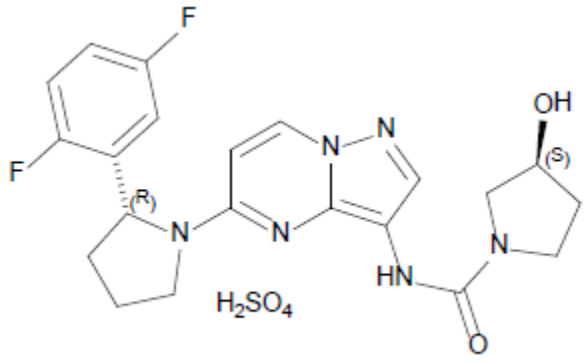
  – Loxo asserts that an approval in solid tumors with NTRK-fusion proteins does not violate the requirement that the first approval must be for treatment of a disease that primarily affects pediatric patients because adults and pediatric patients are not all appropriate candidates for the same use of larotrectinib (i.e., pediatric patients with infantile fibrosarcoma is used as neoadjuvant therapy, whereas for treatment of adults with solid tumors with NTRK-fusion proteins, larotrectinib would be used for disease control without surgical intent).

- *On July 21, 2017*, Loxo submitted a request for review of the proposed proprietary name (b) (4) and FDA issued a second Proprietary Name Request Unacceptable letter, on November 7, 2017, because the proposed name may be confused with another currently marketed drug (Tresiba).

- *On August 15, 2017*, Loxo submitted a CMC-only meeting request to discuss the content of the CMC section of the larotrectinib NDA and to provide a comprehensive CMC update. The meeting was cancelled by Loxo following receipt of FDA's October 12, 2017, Preliminary Meeting Responses.

Chemistry, Manufacturing, and Controls (CMC)

Larotrectinib is a small molecule new molecular entity with a molecular formula of 526.51 g/mol and molecular formula of $C_{21}H_{24}F_2N_6O_6S$. The structure of larotrectinib is reproduced below:



Two formulations are proposed for commercial distribution. A powder in capsule formulation will be available in 25 mg and 100 mg dose strengths. This formulation has no excipients other than the hard gelatin capsule. An oral solution formulation is available as a 20 mg/mL liquid. This formulation includes [redacted] (b) (4) Hydroxypropyl Betadex and several proprietary [redacted] (b) (4) agents.

Nonclinical

Larotrectinib is an orally-bioavailable inhibitor of tropomyosin receptor kinases (TRK), including some TRK fusion proteins identified in malignancies. Loxo has performed 3-month repeat-dose toxicology studies in the rat and monkey and a full panel of genetic toxicology studies with larotrectinib. Loxo also states that embryofetal toxicity studies in the rat and rabbit and a juvenile toxicology study in the rat are ongoing and the final reports of these studies will available at the time of NDA submission.

Clinical

NTRK fusion proteins are commonly identified in certain rare tumors, i.e., infantile fibrosarcoma, secretory/juvenile breast cancer, and mammary analogue secretory cancers (MASC) of the salivary glands but are rarely identified in commonly occurring tumors.

Table 1, copied from the meeting package, provides an overview of the clinical trials conducted by Loxo, forming the primary source of safety and efficacy data in the proposed NDA.

Table 1: Overview of Larotrectinib Clinical Trials

Study ID	Phase	Country	Study Title	Dosing Regimen	Study Population	Enrollment as of 17-Jul-2017	ISS Population	ISE Population
LOXO-TRK-14001	1	USA	A Phase 1 Study of the Oral TRK Inhibitor Larotrectinib in Adult Patients with Solid Tumors	Escalation Phase: Dosing schedule: continuous, 28-day cycles until PD or intolerability Dose levels: 50 mg QD, 100 mg QD, 200 mg QD; 100 mg BID, 150 mg BID, 200 mg BID Expansion Phase: Dose 100 mg BID	Escalation Phase: Adult Solid Tumors Expansion Phase: Evidence of the NTRK or TRK molecular characteristic such as an NTRK translocation or amplification	66	66	8*
LOXO-TRK-15002	2	USA/ EU/ South Korea, Singapore	A Phase 2 Basket Study of the Oral TRK Inhibitor Larotrectinib in Subjects with NTRK Fusion-Positive Tumors	Dosing schedule: continuous, 28-day cycles until PD or intolerability Dose: 100 mg BID	Adult Solid Tumors – TRK fusion+ Consists of 8 baskets	47	47	35*
LOXO-TRK-15003	1/2	USA	A Phase 1/2 Study of the Oral TRK Inhibitor Larotrectinib in Pediatric Patients with Advanced Solid or Primary Central Nervous System Tumors	Dosing schedule: continuous, 28-day cycles until PD or intolerability Escalation Phase: Adult equivalent doses: 100 mg BID, 150 mg BID, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2 Expansion Phase: 100 mg/m^2 BID (maximum of 100 mg BID) Phase 2: 100 mg/m^2 BID (maximum of 100 mg BID)	Phase 1: Pediatric Advanced Solid or Primary Central Nervous System Tumors Expansion: Same as above to further explore dose Phase 2: 3 cohorts-infantile fibrosarcoma, solid tumors with NTRK gene fusions, and primary CNS tumors with NTRK gene fusions	31	31	12*

* ISE population is comprised of the first 55 NTRK fusion RECIST evaluable patients enrolled across studies LOXO-TRK-14001, LOXO-TRK-15002 and LOXO-TRK-15003. Additional NTRK fusion patients enrolled in these studies are described in the interim CSRs and included in the ISS and supplemental ISE analysis sets.

Source: Copied from meeting package.

In addition, Loxo will provide information from eight single patient protocols conducted under Loxo IND 121211 in the U.S., a "Named Patient Use" case in Germany, and a "compassionate use" case in Israel, and three Special Access Scheme cases in Australia.

Loxo proposes to establish efficacy based on a high magnitude and durability of overall response rate (ORR) as determined by an independent review committee (IRC) per RECIST version 1.1 in a pooled analysis of the first 55 patients with non-CNS primary tumors harboring a documented TRK gene fusion (local test) enrolled in Studies LOXO-TRK-14001, LOXO-TRK-15002, or LOXO-TRK-15003, with at least one measurable lesion at baseline who received at least one dose of larotrectinib across the three trials listed in the table above, using a data cut-off date of July 17, 2017. The point estimate of the ORR will be calculated with 2-sided 95% exact binomial confidence interval (CI) using the Clopper-Pearson method reported. Loxo proposes that the effectiveness of larotrectinib will be demonstrated if the lower limit of the 2-sided 95% CI exceeds 30%. In addition, ORR based on local investigator assessment, time to response (TTR), and DOR will be provided.

Additional efficacy data may be provided in 7 of the 23 patients with NTRK fusion tumors enrolled subsequent to the 55 patients constituting the primary efficacy database (12 in LOXO-TRK-15002 and 11 in LOXO-TRK-15003). As of the data cut-off on July 17, 2017, these 7 patients had measurable disease at baseline, a non-primary CNS tumor, and at least one post-baseline imaging assessment, whereas 12 patients have no post-baseline imaging and 4 patients

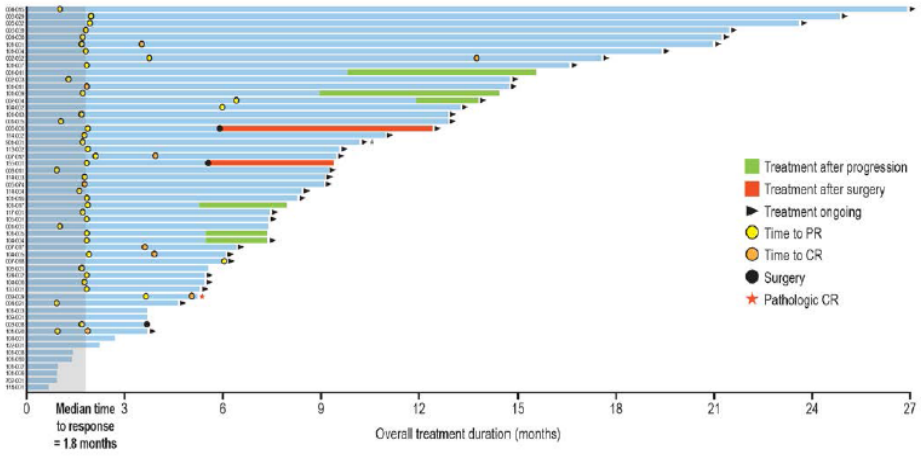
did not meet the criteria for inclusion in the efficacy assessment (2 patients had non-measurable disease at baseline and 2 patients had primary CNS tumors).

The proposed safety database will include all patients, irrespective of TRK fusion status, who are enrolled in Studies LOXO-TRK-14001, LOXO-TRK-15002, and LOXO-TRK-15003 and who receive at least one dose of larotrectinib. It is anticipated that approximately 144 patients will be included in the safety database with a data cut-off date of July 17, 2017.

Results
According to the meeting package, 13 types of cancer were represented in the primary efficacy dataset of 55 patients; the cancer types with the highest incidence (>10%) were salivary gland (22%), soft tissue sarcoma (20%), and infantile fibrosarcoma (13%). The majority (82%) of patients had prior systemic therapy and 93% had an ECOG performance status of 0 or 1.

Among the 55 patients, the ORR was 78.2% (95% CI: 65.0, 88.2) by investigator assessment and 74.5% (95% CI: 61.0, 85.3) by IRC assessment. Among the 41 patients with a response identified by IRC assessment, 20 (49%) have response durations of at least 6 months, 7 (17%) have response durations of at least 12 months, and 6 (15%) progressed with a response duration of less than 6 months.

Figure 1: Swimmer Plot of Time to Response and Time on Treatment for NTRK Fusion Patients (N=55) based on Investigator Response



*CR = complete response; PR = partial response. Response is based on the treating Investigator's assessment using RECIST 1.1. Analysis is based on visit cutoff of 17-Jul-2017. Data exported on 17-Aug-2017. Response assessments are based on RECIST (version 1.1).

Source: Copied from meeting package.

In the safety population, the most frequently reported treatment emergent adverse events (TEAEs), regardless of relationship to larotrectinib, were fatigue (37%), nausea (28%), dizziness (26%), anemia and vomiting each (25%), increased aspartate aminotransferase increase (AST) (24%), constipation (22%), cough (22%), and increased alanine aminotransferase increase (ALT) (21%).

Companion Diagnostic Device Development

Loxo relied upon local laboratory tests to determine patient eligibility for enrollment in clinical trials. Loxo reports that of the 55 patients in the efficacy dataset, 50 patients had NTRK fusions detected by next generation sequencing and 5 patients had NTRK fusions detected by fluorescent in situ hybridization.

In partnership with Ventana Medical Systems/Roche Tissue Diagnostics (Tucson, Arizona, US), Loxo is developing a pan-TRK IHC assay for the identification of high TRK protein expression in solid tumors as a proxy for NTRK fusion detection. Thermo Fisher Scientific (Hemel Hempstead, Herts, UK) and Illumina (San Diego, California, US) have developed NGS multi-gene panels (Oncomine™ Dx Target and TruSight Tumor 170, respectively) that are performed on DNA and RNA extracted from solid tumors and can detect NTRK fusions. Loxo is currently negotiating partnerships with these companies to pursue pre-market approval of these assays as companion diagnostics for larotrectinib.

Table 2: Companion Diagnostic Development Summary

Source: Copied from meeting package.

Clinical Pharmacology

Study reports and pharmacokinetic (PK) datasets will be included in the NDA for the following larotrectinib clinical pharmacology studies in healthy subjects and trials in patients:

- Relative bioavailability of the capsule and oral solution formulations and food effect study (LOXO-TRK-16007)
- QTc study (LOXO-TRK-16009)
- Absolute bioavailability and ADME study (LOXO-TRK-16011)
- DDI study with itraconazole (strong CYP3A4 inhibitor) and rifampin (strong CYP3A4 inducer) (LOXO-TRK-16010)
- DDI study with midazolam (sensitive CYP3A4 substrate) (LOXO-TRK-16012)
- Dose escalation and expansion trial in adult patients (LOXO-TRK-14001)

- Dose escalation and expansion trial in pediatric patients ≥ 1 month of age (Study LOXO-TRK-15003)
- Trial in patients ≥ 12 years of age with NTRK fusion-positive tumors (Study LOXO-TRK-15002)

The hepatic impairment and renal impairment studies are ongoing. Loxo plans to submit the final report for the hepatic impairment study as a post-marketing commitment. In vitro study reports that characterize distribution and metabolism of larotrectinib and ability of larotrectinib to act as substrates, inhibitors, or inducers of drug metabolizing enzymes and transporters, will be included in the NDA. Bioanalytical methods and validation reports will be submitted in the NDA. Loxo plans to perform population pharmacokinetic (popPK), exposure-response (E-R), and concentration-QTc analyses.

DISCUSSION OF FDA RESPONSES TO SPONSOR QUESTIONS

Clinical

Loxo's position on Question #1 is provided on page 53-54 of briefing package.

1) Does the Agency agree that the overall response rate and duration of response are of sufficient magnitude and duration to form the basis of an NDA, in support of the proposed indication?

FDA Response: FDA agrees that the summary level efficacy results of ORR and DOR are of sufficient magnitude to support the filing of an NDA seeking the proposed indication for larotrectinib.

Loxo's Response (provided via email 11/16/2017): Thank you. No further discussion is needed.

Discussion During Meeting: No discussion occurred.

Loxo's position on Question #2 is provided on page 54 of briefing package.

2) Does the Agency agree that the safety database, pooled from Studies LOXO-TRK-14001, LOXO-TRK-15002, and LOXO-TRK-15003, is adequate to support the review of safety for larotrectinib in adult and pediatric patients?

FDA Response: The proposed safety database, comprising 144 patients treated with larotrectinib in Studies LOXO-TRK-14001, LOXO-TRK-15002, or LOXO-TRK-15003, may be adequate to support the review of safety for larotrectinib in adult and pediatric patients; however, Loxo should justify why the 144-patient safety database is sufficient to characterize the safety of LOXO-101 and is sufficient to make a risk:benefit assessment. Loxo should also include narratives from patients treated in single patient

protocols and data on patients in clinical pharmacology studies who experienced adverse events of greater than Grade 1 severity in the text summary of the SCS.

Loxo's Response (provided via email 11/16/2017): These data will be provided as requested. No further discussion is needed.

Discussion During Meeting: No discussion occurred.

Loxo's position on Question #3 is provided on page 54-57 of briefing package.

3) A data cut-off of 17-Jul-2017 supported the safety analyses and independent review committee (IRC) response assessments contained in this briefing book, and planned for Wave 2 of a rolling submission (Appendix B). As a reminder, Wave 1 of the rolling submission would occur in December 2017.

a. The Sponsor proposes to submit updated safety and efficacy data, with a data cutoff date of 19-Feb-2018, as part of the Day 60 Safety Update Report, in mid-May 2018. These submissions would come in the form of an addendum to the ISS and ISE. Does the Agency agree with the timing of this submission?

FDA Response: FDA agrees that the datasets and text for the ISS should be updated as part of the 60-day safety update. FDA also agrees that additional efficacy data, to include updated datasets and text in the ISE, using the February 19, 2018 data cut-off data will be considered during the review of this application as part of the risk:benefit assessment. However, 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.

Loxo's Response (provided via email 11/16/2017): The Sponsor agrees to provide addendums to the CSRs as requested. No further discussion is needed.

Discussion During Meeting: No discussion occurred.

b. As part of the 60 Day Safety Update Report, the Sponsor proposes to submit updated SAEs from the Global Safety Database for ongoing studies and all CRFs for patients who died during the reporting period (defined as 18-Jul 017 to 19-Feb-2018). Does the Agency agree?

FDA Response: FDA agrees. As stated in the minutes of the July 25, 2017 meeting, "FDA agrees to Loxo's proposal for inclusion of narratives and CRFs in the NDA. However, Loxo should be prepared to submit CRFs not included in the original NDA in a timely fashion if requested by FDA during the NDA review."

Loxo's Response (provided via email 11/16/2017): The Sponsor agrees to submit CRFs not included in the original NDA in a timely fashion if requested by the FDA during the NDA review. No further discussion is needed.

Discussion During Meeting: No discussion occurred.

c. Table 22, Table 23 and Table 24 below summarize the content planned for the Day 60 Safety Update Report. Does the Agency find this proposal acceptable?

FDA Response: FDA agrees that the proposed data package for the Day 60 Safety Update Report and proposal for updated efficacy information, as summarized in Table 22 (Integrated Summary of Safety Tables for the Day 60 Update), Table 23 (Integrated Summary of Efficacy Tables for the Day 60 Update), and Table 24 (Integrated Summary of Efficacy Figures for the Day 60 Update including a swimmers plot, waterfall plot, and Kaplan-Meier plot of DoR, PFS, and OS) appears acceptable.

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.

Loxo's Response (provided via email 11/16/2017): The Sponsor agrees. No further discussion is needed.

Discussion During Meeting: No discussion occurred.

Loxo's position on Question #4 is provided on page 54 of briefing package.

4) The Sponsor will provide individual patient narratives for all patients with NTRK fusions included in the ISE database. Does the Agency find the content and format of these narratives acceptable?

FDA Response: FDA agrees with the proposed narrative format that will include:

- Prior cancer treatment (s) and best response to these treatments
- Notable non-cancer history
- Information regarding treatment including study day(s) on which dose interruption, dose modification, or treatment discontinuation occurred

- Clinical responses (per statements and other data in medical records) and objective responses (per RECIST v1.1) to larotrectinib as determined by the local investigator
- Adverse reactions
- Date and site of disease progression
- Study day of first documentation of response and study day of documented progression

Additionally, include IRC-assessed response category and DOR.

Loxo's Response (provided via email 11/16/2017): The Sponsor agrees. No further discussion is needed.

Discussion During Meeting: No discussion occurred.

Clinical Pharmacology

Loxo's position on Question #5 is provided on page 57 of briefing package.

5) Does the Agency agree that the proposed analysis plan for the population pharmacokinetic and pharmacodynamic modeling of larotrectinib is acceptable?

FDA Response: FDA agrees that the proposed analysis plan is acceptable.

Loxo's Response (provided via email 11/16/2017): Thank you. No further discussion is needed.

Discussion During Meeting: No discussion occurred.

Loxo's position on Question #6 is provided on page 58 of briefing package.

6) A comprehensive clinical pharmacology program inclusive of seven clinical pharmacology studies is being conducted. At the time of the NDA submission, and as outlined during the Type B Guidance meeting held on 25-Jul-2017, five Clinical Study Reports (CSRs) will be available with two studies (hepatic and renal impairment) potentially still ongoing. On 13-Oct-2017, the Agency informed the Sponsor that a renal impairment study would not be required, though it was nearly complete at the time of receiving this communication. The Sponsor will submit the final CSR for the renal impairment study when available. With regard to the hepatic impairment study, does the Agency agree that the final CSR may be provided as a post marketing commitment?

FDA Response: The report for the hepatic impairment study can be submitted as a post-marketing requirement. In the NDA submission, provide major milestones (e.g., study completion date, submission of final study report) for the hepatic impairment study.

Loxo's Response (provided via email 11/16/2017): The Sponsor may be able to submit the CSR for the hepatic impairment study during the NDA review. As of 16 November 2017, the Sponsor has completed enrollment of the mild and moderate cohorts (n=8 each) and has partially enrolled the severe cohort (6 of 8), with the appropriate number of matched healthy controls. At the time of the NDA submission, the timelines for study completion and the submission of the final report will be provided.

Discussion During Meeting: No discussion occurred.

Regulatory

Loxo's position on Question #7 is provided on page 58-59 of briefing package.

7) The Sponsor believes this NDA submission will clearly establish clinical benefit of larotrectinib in the treatment of adult and pediatric NTRK fusion patients with unresectable or metastatic solid tumors who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative. The rapid onset, rate, depth and durability of responses seen for larotrectinib are exceedingly uncommon for an anti-cancer therapeutic in an advanced cancer population. An improvement in tumor related symptoms for many patients, and the safety profile of larotrectinib, also read favorably on the overall clinical benefit argument for larotrectinib. It is not clear what outstanding clinical questions remain for larotrectinib in this very rare and heterogeneous population of NTRK fusion cancers, where trial design, ethical and enrollment feasibility issues would complicate the completion of a confirmatory study.

a. Does the Agency agree that larotrectinib offers clinical benefit to the indicated patient population and merits consideration for regular approval?

FDA Response: Because the proposed treatment effect of larotrectinib 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 more appropriate for the proposed NDA. Additional post-marketing studies will be required to verify and further characterize the clinical benefit of larotrectinib in pediatric and adult patients with unresectable or metastatic solid tumors with NTRK-fusion proteins. Furthermore, if larotrectinib is approved, the indication, including qualifications regarding prior therapy and whether any specific tumor histology is excluded from the indication, 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).

Loxo's Response (provided via email 11/16/2017): Thank you for the comments. The Sponsor looks forward to additional dialogue during the NDA review.

Discussion During Meeting: No discussion occurred.

b. Does the Agency agree with the proposed post-marketing commitments outlined below?

FDA Response: Please refer to FDA's response to Question 7a above regarding the regulatory pathway for approval of larotrectinib, the limitations of the proposed data package for the NDA, and the potential for post-marketing requirements to verify and further describe the clinical benefit of larotrectinib in patients with solid tumors that have documented NTRK-fusion proteins. Although FDA does not object to Loxo's proposal to provide additional data from ongoing studies to further characterize the efficacy and safety of larotrectinib, FDA will discuss post-marketing requirements and commitments with Loxo during the NDA review period, according to 21st Century Review timelines for new molecular entity NDAs.

Loxo's Response (provided via email 11/16/2017): Thank you for the comments. The Sponsor looks forward to additional dialogue during the NDA review.

Discussion During Meeting: No discussion occurred.

Loxo's position on Question #8 is provided on page 59-60 of briefing package.

8) In light of the data from the pooled safety analysis from Studies LOXO-TRK-14001, LOXO-TRK-15002, LOXO-TRK-15003, the Sponsor believes the risks associated with treatment with larotrectinib can be managed adequately with appropriate labeling and routine pharmacovigilance activities. Does the Agency agree that a REMS or Medication Guide will not be required for larotrectinib, if approved for the proposed indication?

FDA Response: Although FDA will not require inclusion of a REMS or Medication Guide for filing of the planned NDA, FDA will make a final determination regarding whether a REMS or Medication Guide will be required during the NDA review.

Loxo's Response (provided via email 11/16/2017): Thank you. No further discussion is needed.

Discussion During Meeting: No discussion occurred.

Loxo's position on Question #9 is provided on page 60-61 of briefing package.

9) The Sponsor wishes to implement an expanded access program and close studies LOXOTRK-14001, LOXO-TRK-15002 and LOXO-TRK-15003 to additional enrollment. Does the Agency agree with this plan?

FDA Response: FDA is not opposed to closing LOXO-TRK-14001 to further enrollment; however, FDA anticipates that additional efficacy and safety information will be needed to verify and further characterize the clinical benefit of larotrectinib in patients with refractory solid tumors with documented NTRK-fusion. Therefore, FDA is concerned that closing LOXO-TRK-15002 and LOXO-TRK-15003 to enrollment may hinder timely acquisition of this data. During the NDA review, FDA will consider the additional data needed to support regular approval of larotrectinib (e.g., additional follow-up and a broader clinical experience) and will have additional discussions with Loxo regarding the source and timing of submission of this data.

Loxo's Response (provided via email 11/16/2017): Thank you. No further discussion is needed.

Discussion During Meeting: No discussion occurred.

Loxo's position on Question #10 is provided on page 61 of briefing package.

10) Based on the proposed NDA for adult and pediatric patients with NTRK fusion solid tumors, does the Agency agree that larotrectinib qualifies for a rare pediatric disease priority review voucher?

FDA Response: No. FDA does not agree that larotrectinib would qualify for a rare pediatric disease priority review voucher based on the proposed NDA for adult and pediatric patients with NTRK fusion solid tumors because the serious or life-threatening manifestations of NTRK fusion solid tumors do not primarily affect individuals aged from birth to 18 years of age.

Loxo's Response (provided via email 11/16/2017): Thank you for the response. No further discussion is needed at this time. However, given the complexities and subtleties of the statutes, regulations and guidance documents surrounding the rare pediatric disease voucher program, the Sponsor may re-approach this topic at a future date.

Discussion During Meeting: No discussion occurred.

Loxo's position on Question #11 is provided on page 61 of briefing package.

11) Does the Agency agree that the proposed filing format and the layout of the proposed NDA table of contents is adequate to support the review of the NDA?

FDA Response: The proposed format of the NDA based on the Table of Contents provided is acceptable.

Loxo's Response (provided via email 11/16/2017): Thank you. No further discussion is needed.

Discussion During Meeting: No discussion occurred.

Loxo's position on Question #12 is provided on page 61 of briefing package.

12) Does the Agency agree with the proposed timelines for submission of the NDA documents?

FDA Response: FDA agrees with the proposed schedule for the rolling submission.

Loxo's Response (provided via email 11/16/2017): Thank you. No further discussion is needed.

Discussion During Meeting: Loxo will submit an updated proposed schedule for the rolling submission to FDA, and stated that the first "wave" of their rolling submission is proposed to occur the week of December 18, 2017.

13) Does the Agency wish to schedule an orientation meeting with the Sponsor after the submission of the NDA to outline the major components of the NDA?

FDA Response: Yes, FDA will contact Loxo to schedule an Application Orientation Meeting after submission of the final component of the proposed NDA.

Loxo's Response (provided via email 11/16/2017): Thank you. No further discussion is needed.

Discussion During Meeting: No discussion occurred.

14) Does the Agency foresee that the proposed NDA will be reviewed by the ODAC?

FDA Response: It is premature to comment on whether an ODAC meeting will be needed. A final determination regarding the need for referral to the ODAC will be made after the NDA is submitted.

Loxo's Response (provided via email 11/16/2017): Thank you. No further discussion is needed.

Discussion During Meeting: No discussion occurred.

ADDITIONAL FDA COMMENTS

15) Please refer to the additional clinical pharmacology comments in the minutes (dated July 31, 2017) for the Type B Guidance meeting on July 25, 2017.

Loxo's Response (provided via email 11/16/2017): Thank you. No further discussion needed.

Discussion During Meeting: No discussion occurred.

16) A summary of the ORR as determined by radiologic review prior to clinical assessment and the ORR following clinical assessment by the IRC should have been provided in the background package to the pre-NDA meeting, as agreed to during the July 25, 2017 meeting. Please clarify when Loxo will submit this information to the IND.

Loxo's Response (provided via email 11/16/2017): We apologize for our oversight in not including the requested information in the background package. We have included this information below and will also submit it to the IND.

Based on IRC assessment, the ORR by radiological review was 73% (n=40; 95% CI: 59%-84%) and the ORR following clinical assessment was 75% (n=41; 95% CI: 61%-85%). A patient with infantile fibrosarcoma with pathologic CR following surgical resection contributed to the ORR including clinical assessment, but had a best overall response of SD (unconfirmed PR) as determined by radiologic review prior to clinical assessment.

Discussion During Meeting: No discussion occurred.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed and agreements reached as summarized in the minutes above and the Preliminary Meeting Response issued on October 12, 2017 for the pre-NDA CMC meeting scheduled for October 18, 2017. Loxo committed to submission of a complete application in March 2018, with the exception of the safety and efficacy updates and drug product stability data which will be submitted in May 2018 (on or before day 60).

- Loxo confirmed that the application will include a comprehensive and readily located list of all clinical sites and manufacturing facilities directly or by reference in the application.

- FDA reiterated that an inclusion of a REMS or Medication Guide is not required for filing of the planned NDA. FDA will make a final determination regarding whether a REMS or Medication Guide will be required during the NDA review.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. Loxo stated their intent to submit a complete application and therefore, there are no agreements for late submission of application components.

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.

On May 9, 2017, larotrectinib was granted orphan drug designation for treatment of solid tumors with NTRK-fusion proteins; therefore, an NDA seeking approval of larotrectinib for this orphan indication is exempt from the requirements of PREA. 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 application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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

molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* 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 Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

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 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

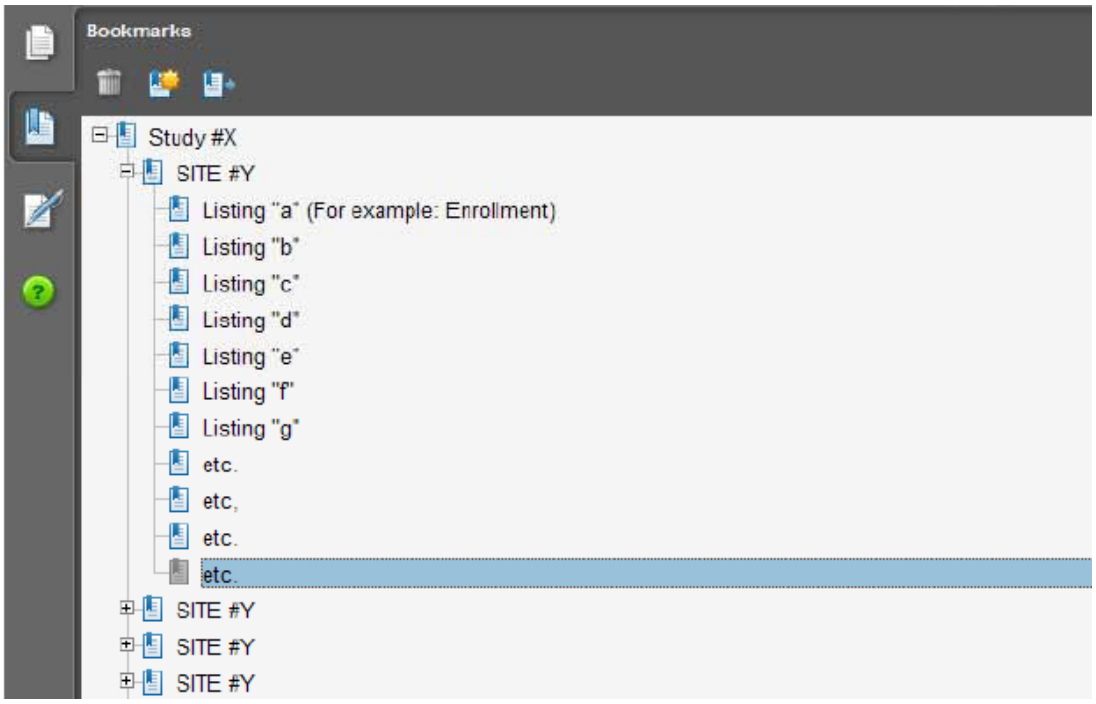
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, 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
No Issues Requiring Further Discussion

ACTION ITEMS
No Action Items

ATTACHMENTS AND HANDOUTS
No Attachments and Handouts

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

/s/

IDARA UDOH
11/29/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 121211

MEETING MINUTES

Loxo Oncology, Inc.
Attention: Katie Cairati, M.S.
Executive Director, Global Regulatory Affairs
701 Gateway Boulevard, Suite 420
South San Francisco, CA 94080

Dear Ms. Cairati:

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

We also refer to the teleconference between representatives of your firm and the FDA on July 25, 2017. The purpose of the meeting was to reach agreement on the content and timing of the planned NDA submission for larotrectinib, for the proposed indication of "the treatment of unresectable or metastatic solid tumors with NTRK-fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments."

A copy of the official minutes of the teleconference 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 (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
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:	Type B
Meeting Category:	Guidance
Meeting Date and Time:	July 25, 2017; 10:00 AM – 11:00 AM, EST
Meeting Location:	Teleconference
Application Number:	IND 121211
Product Name:	larotrectinib
Indication:	Treatment of patients with unresectable or metastatic solid tumors with NTRK-fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments
Sponsor/Applicant Name:	Loxo Oncology, Inc.
Meeting Chair:	Martha Donoghue
Meeting Recorder:	Idara Udoh

FDA ATTENDEES

Patricia Keegan, Director, Division of Oncology Products 2 (DOP2)
Martha Donoghue, Clinical Team Leader, DOP2
Leigh Marcus, Clinical Reviewer, DOP2
Whitney Helms, Nonclinical Supervisor, Division of Hematology, Oncology, Toxicology (DHOT)
Idara Udoh, Senior Regulatory Health Project Manager, DOP2
Kwadwo Korsah, Regulatory Health Project Manager, DOP2
Hong Zhao, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology V (DCP V)
Saeho Chong, Clinical Pharmacology Reviewer, DCP V
Olen Stephens, Product Quality Reviewer, Office of Pharmaceutical Quality
Weishi Yuan, Biometrics Reviewer, Division of Biometrics V

LOXO ONCOLOGY, INC. ATTENDEES
Nisha Nanda, Ph.D., Development Strategy
Katie Cairati, Regulatory Affairs
(b) (4), Regulatory Affairs Consultant
Cindy Rocha, Project Manager
Penelope Sinanian, Clinical Operations
Nora Ku, M.D., Clinical Development
Michael Cox, Pharm.D., Clinical Development
(b) (4) Pharmacology Consultant
(b) (4) Biostatistics Consultant
Joshua Bilenker, M.D., Chief Executive Officer
(b) (4) Ph.D., Manufacturing Consultant
Lars Holzhausen, Ph.D, Regulatory Affairs

MEETING PURPOSE

On May 24, 2017, Loxo requested a Type B, pre-NDA meeting to reach agreement on the content and timing of the planned NDA submission for larotrectinib (formerly named LOXO-101), for the proposed indication of "the treatment of unresectable or metastatic solid tumors with NTRK-fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments."

FDA granted the meeting as Guidance meeting on June 9, 2017 since a pre-NDA meeting will be requested when the complete clinical data intended to support an NDA are available.

The briefing package for this meeting was received on June 27, 2017.

BACKGROUND

Regulatory History
On February 28, 2014, IND 121211 was submitted to the Division of Oncology Products 2 (DOP2) for larotrectinib for the treatment of patients with solid tumors. The IND contained Protocol LOXO-TRK-14001 entitled "A Phase 1a/1b Study of the Oral TRK Inhibitor LOXO-101 in Subjects with Adult Solid Tumors," and was allowed to proceed on May 28, 2014.

On June 29, 2015, Loxo submitted Protocol-TRK-15002, entitled "A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects with NTRK Fusion-Positive Tumors." The study is an open-label, multicenter trial enrolling patients with tumors harboring an NTRK1, NTRK2, or NTRK3 gene fusion. FDA issued an Information Request on July 21, 2015 seeking clarification regarding dose modification, sample size, and eligibility criteria in the study. Loxo provided a revised protocol LOXO-TRK-15002 on August 17, 2015 incorporating FDA recommendations.

On August 21, 2015, Loxo submitted a meeting request to discuss and obtain clinical guidance regarding the development of larotrectinib in pediatric patients with advanced solid tumors,

including primary central nervous system (CNS) tumors. The meeting was granted but later cancelled upon Loxo's request because FDA's October 21, 2015 preliminary responses were considered clear and complete.

On August 31, 2015, larotrectinib was granted orphan drug designation for the treatment of soft tissue sarcoma.

On February 23, 2016, a Type B meeting was held via teleconference to discuss clinical study LOXO-TRK-15002 and seek FDA input regarding the larotrectinib development program, including the planned efficacy analyses intended to demonstrate the clinical benefit of larotrectinib in adult patients with cancers harboring NTRK fusions. During the meeting, FDA recommended that Loxo expand the eligibility criteria for Study LOXO-TRK-15002 to permit enrollment of patients with tumors harboring an NTRK mutation. FDA agreed that Loxo could amend the protocol to enroll patients as young as 12 years of age and did not object to the enrollment of patients with ECOG performance status 3 into the trial.

Additionally, for patients who cannot enroll into the trial, FDA stated that expanded access programs (e.g., single patient protocols) could provide access to patients and provide supportive data regarding its clinical effect in patients with different tumors. In response to this advice, Loxo subsequently submitted the following six single patient protocols for the treatment of patients with cancers harboring an NTRK gene fusion to IND 121211:

- LOXO-TRK-16004, for treatment of a patient with with soft tissue liposarcoma (received April 25, 2016)
- LOXO-TRK-16005, for treatment of a patient with metastatic breast cancer (received July 26, 2016)
- LOXO-TRK-16006, for treatment of a patient with an advanced primary CNS malignancy (received August 1, 2016)
- LOXO-TRK-16008, for treatment of an adult patient with secondary acute myelogenous leukemia (received September 29, 2016). A subsequent protocol amendment provided for use of the liquid formulation of larotrectinib as an alternative to capsules due to the patient's difficulty swallowing (received October 11, 2016)
- LOXO-TRK-17018, for treatment of a patient with locally advanced recurrent secretory breast cancer (received May 4, 2017)
- LOXO-TRK-17019, for treatment of a patient with recurrent breast cancer (received May 16, 2017).

On April 4, 2016, Loxo submitted a meeting request to obtain FDA input regarding the nonclinical and clinical pharmacology development programs for larotrectinib. The meeting was granted but later cancelled upon Loxo's request following receipt of FDA's June 1, 2016,

Preliminary Meeting Comments document. As conveyed in FDA's June 1, 2016, response to Question #11, a separate Advice/Information Request letter was issued to provide FDA feedback regarding Loxo's plan to study the effects of larotrectinib on cardiac electrophysiology.

On May 12, 2016, Loxo submitted a Breakthrough Therapy Designation (BTD) request for the treatment of advanced solid tumors with NTRK fusions. On July 11, 2016, FDA granted BTD designation to larotrectinib for the treatment of unresectable or metastatic solid tumors with NTRK fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments.

On June 16, 2016, larotrectinib was granted rare pediatric disease designation for the treatment of infantile sarcoma.

On November 9, 2016, Type B Breakthrough Therapy-Initial Comprehensive Multidisciplinary meeting was held between FDA and Loxo to discuss the overall development program for larotrectinib and plan future interactions with FDA. During the meeting, FDA recommended that Loxo pre-specify the number of patients upon which efficacy analysis will be based (i.e. 55 patients), and stated that any additional patient data will be considered supportive. Loxo agreed to submit an independent radiology review charter for FDA review and concurrence prior to initiating the central review process. On January 26, 2017, the draft review charter, entitled "Rationale for and Summary of Key Elements of a Proposed Combined Review Charter for Larotrectinib" was received, and FDA issued an Advice/Information Request letter on May 12, 2017 addressing Loxo's questions.

On January 9, 2017, Loxo submitted an Initial Pediatric Study Plan (iPSP) for describing a plan for seeking a partial waiver for development of larotrectinib for pediatric patients 0 to <1 month of age. FDA issued a Written Response letter with additional feedback on the iPSP, and on April 20, 2017 Loxo submitted its agreed iPSP. FDA issued an Initial Agreement letter on May 18, 2017; however, on May 9, 2017 larotrectinib was granted orphan drug designation for treatment of solid tumors with NTRK-fusion proteins.

On March 8, 2017, Loxo submitted a request for review of the proposed proprietary name "(b) (4)". On June 5, 2017, FDA issued a letter informing Loxo that this proposed proprietary name was unacceptable because it may be confused with another currently marketed drug (Trokendi XR).

On July 21, 2017, Loxo submitted a request for review of the proposed proprietary name "(b) (4)".

Chemistry, Manufacturing, and Controls (CMC)

Larotrectinib drug substance is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1- yl) pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate. The drug product is available in the form of capsules for oral administration or solution for oral administration. LOXO-101 capsules (25 mg and 100 mg) are opaque white in color, contain only LOXO-101 drug substance and are distinguishable by size (capsule sizes 2 and 0, respectively). LOXO-101 oral solution is a 20 mg/mL liquid larotrectinib formulation.

Nonclinical

Larotrectinib is an inhibitor of the tropomyosin receptor kinase (TRK) family, TRKA, TRKB, and TRKC. Loxo proposes to submit the completed nonclinical module for the planned NDA in December 2017. According to Loxo, the nonclinical studies planned for submission were conducted using larotrectinib sulfate with doses expressed as free base and include multiple studies investigating the primary and secondary pharmacological effects and pharmacokinetics of the drug as well as stand-alone safety pharmacology studies investigating larotrectinib's effects on cardiovascular, respiratory, CNS, and gastric endpoints; toxicology studies of up the 13 weeks durations in rats and monkeys; a full battery of genotoxicity tests; embryofetal development studies in rats and rabbits; juvenile animal studies in rats; and an in vitro phototoxicity study.

Clinical

NTRK fusion proteins have been identified rarely in commonly occurring tumors, and commonly in rare tumors such as infantile fibrosarcoma, secretory/juvenile breast cancer, and mammary analogue secretory cancers (MASC) of the salivary glands.

There are currently three clinical studies of larotrectinib in cancer patients: a dose-escalation study in adult patients with advanced solid tumors (Study LOXOTRK-14001) being conducted in the United States (U.S.); a dose-escalation and expansion study in pediatric patients (≥ 1 month of age) with advanced cancer or with primary CNS tumors (Study LOXO-TRK-15003) being conducted in the U.S. and Europe; and a basket study in patients age 12 and older with NTRK fusion-positive tumors (Study LOXO-TRK-15002) being conducted in the U.S., Europe, and Asia. There are also six single patient protocols under Loxo IND 121211 in the U.S., a "Named Patient Use" case in Germany, and a "compassionate use" case in Israel.

The primary efficacy analysis for the proposed NDA will be based on a pooled analysis of 55 patients who have tumors with a documented TRK gene fusion enrolled in Studies LOXO-TRK-14001, LOXO-TRK-15002, and LOXO-TRK-15003 (Table 1, below).

Table 1: Studies providing data for the pooled analysis supporting the proposed NDA

Study number, Conduct dates, Location	Active protocol version for SAP	Study design and objectives	Study drug doses	Total patients receiving larotrectinib†	Patients in primary efficacy analysis
Study 14001 May 2014–ongoing US	4.0	Multicenter, Phase 1, open-label, 3 + 3 dose escalation study in adult patients with advanced solid tumors. Objectives are to characterize safety, PK, and to identify the maximum tolerated or appropriate dose of larotrectinib for dose expansion cohort, for which *NTRK* status is required.	50–200 mg QD, 100–150 mg BID	64+	8
Study 15002 Sep 2015–ongoing US, Europe, Asia	6.0 (US) 6.2 (EU)	Multicenter, Phase 2, open-label study in patients 12 years of age or older with an advanced cancer bearing an *NTRK* fusion mutation. "Basket" of tumor types may include nonsmall cell lung, thyroid sarcoma, colorectal, salivary, biliary, primary CNS, and other. Objectives are to determine the overall response rate (CR + PR) and study other efficacy parameters.	100 mg BID	38+	35
Study 15003 Dec 2015–ongoing US, Europe	7.0	Multicenter, Phase 1/2, open-label, dose escalation study in pediatric patients with advanced solid or primary CNS tumors. Objectives are to characterize safety and DLT, PK, efficacy, and to identify the maximum tolerated or appropriate dose of larotrectinib for Phase 2 portion in patients with *NTRK* fusion.	Dosing based on body surface area using adult equivalent of 100 and 150 mg BID then 100–200 mg/m^2	24+	12
Totals					55

† Patients without documented *NTRK* fusion were eligible for Studies 14001 and 15003.

Source: copied from Loxo's briefing package

The primary endpoint is overall response rate (ORR) as determined by an independent review committee (IRC) per RECIST version 1.1. ORR will be estimated based on the proportion of patients with best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR).

The 55 patients included in the Primary Analysis Set (PAS) meet the following criteria:

- Documented *NTRK* fusion as determined by local testing
- Non-CNS primary tumor with one or more measurable lesions at baseline as assessed by RECIST 1.1
- Received one or more doses of larotrectinib.

The Summary of Clinical Efficacy (SCE) will be based primarily on ORR and duration of response (DOR) as assessed by an IRC. The proposed Summary of Clinical Safety (SCS) will include all patients, irrespective of TRK fusion status, who are enrolled in Studies LOXO-TRK-14001, LOXO-TRK-15002, and LOXO-TRK-15003 and who receive at least one dose of larotrectinib. It is anticipated that approximately 130 patients will be included in the SCS. Loxo plans a July 14, 2017 data cutoff date for both the SCE and SCS.

The point estimate of the ORR will be calculated as the proportion of patients in the PAS with IRC-confirmed measurable disease with BOR of confirmed CR or confirmed PR. A 2-sided 95% exact binomial confidence interval (CI) using the Clopper-Pearson method will be reported. Loxo proposes that the effectiveness of larotrectinib will be demonstrated if the lower limit of the 2-sided 95% CI exceeds 30%.

Secondary endpoints include ORR based on local investigator assessment, time to response (TTR), time to best response (TTBR), DOR, disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).

Clinical Pharmacology

Loxo has completed or initiated the conduct of the following studies to characterize the metabolism and pharmacokinetics (PK) of larotrectinib (Tables 2, 3, and 4).

Table 2. Completed biopharmaceutic and pharmacokinetic studies using human biomaterials planned for inclusion in the NDA

CTD Location	Study Number	Short Study Title
5.3.1	**Reports of biopharmaceutic studies**	
5.3.1.3	**In Vitro – in Vivo correlation Study reports and related information**	
5.3.1.3	LOXO-101-DMPK-041	BCS solubility test
5.3.2	**Report of Studies pertinent to Pharmacokinetics using Human Biomaterials**	
5.3.2.2	**Reports of hepatic metabolism and drug interaction studies**	
5.3.2.2	LOXO-101-DMPK-010	Assessment of ARRY-470 as an Inhibitor of the Cytochromes P450 in Human Liver Microsomes
5.3.2.2	LOXO-101-DMPK-011	In Vitro Assessment of the CYP Induction Potential of ARRY-470 in Primary Cultures of Human Hepatocytes
5.3.2.2	LOXO-101-DMPK-047	In Vitro Evaluation of LOXO-101 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes
5.3.2.2	LOXO-101-DMPK-048	In Vitro Evaluation of LOXO-101 as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes and Cryopreserved
5.3.2.3	**Reports of studies using other human biomaterials**	
5.3.2.3	LOXO-101-DMPK-022	Inhibition of Drug Transporters by LOXO-101
5.3.2.3	LOXO-101-DMPK-028	Assessment of LOXO-101 as a Substrate of Human P-gp (MDR1), BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3
5.3.2.3	LOXO-101-DMPK-034	Assessment of LOXO-101 as Substrate of Trans-Cellular Transport Mediated by BCRP in Cells Expressing Human
5.3.2.3	LOXO-101-DMPK-044	Kinetics of LOXO-101 transport by human P-gp and BCRP

Source: copied from Loxo's briefing package

Table 3. Overview of ongoing and completed clinical pharmacology studies providing data planned for inclusion in the NDA

CTD Location	Study Number	Brief Study Title	Dosing Regimen of	Study Population	Enroll-ment	Study Start	Report Availability
5.3.1	**Reports of biopharmaceutic studies**						
5.3.1.1	**Bioavailability Study reports and related info**						
5.3.1.1	LOXO-TRK-16007	Relative Bioavailability of Larotrectinib Administered as a Capsule with and without Food	100 mg SD, PO	Healthy volunteers	18	Nov 2016	Q2 2017
5.3.1.1	LOXO-TRK-16011	Metabolism Study of an Oral Dose of [^{14}C]-Larotrectinib and IV Microtracer Dose of [^{14}C]-Larotrectinib Given at T_{max} of an Oral Dose of Non-labeled larotrectinib	100 mg SD, PO; 11 mcg SD, IV+100mg SD, PO	Healthy volunteers	6 + 6	May 2017	Q1 2018
5.3.3	**Reports of human pharmacokinetic (PK) studies**						
5.3.3.4	**Extrinsic factor Study reports and related info**						
5.3.3.4	LOXO-TRK-16010	DDI of the Effect of Itraconazole and Rifampin on the Pharmacokinetics of larotrectinib	100 mg SD, PO	Healthy volunteers	12 + 12	Feb 2017	Q3 2017
5.3.3.4	LOXO-TRK-16012	DDI of the Effect of larotrectinib on Oral Midazolam	100 mg BID for 10 days, PO	Healthy volunteers	16	Apr 2017	Q4 2017
5.3.4	**Reports of human pharmacodynamic (PD) Studies**						
5.3.4.1	**Healthy subject PD and PK/PD study reports and related info**						
5.3.4.1	LOXO-TRK-16009	Single-Dose, Placebo-Controlled, Dose-Escalation in Healthy	100, 200, 400, 600, 900, 1300 mg SD, PO	Healthy volunteers	48	Apr 2017	Q4 2017

Source: copied from Loxo's briefing package

Table 4. Overview of ongoing and planned clinical pharmacology studies to be conducted as post-marketing commitments

CTD Location	Study Number	Brief Study Title	Dosing Regimen of Larotrectinib	Study Population	Planned Enrollment	Planned Study Start	Report Availability
5.3.4	**Reports of human pharmacodynamic (PD) Studies**						
5.3.4.1	**Healthy subject PD and PK/PD study reports and related info**						
5.3.4.1	LOXO-TRK-16013	Study of larotrectinib in Subjects with Mild, Moderate and Severe Hepatic Impairment and Matched Controls	100 mg SD	Otherwise healthy volunteers	32-40	May 2017	Q2 2018
5.3.4.1	LOXO-TRK-17014	Study of larotrectinib in Subjects with Renal Impairment	100 mg SD	Otherwise healthy volunteers	16	Aug 2017	Q2 2018

Abbreviations: BID = twice daily dosing; DDI = drug-drug interaction; IV = intravenous; PK = pharmacokinetics; SD = single dose

Source: copied from Loxo's briefing package

DISCUSSION OF FDA RESPONSES TO SPONSOR QUESTIONS

Clinical

Loxo's position on Question #1 is provided on page 33 of briefing package.

1) **Does FDA find acceptable the Statistical Analysis Plan (SAP) for the pooled efficacy analysis for Studies LOXO-TRK-14001, -15002, -15003?**

FDA Response: Yes. The statistical analysis plan is acceptable.

Loxo's Response (provided via email 7/24/2017): Thank you. No further discussion is requested.

Discussion During Meeting: No discussion occurred.

Loxo's position on Question #2 is provided on page 33 of briefing package.

2) **Does FDA find acceptable the (b) (4) (IRC) for the independent radiology review for Studies LOXO-TRK-14001, -15002, -15003?**

FDA Response: The IRC charter is acceptable; however, the application should provide a narrative summary for each case in which there was disagreement between the radiology reviewer assessment of best overall response (BOR) and the independent clinical reviewer assessment of BOR. A summary of the overall response rate (ORR) as determined by radiologic review prior to clinical assessment and the ORR following clinical assessment by the IRC should be provided in the background package to the pre-NDA meeting.

Loxo's Response (provided via email 7/24/2017): Thank you. No further discussion is requested.

Discussion During Meeting: No discussion occurred.

Loxo's position on Question #3 is provided on pages 33-34 of briefing package.

3) **The Sponsor plans a 14-July-2017 data cut-off for Studies LOXO-TRK-14001, -15002, and -15003 in the preparation of the SCS and SCE for the NDA. As such, the Clinical Study Reports (CSRs) for these studies will be interim and not final in nature. Does FDA agree that this approach acceptable?**

FDA Response: The proposal for submission of interim study reports is acceptable based on the proposed efficacy dataset and data cut-off date. It is FDA's understanding that the SCE will include data for both investigator- and IRC-assessed response for the first 55

patients with documented NTRK fusions enrolled across the three clinical trials and that all responding patients will have a minimum follow up duration of 6 months from the time of onset of response. Please confirm that data will be provided by study in each of the interim study reports, including patients with CNS malignancies or shorter periods of follow-up. Please also clarify whether Loxo plans to provide available efficacy information from the patients who are treated with larotrectinib under expanded access protocols.

The proposal to submit an SCS in which safety data are pooled across all trials and will include data from all patients who received at least one dose of larotrectinib in the clinical trials (a minimum of 125 patients), and to provide the safety information by study in the interim study reports, is acceptable.

Loxo's Response (provided via email 7/24/2017): For the single patient protocols, the Sponsor will provide both safety and efficacy narratives that will be descriptive in nature. When available, radiographic and photographic evidence of response will be provided. We wish to clarify Agency expectations around the duration of follow-up for the first 55 patients with documented NTRK fusions enrolled across the three clinical trials, namely FDA's "understanding that…all responding patients will have a minimum follow up duration of 6 months from the time of onset of response." We refer to the meeting minutes from the Breakthrough Therapy Designation Multidisciplinary meeting held on November 9, 2016, specifically question 3 and FDA's written response:

> "3. Does the Agency agree that a primary efficacy analysis that includes 55 RECIST evaluable NTRK fusion patients enrolled in Studies LOXO-TRK-14001, 15002, and 15003 would form the basis of an NDA?
>
> **FDA Response:** Based on the preliminary data cited above, indicating a lower limit of the 95% confidence interval (CI) for the centrally-reviewed, observed response rate (ORR) that excludes an ORR of approximately 44%, a duration of response that appears greater than 6 months (*with a minimum duration of follow-up of at least 6 months for the majority of patients)[emphasis added]*, and responses that appear to generally occur across tumor types and fusion partners, FDA does not object to Loxo conducting an analysis that includes 55 patients with NTRK fusion positive tumors for whom there is no satisfactory alternative therapy. However, FDA recommends that Loxo discuss the results of the primary efficacy analysis with FDA in order to obtain guidance regarding whether these results are adequate to form the basis of an NDA in a future meeting."

During this meeting, the Agency advised "*a minimum duration of follow-up of at least 6 months for the majority of patients,"* which departs from the advice provided above in two regards. First, "six months of follow up" is different than "a minimum follow up duration of 6 months from the time of onset of response." Second, "the majority of patients" is different than "all responding patients."

The Sponsor had relied upon the previous Agency advice of November 9, 2016 to identify the data cut-off date of July 17, 2017 for the NDA submission. This cut-off date allows for at least 6 months of follow-up from the first dose of larotrectinib for all 55 patients included in the SCE. As of this data cut-off date, at least 6 months of follow-up from the time of onset of response will be available for 34 of the 43 responding patients. Furthermore, the data cut-off for the 60-day update of the NDA is planned for mid-December 2017. This data cut-off will include an efficacy update for all 55 including at least 6 months of follow-up from the time of onset of response for the remaining 9 responding patients. Thus, the Sponsor can satisfy the Agency's desire to see that "all responding patients will have a minimum follow up duration of 6 months from the time of onset of response," though not until the 60-day update.

May the Sponsor proceed with a data cut-off of July 17, 2017, in keeping with prior Agency advice?

Discussion During Meeting: FDA acknowledged that the minimum 6-month duration of follow-up from the onset of confirmed response will be provided in the efficacy update, so this proposal is acceptable for the initial submission. FDA questioned the feasibility of a later data cutoff date for the efficacy and safety update than December 2017, given submission of the last module of March 2018. Loxo agreed to propose a later cutoff date for safety and efficacy update and proposed to provide alternative data cutoff dates for the safety and efficacy update in the pre-NDA meeting package, which will be held after the pre-NDA CMC meeting; FDA stated this was acceptable.

In response to FDA's question regarding the 55 patients to be included in the PAS, Loxo stated that these patients represent the first 55 patients who had NTRK-fusioned tumors, who had non-CNS disease with investigator-determined measurable disease, and who received one or more doses of larotrectinib with adequate exposure in the effective range. These 55 patients were among the first 58 patients treated and excludes three pediatric patients with thyroid cancer whose tumor was determined to be non-measurable by investigators. FDA stated that this definition for the efficacy population was acceptable and requested that Loxo clearly describe the approach taken to select the 55 patients in the NDA submission.

Loxo's position on Question #4 is provided on pages 34-35 of briefing package.

4) **Does FDA agree with the proposed strategy for presentation of the integrated safety analysis?**

a) The SCS will consist of patients with advanced cancer pooled from Studies LOXOTRK-14001, -15002, -15003 (N ≥ 125) (Table 14).

FDA Response: FDA agrees with the proposed strategy for the SCS that will contain all safety data from patients with advanced cancer pooled from Studies

LOXOTRK-14001, -15002, -15003, including the narratives from patients treated in single patient protocols.

Loxo's Response (provided via email 7/24/2017): Thank you. No further discussion is requested.

Discussion During Meeting: No discussion occurred.

b) Safety data for healthy volunteers enrolled in the clinical pharmacology studies (Table 15) will be provided within the final CSRs, separate from the SCS.

FDA Response: This is acceptable provided that none of the patients in the clinical pharmacology study experienced an AE of greater than Grade 1 in severity.

Loxo's Response (provided via email 7/24/2017): For clinical pharmacology studies where an AE of greater than Grade 1 in severity occurs, the study and the safety data will be described and discussed in the SCS.

The Sponsor would welcome further discussion on this topic during the meeting.

Discussion During Meeting: Loxo proposed to include data on patients in clinical pharmacology studies who experienced adverse events of greater than Grade 1 severity in the text summary for that trial in the SCS. FDA stated that the proposal was acceptable.

Loxo's position on Question #5 is provided on page 36 of briefing package.

5) **The Sponsor plans to request a waiver to present all clinical laboratory values only in SI units in the CSRs, and in the SCS. Does the Agency agree with this approach?**

FDA Response: Yes, this proposal is acceptable, although FDA prefers for clinical laboratory values to be presented using conventional U.S. units as well as SI units in order to facilitate a more efficient review.

Loxo's Response (provided via email 7/24/2017): Thank you. No further discussion is requested.

Discussion During Meeting: No discussion occurred.

Loxo's position on Question #6 is provided on page 36 of briefing package.

6) **As per the Study Data Standards Resources page on the FDA website (https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm), the Sponsor plans to provide nonclinical and clinical datasets as described in Table 12 and Table 13 agree?**

FDA Response: Yes, the proposed plan is generally acceptable. In addition, please provide datasets with pooled data for the 55 patients included in the PAS analysis in the original submission as well as the update to facilitate the review.

Please confirm that the proposed NDA will contain a mock-up define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses and variables for subgroup analyses, etc. Variables used for sensitivity analysis of the SAP should be included as well.

In your NDA submission, please include:

(a) SAS programs that produced all efficacy results

(b) All raw as well as derived variables in .xpt format

(c) SAS programs by which the derived variables were produced from the raw variables, and

(d) Results of any interim analysis if ever performed.

Loxo's Response (provided via email 7/24/2017): The Sponsor confirms that the proposed NDA will contain a mock-up defined file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses and variables for subgroup analyses.

The Sponsor would like to clarify the meaning of "raw" in item (b) above. The Sponsor's interpretation is that this refers to SDTM datasets. Is this correct?

Discussion During Meeting: FDA confirmed that "raw dataset" refers to SDTM datasets. In response to FDA's query, Loxo confirmed that CDISC-compliant datasets will be provided for the PAS efficacy data in the original submission and the efficacy update, and for the pooled safety analyses in the original submission and safety update.

Loxo's position on Question #7 is provided on page 36 of briefing package.

7) **As per ICH E3, the Sponsor will prepare safety narrative for deaths, Serious adverse events (SAEs) and discontinuations due to study drug and will provide full Case Report Forms (CRFs) for all patients meeting these criteria. The Sponsor does**

not plan to provide additional CRFs. The CRFs will be provided as bookmarked, hyperlinked PDFs as described below. Does the Agency agree?

FDA Response: FDA agrees to Loxo's proposal for inclusion of narratives and CRFs in the NDA. However, Loxo should be prepared to submit CRFs not included in the original NDA in a timely fashion if requested by FDA during the NDA review.

Loxo's Response (provided via email 7/24/2017): Thank you. No further discussion is requested.

Discussion During Meeting: No discussion occurred.

Regulatory

Loxo's position on Question #8 is provided on page 37 of briefing package.

8) **Larotrectinib has received Breakthrough Therapy Designation and is therefore eligible for priority review and a rolling submission. A rolling submission/ review would allow the Sponsor to comply with Agency advice from the Type B EOP1 CMC meeting of 7-Dec-2016 regarding the availability of 6-month stability data, while potentially expediting the review of an investigational agent that could treat a serious condition and fill an unmet medical need. Does the FDA agree that the general timing proposed in the briefing package (Table 12 and Table 13) would be acceptable, if a priority review is granted?**

FDA Response: FDA agrees to conduct a rolling review of the proposed NDA. A formal decision regarding priority review will be made by FDA following receipt of the final component of the NDA rolling submission. It is premature to provide comments on the general timing proposed in the briefing package as there is insufficient information regarding quality aspects of the product necessary for FDA to reach agreement on the proposed timing.

FDA reiterates the advice given in the Type B End-of-Phase 1 (EOP1) CMC meeting held on December 7, 2016, that the proposal for the CMC components in the initial submission is still considered risky. During the EOP1 CMC meeting, FDA expressed willingness to consider primary stability datasets with less than the typical expectation of three batches for each strength, with 12 months of long-term stability data for each batch. The proposal in this Type B meeting package consists of three drug product lots with three months of data at the time of NDA submission and a later amendment that includes the 6 month stability updates for these lots. FDA reiterates that this strategy relies heavily on Loxo's ability to adequately establish a bridge between supportive stability batches and the primary stability batches in order to grant a commercially viable shelf life. FDA notes that at the time of the CMC EOP1 meeting, Loxo intended to manufacture the primary stability batches with drug substance batches from the commercial manufacturer, (b) (4), whereas the supportive stability batches were manufactured using drug

substance manufactured by [redacted]. At a minimum, 6 months of long-term and accelerated stability data will be necessary for all three lots of both capsule strengths in order to establish stability trends that could differ between the supportive and primary stability data sets. FDA advises that this submission plan could delay the action date for the NDA as it will require review and possible information requests after submission of the stability update.

FDA also reiterates concerns regarding the oral liquid formulation. Because the supportive stability batch manufactured a [redacted] may not represent the exact commercial process, bridging this batch to the [redacted] batches many not be sufficient to compensate for reduced stability data for the primary stability batches. Without an adequate CMC bridge, the shelf life for the oral solution will be based only on primary stability data and may not be commercially viable. In the NDA submission, provide a clear comparison between the manufacturing process used for the [redacted] supportive stability batch and the intended commercial manufacturing process.

FDA requests an update regarding the status of the primary stability batches for both the capsule and oral solution formulations (manufacturing date, batch release data, and available stability data).

Regarding the proposal to submit a 60-day safety update instead of a 120-day safety update, please clarify the proposed timing of the data cutoff for the safety information that will be included in this safety update. Given the relatively small size of the proposed safety database, FDA considers it vital to have comprehensive safety information that is as up to date as possible available during NDA review.

Loxo's Response (provided via email 7/24/2017): As requested, below is the status of the primary stability batches for both the capsule and oral solution formulations (manufacturing date, batch release data, and available stability data).

Drug product for registration stability and commercial use are being produced at:

[redacted]

The tentative manufacturing plan is as follows:

Primary Stability Batches for LOXO-101 Capsules, 25 mg and 100 mg

Manufacturing Location / Strength	Drug Substance Manufacturing Site	Date of Manufacture
Primary Stability Batches		
[redacted] 25 mg	[redacted]	July 2017
100 mg		July 2017
25 mg		August 2017

(b) (4)	100 mg	(b) (4)	August 2017
	25 mg		August 2017
	100 mg		August 2017

Primary Stability Batches for LOXO-101 Solution

Manufacturing Location	Drug Substance Manufacturing Site	Date of Manufacture
Primary Stability Batches		
(b) (4)		August 2017
		September 2017
		September 2017

As outlined in the meeting request for this Type B meeting, the Sponsor is planning on submitting a Type B CMC meeting request in mid-August 2017 for a meeting in mid-October 2017. At this time, we will provide a full update on drug substance and drug product, including batch release and stability data.

The data cut-off date for both efficacy and safety data for the 60-day update is mid-December 2017.

Discussion During Meeting: FDA advised Loxo that the meeting package for the pre-NDA CMC meeting should contain extensive product characterization and comparison between the developmental manufacturing process and intended commercial process, developmental and representative commercial batch data, as well as all available stability data. Loxo should prepare the list of manufacturers typically reported on the Form FDA 356h and include this in the CMC meeting package.

Loxo's position on Question #9 is provided on pages 37-38 of briefing package.

9) **Is the proposed plan presented below for the content of the Biomonitoring (BIMO) section of the NDA acceptable?**

FDA Response: Loxo's proposal for the content of the BIMO section of the NDA is acceptable. However, FDA requests that Loxo also provide the Office of Scientific Investigations (OSI) requested information under Item III of the OSI requests in the BIMO section of the NDA. The Clinsite data file is used for loading the OSI clinical site selection tool. Submitting this data file is voluntary, but having the loaded SST for use in clinical site selection for inspection significantly accelerates the conduct of all clinical inspections needed in support of the pending NDA.

Loxo's Response (provided via email 7/24/2017): Thank you. We will provide the requested information. No further discussion is requested.

Discussion During Meeting: No discussion occurred.

ADDITIONAL FDA COMMENTS

Clinical Pharmacology

10) The Clinical Pharmacology package in support of the larotrectinib NDA filing should also include justification for clinical dose selection and exposure response analyses.

11) In the planned NDA submission, 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 the 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 dosage and administration.

    b. What are the exposure-response relationships for efficacy, safety and biomarkers?

    c. What is the effect of larotrectinib on QT/QTc interval?

    d. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion) of larotrectinib?

    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 the recommendation with regard to meals or meal types.

    f. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, body weight, disease, and organ dysfunction) influence the exposure, efficacy, or safety of larotrectinib? What dose modifications are recommended?

12) In the planned NDA submission, apply the following advice in preparing the clinical pharmacology sections:

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

    b. Provide a final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.

c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID numbers in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.

d. Provide all concentration-time and derived pharmacokinetic 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.

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

13) Refer to the following guidance for general expectations on submitting pharmacometrics data and models: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CD ER/ucm180482.htm.

14) Submit study reports of population pharmacokinetics (popPK) analyses and exposure-response (measures of effectiveness, biomarkers and toxicity) relationship analyses in the targeted patient population. Refer to the Guidances for Industry available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guida nces/ucm072137.pdf for popPK analyses and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationship analyses.

15) With regards to the physiologically-based pharmacokinetic (PBPK) submission:

a. Include the purpose of the simulations, assumptions, detailed process of PBPK model building and verification, a summary of model input parameters, version of software, simulation results, and conclusions in the study report.

b. Provide the study report as PDF files (screenshots can be incorporated if required).

c. Include the model files used to generate the final PBPK simulations. These files should be executable by FDA reviewers using the specified software.

d. Include appropriate supporting documentations such as any special instructions and file definitions.

16) Include the following items in the QT study report:

a. Electronic copy of the study report

b. Electronic or hard copy of the clinical protocol

c. Electronic or hard copy of the Investigator's Brochure

d. Annotated CRF

e. A data definition file which describes the contents of the electronic data sets

f. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses

g. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)

h. Data set whose QT/QTc values are the average of the above replicates at each nominal time point

i. 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

j. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

l. A completed Highlights of Clinical Pharmacology Table

Loxo's Response (provided via email 7/24/2017): Thank you. We acknowledge the additional comments. No further discussion is requested.

Discussion During Meeting: No discussion occurred.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from 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 application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* 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.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards 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. For clinical

and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.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 the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

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).

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

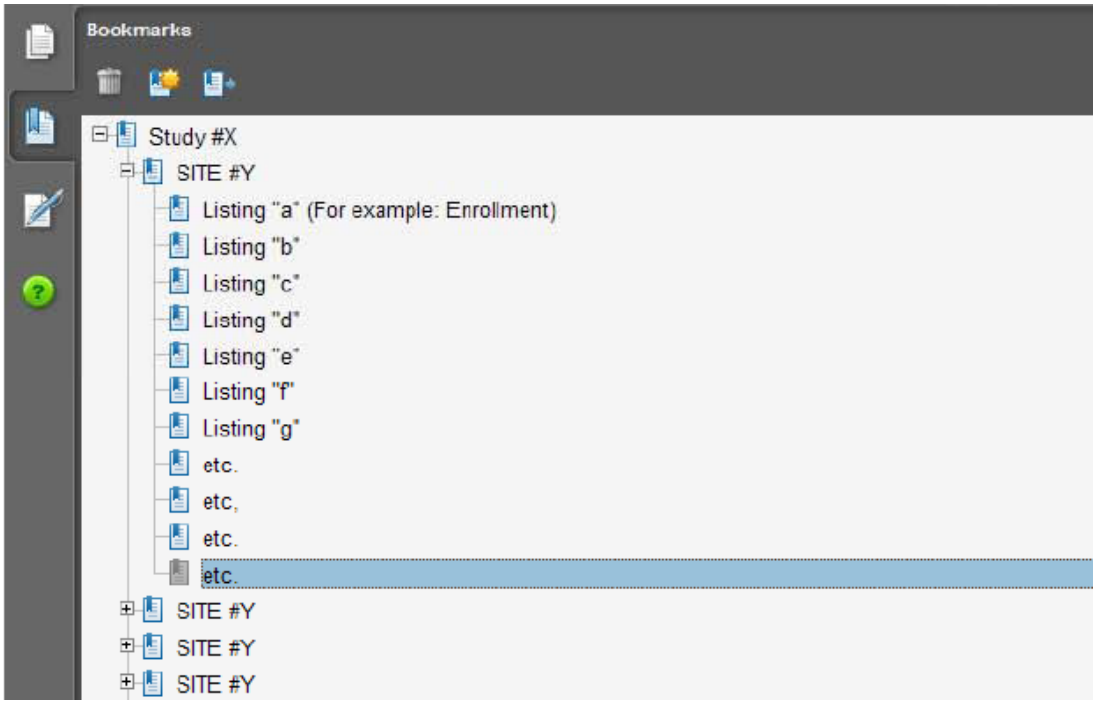
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, 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

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

ISSUES REQUIRING FURTHER DISCUSSION
No issues requiring further discussion.

ACTION ITEMS
No action items.

ATTACHMENTS AND HANDOUTS
No attachments and handouts.

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

/s/

IDARA UDOH
07/31/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 121211

MEETING MINUTES

Loxo Oncology, Inc.
Attention: Katie Cairati, M.S.
Executive Director, Regulatory Affairs
400 Oyster Point Boulevard, Suite 520
South San Francisco, CA 94080

Dear Ms. Cairati:

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

We also refer to the meeting between representatives of your firm and FDA on November 9, 2016. The purpose of the meeting was to provide an overview and update on the overall development program for LOXO-101, and to discuss and plan future interactions with the Agency.

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 (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
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:	Type B
Meeting Category:	Breakthrough Therapy-Initial Comprehensive Multidisciplinary
Meeting Date and Time:	November 9, 2016; 12:30 PM – 2:00 PM, EST
Meeting Location:	White Oak Building 22, Conference Room 1419
Application Number:	IND 121211
Product Name:	LOXO-101
Indication:	Unresectable or metastatic solid tumors with NTRK-fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments
Sponsor/Applicant Name:	Loxo Oncology, Inc.
Meeting Chair:	Martha Donoghue
Meeting Recorder:	Idara Udoh

FDA ATTENDEES

Center for Drug Evaluation and Research (CDER)

Division of Oncology Products 2, Office of New Drugs (OND)
Patricia Keegan, Director
Martha Donoghue, Associate Director (Acting)
Leigh Marcus, Clinical Reviewer
Idara Udoh, Senior Regulatory Health Project Manager

OND Division of Hematology Oncology and Toxicology
Whitney Helms, Nonclinical Team Leader
Shawna Weis, Nonclinical Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology V
Hong Zhao, Clinical Pharmacology Team Leader

Office of Biostatistics, Division of Biometrics V (DBV)
Xiaoping Jiang, Biometrics Reviewer
Jonathan Vallejo, Biometrics Reviewer
Uma Siangaphoe, Biometrics Reviewer

Office of Orphan Products Development (OOPD)
Gayatri R. Rao, Director
John Milto, OOPD Reviewer
Henry H. Startzman, Director, Orphan Drug Designation Program

Immediate Office, OND
Gregory Reaman, Associate Director

Center for Devices and Radiological Health (CDRH)
Division of Molecular Genetics and Pathology*, *Office of In Vitro Diagnostics and Radiological Health
Reena Philip, Director
Anand Pathak, Team Leader
Janaki Veeraraghavan, Reviewer

LOXO ONCOLOGY, INC. ATTENDEES
Nisha Nanda, Ph.D., Development Strategy
Anne Frederick, Ph.D., Regulatory Affairs
Katie Cairati, Regulatory Affairs
(b) (4) Regulatory Affairs (Consultant)
Nora Ku, M.D., Clinical Development
Michael Cox, PharmD., Clinical Development
(b) (4) Biostatistics (Consultant)
Jacob Van Naarden, Chief Business Officer/Lab Medicine Liaison
Joshua Bilenker, M.D., Chief Executive Officer

MEETING PURPOSE

On September 14, 2016, Loxo Oncology, Inc. ("Loxo") requested an Initial Comprehensive, Multidisciplinary Breakthrough Therapy Type B meeting to provide an overview and update on the overall development program for LOXO-101, and to discuss and plan future interactions with the Agency.

The meeting briefing package for this meeting was received on October 11, 2016. FDA sent Preliminary Comments to Loxo on November 8, 2016.

PROPOSED INDICATION

For the treatment of unresectable or metastatic solid tumors with NTRK-fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments.

BACKGROUND

Regulatory History

On February 28, 2014, Loxo submitted clinical protocol LOXO-TRK-14001, entitled "A Phase 1a/1b Study of the Oral TRK Inhibitor LOXO-101 in Subjects with Adult Solid Tumors" to IND 121211. The study was allowed to proceed on March 28, 2014 and was initiated in May 2014.

On June 29, 2015, Loxo submitted a new clinical protocol LOXO-TRK-15002, entitled "A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects with NTRK Fusion-Positive Tumors." This study is an open-label study enrolling patients with tumors harboring an NTRK1, NTRK2, or NTRK3 gene fusion. FDA issued an Information Request on July 21, 2015 for clarification regarding dose modification, sample size, and eligibility criteria of the study. Loxo provided a revised protocol LOXO-TRK-15002 on August 17, 2015 incorporating FDA recommendations outlined in the Information Request.

On August 21, 2015, Loxo submitted a meeting request to discuss and obtain clinical guidance regarding the development of LOXO-101 in pediatric patients with advanced solid tumors, including primary central nervous system (CNS) tumors. The meeting was granted but later cancelled upon Loxo's request because FDA's October 21, 2015 preliminary responses were considered clear and complete.

On August 31, 2015, LOXO-101 was granted orphan drug designation for the treatment of soft tissue sarcoma.

On February 23, 2016, a Type B meeting was held via teleconference to discuss clinical study LOXO-TRK-15002 and seek FDA input regarding the LOXO-101 development program, including the planned efficacy analyses intended to demonstrate the clinical benefit of LOXO-101 in adult patients with cancers harboring NTRK fusions. During the meeting, FDA recommended that Loxo expand the eligibility criteria for Study LOXO-TRK-15002 to permit enrollment of patients with tumors harboring an NTRK mutation. FDA agreed that Loxo could amend the protocol to enroll patients as young as 12 years of age and did not object to the enrollment of patients with ECOG performance status 3 into the trial.

Additionally, for patients who cannot enroll into the trial, FDA stated that expanded access programs (e.g., single patient protocols) could provide access to patients and provide supportive data regarding its clinical effect in patients with different tumors. In response to this advice, Loxo subsequently submitted the following four single patient protocols to IND 121211:

- LOXO-TRK-16004, entitled "Single-patient clinical protocol of LOXO-101 in a patient with soft tissue liposarcoma in the setting of a NTRK gene fusion", received April 25, 2016
- LOXO-TRK- 16005, entitled "Single-Patient Clinical Protocol of LOXO-101 for a Patient with Metastatic Breast Cancer in the Setting of an NTRK Gene Fusion", received July 26, 2016

- LOXO-TRK-16006, entitled "Single-Patient Clinical Protocol of LOXO-101 for a Patient with an Advanced Primary CNS Malignancy in the Setting of an NTRK Gene Fusion", received August 1, 2016
- LOXO-TRK-16008, entitled "Single-patient clinical protocol of LOXO-101 for an elderly patient with secondary acute myelogenous leukemia in the setting of an NTRK gene fusion (LOXO-TRK-16008), received September 29, 2016. A protocol change was submitted on October 11, 2016, requesting that the liquid formulation of LOXO-101 be made available to the patient as an alternative to capsules due to the difficulty swallowing.

On April 4, 2016, Loxo submitted a meeting request to obtain FDA input regarding its nonclinical and clinical pharmacology programs, as part of the overall development program to support an initial marketing authorization for LOXO-101. The meeting was granted but later cancelled upon Loxo's request following receipt of FDA's June 1, 2016, Preliminary Comments document. As conveyed in FDA's June 1, 2016, response to Question #11, a separate Advice/Information Request letter was issued to provide FDA feedback regarding Loxo's plan to study the effects of LOXO-101 on cardiac electrophysiology.

On May 12, 2016, Loxo submitted a Breakthrough Therapy Designation (BTD) request for the treatment of advanced solid tumors with NTRK fusions. On July 11, 2016, FDA granted BTD designation to LOXO-101 for the treatment of unresectable or metastatic solid tumors with NTRK fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments.

On October 10, 2016, Loxo submitted an end-of-phase 1 (EOP1) Chemistry, Manufacturing, and Controls (CMC) Only meeting request to obtain FDA feedback and concurrence on several aspects of its CMC program, including the manufacturing strategy to support product commercialization. This meeting is scheduled for December 7, 2016.

According to the briefing package, LOXO-101 was granted rare pediatric disease designation for the treatment of infantile sarcoma.

Chemistry, Manufacturing, and Controls (CMC)

The proposed drug substance, LOXO-101, is a small molecule with the chemical name of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate. LOXO-101 is manufactured (b) (4) (b) (4) with a molecular formula of $C_{21}H_{24}F_2N_6O_6S$ and a molecular weight of 526.52 (428.4 as the free base). There are three drug product formulations for clinical studies: a capsule formulation consisting of the drug substance (no additional excipients), in opaque white hard gelatin capsules in 25 mg (size 2 capsule) and 100 mg (size 0 capsule) strengths; a liquid solution formulation, LOXO-101 Liquid, containing (b) (4) in a strength of 20 mg/mL (60 mL/bottle); and a powder formulation, LOXO-101 Powder – Compounding Kit, consisting of (b) (4) of drug substance LOXO-101 filled into a (b) (4) bottle (to be compounded (b) (4) into aqueous solution in 20 mg/mL). The latter two formulations are recently developed. The strength of these formulations are expressed in LOXO-101 free base.

Nonclinical

On June 1, 2016, FDA provided feedback on Loxo's proposed toxicology plan to conduct 13-week studies in the rodent and non-rodent and a dose-ranging embryofetal toxicity study, to support an NDA for LOXO-101. Loxo states that they subsequently received feedback from the European health authorities and FDA's Pediatric Subcommittee of the ODAC, requesting data from a juvenile toxicology study to support the development of LOXO-101 in pediatric patients. Loxo is now seeking concurrence on the design of the juvenile toxicology study in the rat.

Loxo states that they plan to conduct a non-Good Laboratory Practice (GLP) dose-ranging study in juvenile rats. Animals will be assigned to four test article groups and one control group, and will be dosed from postnatal days (PND) 7-28 to assess tolerability. Toxicokinetic sampling will be collected on Days 7 and 28, and tolerability will be assessed by body weight, clinical observations and collection of clinical pathology endpoints at the time of study termination. A necropsy will be performed on PND 29, at which time, only organ weights will be collected.

For the definitive GLP-juvenile toxicology study, Loxo will assign animals to three treatment groups and one control group and dose from PND 7-56 (corresponding to relative neurological ages of 0-12 years in humans). Study endpoints will include toxicokinetic sampling on Days 7 and 56, tolerability (mortality, body weight, feed consumption, clinical observations), clinical pathology (at termination and prior to the end of recovery), timing of sexual maturity (examination for balanopreputial separation and vaginal patency), neurobehavioural assessments (auditory startle response, locomotor activity, functional observational battery, and memory (water maze) and, bone measurements by assessment of tibial length (and femoral length at necropsy). Loxo will include clinical pathology, organ weights, gross and histopathological assessments, and, in males, an assessment of spermatogenesis, in 10 rats/sex/group sacrificed at the end of the dosing interval (PND 57) and the end of the recovery period (PND 125).

To evaluate the long-term effects of LOXO-101 on reproductive function, Loxo will evaluate females from this study (20/group) for estrous cyclicity (by vaginal lavage) beginning 2 weeks

prior to initiation of mating. In addition, Loxo will assess mating endpoints between non-litter mates including fertility, conception and copulation indices, live litter sizes, and sex ratio. Females in this subgroup will be euthanized on Lactation Day (LD) 4, and offspring will be euthanized on PND4.

Clinical

Loxo proposes to conduct a primary analysis on 55 patients from the following studies with LOXO-101 to form the basis of an NDA submission:

- LOXO-TRK-14001: a Phase 1 dose escalation study in patients with advanced solid tumors
- LOXO-TRK-15002: a Phase 2 basket study in patients with NTRK fusion positive tumors
- LOXO-TRK-15003: a Phase 1 study in pediatric patients with advanced solid or primary CNS tumors; this study was recently amended to include a Phase 2 efficacy portion.

LOXO-TRK-15002 was initially designed as a multi-center, open-label study in eight cohorts (seven of which were histological defined) of patients (n=152) with different advanced cancers harboring a fusion of NTRK1, NTRK2, or NTRK3. NTRK fusions are rare events in most common malignancies (per Foundation Medicine data, the incidence rate was 0.6% or less in bile duct adenocarcinoma, lung cancer, sarcoma, thyroid cancer, glioblastoma, breast cancer, and colon cancer). Conversely, NTRK fusions are common in certain very rare tumors (percentiles per published reports): mammary analogue secretory carcinoma (100%); infantile fibrosarcoma (90.9%); Spitz neoplasms (nevi) (10.7%); secretory breast carcinoma (91.7%); and congenital mesoblastic nephroma (60.7%). NTRK fusions may also occur in up to 10% of pediatric primary CNS tumors and 25% of pediatric papillary thyroid cancer (the latter of which has a lower metastatic/recurrent potential).

FDA met with Loxo in an EOP1 meeting on February 23, 2016, where Loxo proposed changing the primary analysis of LOXO-TRK-15002 from estimating objective response rate (ORR) in each specific cohort to estimating objective response rate (ORR) based on the first 55 subjects with NTRK-fusion cancers who are enrolled across cohorts 1-6 and those in Cohort 8 with measurable disease (Cohort 7 is enrolling patients with CNS malignancies). Assuming a true ORR of at least 50%, a sample size of 55 treated subjects (i.e., receive at least one dose of study drug) is estimated to provide 80% power to achieve a lower boundary of a two-sided 95% exact binomial confidence interval (CI) around the estimated ORR that exceeds 30%. FDA did not object to a proposal to pool data from 55 patients; however, FDA could not determine whether data from 55 patients would be sufficient to support an initial marketing application in the absence of these data because evaluation of the treatment effects of LOXO-101 will be dependent on the outcomes observed and that this will be a review issue at the time of submission. FDA stated that the evaluation will be dependent upon the outcomes observed and the totality of the evidence. FDA also stated that ORR per independent review should be the primary endpoint, and that FDA would assess the magnitude of the response, duration of response, and the overall evaluation of benefit versus risk.

Due to the rarity of NTRK fusion positive cancers, Loxo has taken steps to facilitate enrollment into clinical trials including: expanding enrollment (e.g., by age) in both LOXO-TRK-15003 and LOXO-TRK-15002, expanding site selection, submitting single patient protocols under Loxo's IND, establishing "just in time" trial site activation (when patients are identified in geographies without open trial sites), assisting patients with travel, grant funding to increase utilization of genomic profiling, and collaborating with patient advocacy organizations.

As of September 14, 2016, 34 patients with NTRK fusion positive cancers (86 enrolled overall) have enrolled into one of three clinical trials (7 in LOXO-TRK-14001; 20 in LOXO-TRK-15002; and 7 in LOXO-TRK-15003). Loxo also plans to open a clinical trial that will enroll up to 12 additional patients with NTRK-fusion positive tumors in Japan. Finally, LOXO-101 is planned for inclusion in NCI-MATCH and NCI-Pediatric MATCH; however, Loxo believes that data from these trials are unlikely to be included in an initial NDA (due to timing).

Efficacy data were presented for 33 patients with NTRK fusion positive tumors enrolled across the three studies. A response assessment had not yet been performed on three patients and one patient withdrew consent before undergoing a response assessment. To date, responses have been observed in 19 patients (63% of the 30 evaluable patients), including two patients who experienced a complete response. Of the responding patients, 7 have maintained an objective response following a minimum of 12 months of LOXO-101 exposure and 14 continue to maintain a response following at least 6 months of LOXO-101 exposure.

To date, responses have been observed in patients with salivary gland tumors (e.g., MASC), infantile fibrosarcoma, soft tissue sarcoma, colon cancer, melanoma, non-small cell lung cancer (NSCLC), gastrointestinal stromal tumor (GIST), cholangiocarcinoma, and thyroid cancer. An additional patient with breast cancer has responded under a single patient protocol.

Clinical Pharmacology

Loxo plans to conduct the following clinical pharmacology studies in healthy subjects who will receive a single 100 mg dose of LOXO-101:

- Relative bioavailability (capsule versus oral solution) and food effect study (n=18).
- Drug-drug interaction study with itraconazole (strong CYP3A inhibitor) and rifampin (strong CYP3A inducer) (n=24).
- Drug-drug interaction study with midazolam (sensitive CYP3A substrate), if warranted (n=12).
- ADME and absolute bioavailability study (n=12).
- Hepatic impairment study (sample size to be determined).
- Renal impairment study, if warranted based on results of the ADME study and data from patients with renal impairment (sample size to be determined).
- QT study, which includes additional single doses of 200 and 400 mg (n=24).

In addition, Loxo plans to conduct population pharmacokinetic and exposure-response analyses.

Development Plans

Loxo plans to submit an NDA based on pooled results of 55 patients with NTRK fusion positive cancers who have been enrolled across three studies. Loxo will submit a statistical analysis plan for FDA review in the second quarter of 2017. Loxo stated in the briefing package that a separate development program may be required for patients with pre-surgical fibrosarcoma (e.g., to convert a morbid surgery into a less morbid surgery).

DISCUSSION OF FDA RESPONSES TO SPONSOR QUESTIONS

Nonclinical

Loxo Oncology's position on Question #1 provided in Section 8.2 (pages 54-56) of briefing package.

1. **Does the Agency agree that the proposed GLP definitive juvenile study in Sprague-Dawley rats will meet the Sponsor's requirements for an NDA for pediatric patients?**

   FDA Response: Yes. The proposed study design appears to be adequate.

   Loxo's Response (Received via email on November 8, 2016): Thank you for the response. No further discussion is requested.

   Discussion During Meeting: No discussion occurred.

Clinical

Loxo Oncology's position on Question #2 provided in Section 8.3 (pages 56-58) of briefing package.

2. **Given the uniformity of data collection across the program, and the expected study size of LOXO-TRK-15002, the Sponsor plans to integrate safety data from all patients across Studies LOXO-TRK 14001, 15002 and 15003 to form the basis of the Summary of Clinical Safety in the NDA. Does the Agency agree that this plan is appropriate, and that an integrated safety database consisting of 100-130 cancer patients is sufficient to support an NDA?**

   FDA Response: FDA agrees with the plan to integrate safety data sets from Studies LOXO-TRK 14001, 15002 and 15003 to form the basis of the Summary of Clinical Safety in the planned NDA. However, Loxo will need to provide justification in an NDA to support why the safety database consisting of 100-130 patients is sufficient to characterize the risk-benefit profile of LOXO-101 in patients with NTRK-positive tumors.

Loxo's Response (Received via email on November 8, 2016): Thank you for the response. No further discussion is requested.

Discussion During Meeting: No discussion occurred.

3. **Does the Agency agree that a primary efficacy analysis that includes 55 RECIST evaluable NTRK fusion patients enrolled in Studies LOXO-TRK-14001, 15002, and 15003 would form the basis of an NDA?**

FDA Response: Based on the preliminary data cited above, indicating a lower limit of the 95% confidence interval (CI) for the centrally-reviewed, observed response rate (ORR) that excludes an ORR of approximately 44%, a duration of response that appears greater than 6 months (with a minimum duration of follow-up of at least 6 months for the majority of patients), and responses that appear to generally occur across tumor types and fusion partners, FDA does not object to Loxo conducting an analysis that includes 55 patients with NTRK fusion positive tumors for whom there is no satisfactory alternative therapy. However, FDA recommends that Loxo discuss the results of the primary efficacy analysis with FDA in order to obtain guidance regarding whether these results are adequate to form the basis of an NDA in a future meeting.

Loxo's Response (Received via email on November 8, 2016): The Sponsor appreciates the Agency's comments. The Sponsor understands the Agency's response as meaning that to form the basis of an NDA, it is acceptable to pool the initial 55 RECIST evaluable NTRK fusion patients enrolled across Studies LOXO-TRK-14001, 15002, and 15003, but that the final determination of the clinical risk benefit profile of LOXO-101 is a review issue and must be discussed in a future meeting.

Discussion During Meeting: FDA acknowledged Loxo's response to this question and is in agreement with its content. FDA also clarified that prior to the analysis of objective response rate, Loxo should pre-specify the number of patients upon which the efficacy analysis will be based (i.e. 55 patients), and that any additional patient data will be considered supportive. Loxo stated its intent to submit the radiology review charter for FDA review and concurrence prior to initiating the central review process.

Loxo Oncology's position on Question #4 provided in Section 8.3 (pages 58-59) of briefing package.

4. **If the estimated ORR is ≥ 50% and the median duration of response is maintained at ≥ 6 months in a sizable number of patients, it may be possible to characterize efficacy before the target sample size of 55 NTRK fusion patients is achieved. The Sponsor may be in a position to approach the Agency, in the context of a pre-NDA meeting, to discuss an earlier NDA filing. Does the Agency agree?**

FDA Response: No. In order for FDA to determine that Loxo has provided substantial evidence to support approval of an NDA for LOXO-101, the magnitude of the centrally confirmed ORR must be sufficiently large for the lower limit of the 95% confidence interval for the observed ORR to exceed a clinically relevant response rate, responses must be durable, and the risk:benefit assessment must favor treatment with LOXO-101 in the targeted patient population. Ultimately, to support a tissue-agnostic indication, Loxo will need to submit data to support the scientific validity of extrapolation of results across indications and NTRK fusion partners. Reducing the size of the efficacy database would limit FDA's ability to extrapolate the results across indications and fusion partners.

Loxo's Response (Received via email on November 8, 2016): Thank you for the response. No further discussion is requested.

Discussion During Meeting: No discussion occurred.

Companion Diagnostics

Loxo Oncology's position on Question #5 provided in Section 8.4 (pages 59-60) of briefing package.

5. Does the Agency agree with the timing of the proposed CDRH interaction?

FDA Response: Yes, the proposed Fourth Quarter 2016 interaction with CDRH is acceptable.

Loxo's Response (Received via email on November 8, 2016): Thank you for the response. No further discussion is requested.

Discussion During Meeting: No discussion occurred.

Loxo Oncology's position on Question #6 provided in Section 8.4 (page 60) of briefing package.

6. If the Sponsor is unable to develop a companion diagnostic assay suitable for a simultaneous regulatory submission, would the Agency approve LOXO-101 on the basis of the lab-developed test (LDT) assays used to enroll the clinical studies, and allow for a companion diagnostic PMA submission as a post-marketing commitment?

FDA Response: As discussed in FDA's In Vitro Companion Diagnostic Devices Guidance (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262327.pdf), FDA may decide to approve a therapeutic product even if an in vitro (IVD) companion diagnostic device is not yet approved or cleared when the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device. Whether FDA will approve the drug, followed by a PMA submission in the post-marketing setting (i.e., as a post marketing commitment), will be determined by FDA during NDA review.

FDA recommends that Loxo continue to bank specimens that were used to determine enrollment for the purpose of conducting a bridging study with the test intended for marketing. To ensure an appropriate bridging study is conducted, it is necessary to obtain a random sampling of test negatives from the laboratories as well as all the test positive cases from patients screened by the local labs, to obtain an estimation of the concordance between the clinical trial assays and the IVD version.

Loxo's Response (Received via email on November 8, 2016): The Sponsor appreciates the Agency's comments. With a diagnostic partner, the Sponsor will be submitting a pre-submission package to CDRH regarding the analytical and clinical validation plans for a Pan-Trk immunohistochemistry (IHC) assay to serve as an aid in identifying patients eligible for treatment with LOXO-101. Due to the extreme rarity of positive control samples, and similar to the tumor-agnostic clinical development plan for NTRK fusion patients, the proposed analytical validation plan is also tumor-agnostic, using samples across tumor types for each standard analytical validation study. The clinical validation plan relies upon testing the banked specimens from studies 14001, 15002, and 15003 with the IHC assay, and conducting an analysis of the primary endpoint based on those patients whose samples test positive as defined by the assay. The Sponsor plans to construct a "negative" sample set from tumor specimens collected from patients in Phase 1 protocols 14001 and 15003 who did not have documented NTRK fusions. The Sponsor would appreciate any advice at the meeting or in the upcoming pre-submission meeting on this proposed validation plan.

Discussion During Meeting: FDA agrees with Loxo's proposal to test NTRK-positive and negative patient specimens in its bridging analysis. FDA recommended that NTRK-positive specimens be preserved for clinical bridging and not analytical validation. Analytical validation can be performed on specimens procured across tumor types outside clinical studies and NTRK-positive cell lines.

Anticipated Future Agency Interactions Regarding the Overall Development Plan for LOXO-101

Loxo Oncology's position on Question #7 provided in Section 8.5 (pages 60-61) of briefing package.

7. **Does the Agency agree with the comprehensiveness, appropriateness, and general timing of the proposed future interactions regarding the development of LOXO-101?**

   FDA Response: See FDA responses above. Ultimately, the timing and appropriateness of an application will be based on the results observed in Loxo's clinical development program. FDA is open to considering additional meetings as warranted to promote development of LOXO-101 for the indication granted breakthrough therapy designation.

   Loxo's Response (Received via email on November 8, 2016): Thank you for the response. No further discussion is requested.

   Discussion During Meeting: No discussion occurred.

Pediatric Development

Loxo Oncology's position on Question #8 provided in Section 8.6 (pages 61-62) of briefing package.

8. **The Sponsor wishes to preserve eligibility for its rare pediatric disease priority review voucher, and has identified two potential filing strategies that appear consistent with the Agency's draft guidance on the topic. The first strategy would be to file an NDA for infantile fibrosarcoma (IFS) as a distinct indication, separate from that of the Breakthrough Therapy Designation indication. The second strategy would be to file an NDA for the Breakthrough Therapy Designation indication, with infantile fibrosarcoma included as part of the indication. Does DOP2 and OOPD collectively agree that the Sponsor will remain eligible to receive a rare pediatric disease voucher with either filing strategy?**

   FDA Response: The current development plan for LOXO-101 appears to be based upon pursuit of a tissue agnostic indication for NTRK fusion tumors that spans adult and pediatric patient populations. Because infantile fibrosarcoma (IFS) is a subset of NTRK fusion-driven tumors, FDA is considering the impact of this development plan on the rare pediatric disease designation for LOXO-101 for treatment of IFS. Rare pediatric disease designation may not be appropriate for LOXO-101 given the proposed development plan; however, FDA is amenable to working with Loxo in support of a Written Request for LOXO-101under the Best Pharmaceuticals for Children Act (BPCA).

   Loxo's Response (Received via email on November 8, 2016): The Sponsor appreciates that FDA is considering the impact of the development plan on the rare pediatric designation for

LOXO-101 for the treatment of IFS. The Sponsor would appreciate further discussion regarding a possible harmonization of the tissue agnostic filing strategy with Agency guidance regarding the rare pediatric disease program.

Discussion During Meeting: FDA acknowledged Loxo's response and clarified that the data is too preliminary at this time to make a definitive decision regarding whether the current development program for LOXO-101 will meet the requirements for a pediatric rare disease priority review voucher. One important factor is the definition of the disease that will be supported by the data of the ongoing trials of LOXO-101. FDA expressed willingness for future communication between Loxo, OOPD, and the review division on this topic as additional data become available. OOPD also recommended that Loxo consider amending the current orphan designation for LOXO-101 from soft tissue sarcoma to a designation specific for the NTRK-fusion tumor indication.

NOTE: Question #9, as presented in the October 10, 2016, briefing package, has been renumbered to include Questions #10-12, in order to facilitate discussion of FDA responses to the questions.

Loxo Oncology's position on Questions #9-12 provided in Section 8.6 (page 63) of briefing package.

9. **If the Agency's response to Question #8 is a recommendation that the Sponsor pursue an independent NDA for IFS, does the Agency agree with the Sponsor's plan to characterize the safety and efficacy of LOXO-101 in this population, as described in the amended protocol for Study LOXO-TRK-15003? Specifically, does the Agency agree that this population could be defined by routine morphologic diagnosis, and therefore, does not require a companion diagnostic?**

FDA Response: Ultimately, whether the single application can support neoadjuvant use of LOXO-101 (i.e., to reduce major morbidity/limb amputation from curative surgery) will depend on the data submitted in the application. FDA agrees that additional data will be required to support the pre-surgical (neoadjuvant) use of LOXO-101. In order to support this indication, Loxo will need to demonstrate that patients derive clinical benefit from neoadjuvant treatment. FDA recommends that Loxo pre-specify criteria for identification of patients for whom surgery would place them at risk for severe morbidity and for determining that treatment with LOXO-101 results in tumor shrinkage enabling less morbid surgical procedures, and ensure adequate documentation of baseline and post-surgical outcomes. FDA recommends long-term follow-up of patients with IFS treated with LOXO-101 in the neoadjuvant setting to show that oncologic outcomes are not compromised (especially in patients whose surgery is downgraded from a morbid surgery to a less morbid surgery). Whether data derived from neoadjuvant use of LOXO-101 in 10 patients with IFS are sufficient to support this use in product labeling should be discussed with FDA during the pre-NDA meeting.

FDA does not object to enrolling patients with IFS based on morphologic diagnosis; however, FDA recommends that Loxo obtain tissue from patients with IFS to retrospectively determine fusion status. Loxo should further investigate, *if possible*, whether NTRK-fusion-test negative patients with IFS are true negatives or potentially have fusions that cannot be detected (an argument can potentially be made if test-negative subjects respond to LOXO-101). Finally, although, FDA does not object to enrollment based on morphologic diagnosis, FDA still considers IFS to be an NTRK-fusion driven cancer where results in other tumors would support use in IFS (and vice versa).

Loxo's Response (Received via email on November 8, 2016): Thank you for the response. No further discussion is requested.

Discussion During Meeting: No discussion occurred.

10. In the setting where LOXO-101 treatment is given prior to curative surgery:

a) Does the Agency agree that treating to best response plus a maximum of 2 cycles is acceptable and appropriate in the pre-surgical setting?

FDA Response: FDA does not object to the treatment plan.

Loxo's Response (Received via email on November 8, 2016): Thank you for the response. No further discussion is requested.

Discussion During Meeting: No discussion occurred.

b) Does the Agency agree with the Sponsor's plan to capture the preservation of limb or limb function and/or cosmetic outcome acceptable and appropriate?

FDA Response: FDA cannot answer this question because no information was submitted in the meeting package describing how Loxo will attempt to capture the preservation of limb or limb function and/or cosmetic outcome. The background to the question referenced Appendix C; however, Appendix C contained the LOXO-TRK-15002 basket protocol, and the protocol amendment for Study LOXO-TRK-15003 submitted on September 16, 2016 does not contain sufficient information regarding how Loxo will assess these parameters.

Loxo's Response (Received via email on November 8, 2016): Thank you for the response. No further discussion is requested.

Discussion During Meeting: No discussion occurred.

c) Does the Agency agree that the Sponsor's plan to evaluate anatomic pathologic response is acceptable and appropriate?

FDA Response: FDA does not object to Loxo's plan to evaluate anatomic pathologic response and will consider this data supportive. Information documenting volumetric reductions in IFS tumors will also be considered supportive.

Loxo's Response (Received via email on November 8, 2016): Thank you for the response. No further discussion is requested.

Discussion During Meeting: No discussion occurred.

11. The Sponsor intends to use the overall safety database for LOXO-101 to support this indication. Does the Agency agree?

FDA Response: FDA agrees that Loxo can use the overall safety database to support the use of LOXO-101 for IFS.

Loxo's Response (Received via email on November 8, 2016): Thank you for the response. No further discussion is requested.

Discussion During Meeting: No discussion occurred.

12. In the context of the overall efficacy observed with LOXO-101 in adult and pediatric patients with NTRK fusion cancers, is the sample size of approximately 10 IFS patients sufficient for establishing efficacy in this population?

FDA Response: FDA cannot answer this question at this time. FDA recommends that LOXO submit data when available for further discussion.

Loxo's Response (Received via email on November 8, 2016): Thank you for the response. No further discussion is requested.

Discussion During Meeting: No discussion occurred.

ADDITIONAL FDA COMMENTS

Clinical Pharmacology

13. Based on preliminary data showing that steady-state maximal concentrations following LOXO-101 100 mg BID may inhibit CYP enzymes (calculated R value greater than 1.1), a clinical DDI study with a probe sensitive CYP3A4 substrate (e.g., midazolam) should be conducted.

Loxo's Response (Received via email on November 8, 2016): Thank you for the response. The Sponsor will be conducting this study.

Discussion During Meeting: No discussion occurred.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

LOXO-101 received orphan drug designation for soft tissue sarcoma, but not the tissue agnostic indication for the treatment of unresectable or metastatic solid tumors with NTRK-fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments. Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an EOP2 meeting. In the absence of an EOP2 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. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the 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

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards

specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* 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.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards 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. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.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 the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

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.

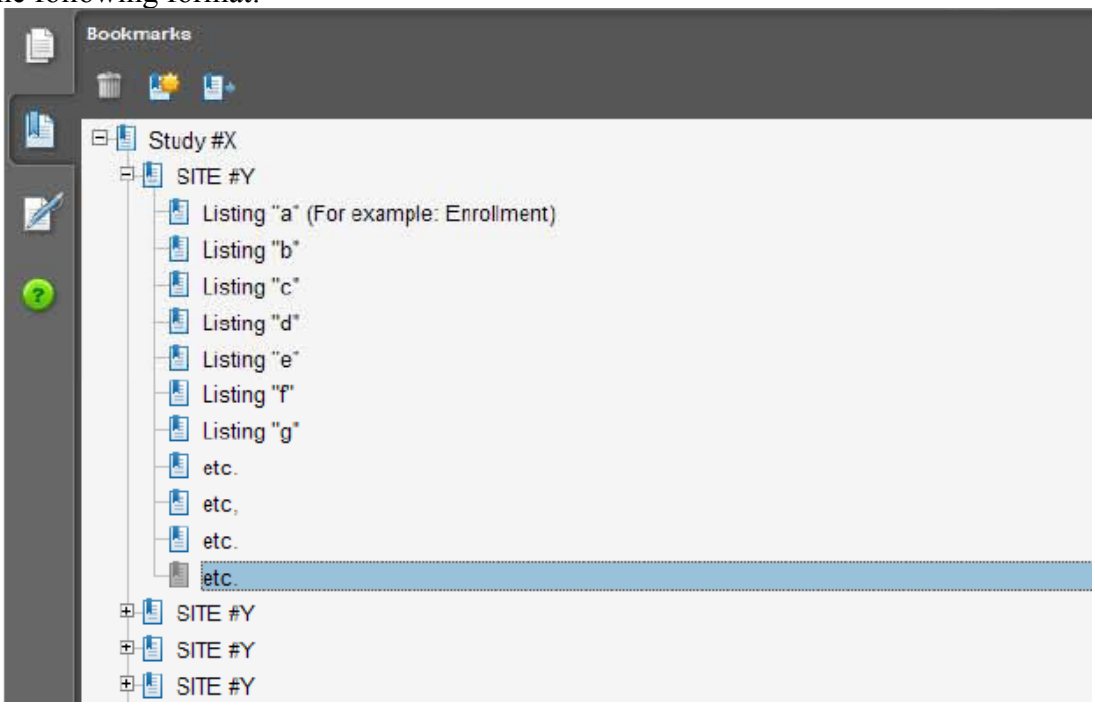
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere 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.

ISSUES REQUIRING FURTHER DISCUSSION
No issues requiring further discussion.

ACTION ITEMS
No action items.

ATTACHMENTS AND HANDOUTS
No attachments and handouts.

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

/s/

IDARA UDOH
11/21/2016

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	121211
Request Receipt Date	12 May 2016
Product	Loxo-101
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	Loxo Oncology
ODE/Division	DOP2/OHOP
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	11 July 2016

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

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):**

LOXO-101 is indicated for the treatment of unresectable or metastatic solid tumors with NTRKfusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments.

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

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

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

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate 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

[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

aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐

v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% 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. Consider the following in your response.

LOXO-101 is an orally bioavailable, adenosine triphosphate (ATP)-competitive, selective inhibitor of tropomyosin-related kinases (TRKA, TRKB, and TRKC).

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

The incidence of NTRK activated rearrangements is unknown, and varies among tumor types. Although very frequent in some rare cancers (see table below), it is below 1% in the most common cancer types such as lung, prostate, and colon.

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

Table 1: Estimated frequency of NTRK rearrangements

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

Disease	N sample	Freq NTRK fusions	Comments
MASC (salivary glands)	15	100%	Rare disease, ~ 100 cases reported in the literature
Secretory breast carcinoma	12	91.7%	< 0.15% of breast CA is secretory
Infantile fibrosarcoma	11	90.9%	5/1.000.000 infants
Congenital mesoblastic nephroma	28	60.7%	8/1.000.000 < 15 y.o.
Papillary thyroid (pre-post RT)	33-62	12.1%-14.5%	(all thyroid) 3.6% of all new cancer cases; papillary is one of the most frequent subsets; however most patients cured without need for systemic therapy
Non-brainstem high grade glioma	58	10.3%	(all high grade gliomas incidence; non-brainstem is a subset) 5/100,000
GIST, NSCLC (adeno), astrocytoma, DIPG, cholangiocarcinoma	31-151	2-3.7%	
Sarcoma, lung – NET, GBM	60-162	1%-1.7%	
Low grade glioma, colon, breast, melanoma, HNSCC	374-1072	<1%	

The Sponsor provided data regarding these rearrangements from the Foundation of Medicine, summarized in Table 2.

Table 2: Incidence of NTRK rearrangements in different tumor types – Foundation of Medicine data

Disease		N samples	NTRK fusions
Sarcoma	NOS	2667	0.56%
Lung	adenocarcinoma	7616	0.09%
	squamous	1271	0%
	NOS	1740	0.11%
Salivary	Salivary gland carcinoma (NOS)	523	1.72%
Thyroid	Thyroid CA (NOS)	545	0.92%
CNS	glioblastoma	1968	0.05%
Biliary	(liver) Cholangiocarcinoma	968	0.10%
Colorectal	Colorectal adenocarcinoma	5034	0 12%
Other	Breast CA (NOS)	7053	0.07%
	melanoma	472	0%
	bile duct adenocarcinoma	167	0.6%
	GEJ adenocarcinoma	983	0.10%
	GIST	78	1.28%
	Unknown primary adenocarcinoma	1971	0.10%
	Unknown primary NOS	401	0.25%
	Uterine carcinoma	1019	0.10%

There are no approved drugs specifically targeting NTRK gene fusions. Eligibility requirements for all LOXO-101 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. Loxo agreed to consult CDRH for advice in the development of a companion diagnostic.

Regulatory History:

- New IND 121211 submitted 28 Feb 2015
- End of Phase 1 meeting 23 Feb 2016

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) as determined by RECIST v1.1 criteria and RANO criteria (for CNS tumors) from a single-arm trial are being used to support this breakthrough therapy designation request. ORR in a limited number of patients serves as a surrogate and will be used (along with duration of response) as the primary endpoint of the ongoing registration trial.

The proposed primary efficacy analysis will take place when 55 patients with tumors harboring NTRK-fusions, irrespective of tumor histology, are evaluable for response and followed-up for duration of response (DOR) and other endpoints.

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; however, to date, it appears that the sponsor has enrolled patients who need systemic therapy.

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

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

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

Not applicable

10. Information related to the preliminary clinical evidence:

Table 3: Clinical Trials Submitted for BTDR LOXO-101 in original submission

Study ID	Phase	Country	Study Title	Dosing Regimen	Study Population	FPFV	Planned Enrolment	Enrolment to date
LOXO-TRK-14001	1	US	A Phase 1 Study of the Oral TRK Inhibitor LOXO-101 in Adult Patients with Solid Tumors	Escalation Phase: Dosing schedule: continuous, 28-day cycles until PD or intolerability Dose levels: 50 mg QD 100 mg QD 100 mg BID 150 mg BID 200 mg QD Expansion Phase: Dose TBD	Escalation Phase: Adult Solid Tumors Expansion Phase: Evidence of the NTRK or TRK molecular characteristic such as an NTRK translocation or amplification	May 12, 2014	Escalation Phase: 48 patients Expansion Phase: 30–60 patients	43
LOXO-TRK-15002	2	US/EU/ Asia	A Phase 2 Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects with NTRK Fusion-Positive Tumors	Dosing schedule: continuous, 28-day cycles until PD or intolerability Dose: 100 mg BID	Adult Solid Tumors – TRK fusion+	September 30, 2015	Up to 151 patients	13
LOXO-TRK-15003	1	US	A Phase 1 Study of the Oral TRK Inhibitor LOXO-101 in Pediatric Patients with Advanced Solid or Primary Central Nervous System Tumors	Dosing schedule: continuous, 28-day cycles until PD or intolerability Escalation Phase: Adult equivalent doses: 100 mg BID 150 mg BID 200 mg BID 300 mg BID Expansion Phase: Dose TBD	Pediatric Advanced Solid or Primary Central Nervous System Tumors	December 21, 2015	Escalation Phase: 36 patients Expansion Phase: 30–60 patients	3

b. Include any additional relevant information.

Twenty nine patients with NTRK fusion cancers have been enrolled across three trials with the following anatomic and histologic diagnoses: mammary analogue secretory cancer (MASC) of the salivary glands, lung cancer, colon cancer, soft tissue sarcoma (STS), gastrointestinal stromal tumor (GIST), thyroid cancer, malignant peripheral nerve sheath tumor (MPNST), cholangiocarcinoma, appendiceal cancer, melanoma, breast cancer, infantile fibrosarcoma (IFS), and undifferentiated tumor. The Sponsor provided response data on 22 of these patients (data centrally confirmed in 12 of these patients). Two patients withdrew consent before receiving study drug.

Fifteen of 20 evaluable patients are responders = ORR 75%, including a patient with a complete response (CR), 1 unconfirmed CR, 7 confirmed partial responses (PR), and 5 unconfirmed PRs (data are immature to determine whether the patients are responders). There are 6 unconfirmed responses due to premature timing of evaluation, and there are 12 of 20 responders that were centrally reviewed. All responders remain on study and none have progressed, including 9 patients with responses lasting more than 6 months.

Table 4: Efficacy for NTRK-mutated subjects on LOXO-101 across all trials (copied from submission)

Patient ID	Age/ Gender	Primary Diagnosis	Sites of Metastases	Fusion	LOXO-101 Dose (mg, BID)	Best Response[1] (% reduction)	Time on Study (Months)[2]	Response ongoing? Y / N
Study LOXO-TRK-14001								
(b) (6)	41/F	Undifferentiated soft tissue sarcoma	Lung	*LMNA-NTRK1*	100	PR (-77%)	17+	Y
	56/M	GIST	Liver	*ETV6-NTRK3*	150	PR (-52%)	13+	Y
	39/M	Sarcoma-parotid re-read as MASC	Lung	*ETV6-NTRK3*	150[3]	PR (-35%)	12+	Y
	66/M	MASC	Lung	*ETV6-NTRK3*	100[4]	PR (-40%)	9+	Y
	33/M	Papillary Thyroid	Lung, Lymph node, other soft tissue mass	*ETV6-NTRK3*	100	PR (-90%)	9+	Y
	28/M	NSCLC	Bone	*TPR-NTRK1*	100	SD (-18%)	9+	NA
002-052	58/M	Papillary Thyroid, re-read as MASC	Lymph node	*ETV6-NTRK3*	100	uPR (-47%)	5+	Y
Study LOXO-TRK-15002								
(b) (6)	72/M	MASC	Lung	*ETV6-NTRK3*	100[5]	CR (100%)	8+	Y
	43/ F	MASC	Lung	*ETV6-NTRK3, G623R NTRK3 mutation*	100	PD	< 1 cycle	NA
	74/M	Stage IV Appendiceal Tumour	Peritoneal/ omental implants	*LMNA-NTRK1*	100	PD	4	NA
	61/F	Malignant peripheral nerve sheath tumor	Lung	*TPM4-NTRK3*	100	PR (-73%)	6+	Y
	54/F	CRC	Liver	*LMNA-NTRK1*	100	PR (-54%)	5+	Y
	34/F	Breast	Lung	*TPM3-NTRK1*	100	PD	1	NA
	65/M	MASC	Lung	*ETV6-NTRK3*	100	uPR (-57%)	4+	Y
	39/F	Melanoma	Nodes/GI tract	*GON4L-NTRK1*	100	Consent Withdrawn[6]	3	NA
	47/F	Biliary	Omentum	*LMNA-NTRK1*	100	uPR (-49%)	3+	Y
	74/F	CRC	Lung	*TPM3-NTRK1*	100	Consent withdrawn[6]	2	NA
	32/F	NSC Lung	Nodes	*IRF2BP2-NTRK1*	100	uCR	3+	Y
	74/F	CRC	Liver/ nodes	*PLEKHA6-NTRK1*	100	uSD	3	NA
	64/M	CRC	Liver	*TPM3-NTRK1*	100	uPR (-41%)	2+	Y
	56 /F	Melanoma	Skin	*ETV6-NTRK3*	100	Not yet evaluated	1+	NA
	71/ F	Melanoma	Lung /vagina	*ETV6-NTRK3*	100	Not yet evaluated	1+	NA
	24/M	Malignant peripheral nerve sheath tumor	Locally advanced unresectable neck tumor	*LMNA-NTRK1*	100	Not yet evaluated	1+	NA
	70/F	MASC	Lung	*ETV6-NTRK3*	100	Not yet evaluated	<1+	NA
Study LOXO-TRK-15003								
(b) (6)	1.4/F	Infantile fibrosarcoma	-	*ETV6-NTRK3*	Equivalent to 100 mg BID	PR (-90%)[7]	6+	Y
	11/F	Undifferentiated sarcoma	Bone	*STRN-NTRK2*	Equivalent to 100 mg BID	uPR (-40%)	2+	Y
	0.6/M	Infantile fibrosarcoma	-	*ETV6-NTRK3*	Equivalent to 100 mg BID	Not yet evaluated	<1+	NA

Note: blue highlighted patients have not undergone central review

At the RP2D of 100 mg BID, 53% patients experienced gastrointestinal disorders. The most common AEs are Grade 1 and 2 fatigue (33%); constipation and dizziness (each 23%); anemia, increased AST, cough, and diarrhea (each 19%). Grade 3 and 4 adverse events included increased AST/ALT, anemia, delirium, ataxia, enterocutaneous fistula, hypertension, hypoalbuminemia, increased lipase, leukopenia, and increased weight.

In LOXO-TRK-14001, there have been two cases of delirium (both Grade 3) and three cases of ataxia (one Grade 1, one Grade 2, and one Grade 3). The Grade 1 ataxia event and one of the Grade 3 delirium events occurred in the same patient who had a past medical history significant for insomnia, somnolence and forgetfulness, neuropathy, and hypertension, with underlying ataxia, lethargy, and memory impairment noted at the baseline physical exam. The Grade 3 ataxia/dizziness event was recorded from a patient with an extrapyramidal disorder at baseline. The Grade 2 ataxia was from a patient with vomiting after a cruise and etiology was most likely from an underlying viral illness. The second case of delirium was after a patient with possible prior delirium received the first dose of study drug.

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

☒ GRANT:

Provide brief summary of rationale for granting: LOXO101 shows promising activity (ORR 75%) in a variety of heavily pre-treated refractory tumors that harbor NTRK fusions. In addition, these are durable responses and the drug appears to be reasonably tolerated. There are no alternative therapies for these patients.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

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

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

Due to the rarity of these tumors, randomized trials are not likely to be feasible. The Sponsor is conducting Study LOXO 15002, a study designed for registration purposes. Based on study results, LOXO101 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 rate 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 LOXO 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. LOXO101 will be further discussed in an upcoming (June 28/29th) pediatric subcommittee of the ODAC meeting.

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

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/

LEIGH J MARCUS
07/29/2016

STEVEN J LEMERY
07/29/2016