

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218160Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 133193

MEETING PRELIMINARY COMMENTS

Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company
Attention: Viktoriya Ilaria
Senior Director, Global Regulatory Affairs – North America
Lilly Corporate Center, Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Ilaria:

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

We also refer to your February 28, 2023, correspondence, received February 28, 2023, requesting a meeting to gain agreement with the FDA that the proposed New Drug Application submission provides a complete application in support of filing and review of the Retevmo tablet formulation.

Our preliminary responses to your meeting questions are enclosed.

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

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

If you have any questions, contact Opeyemi Udoka, PhD, Regulatory Health Project Manager at Opeyemi.Udoka@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Emily Pak, PharmD
Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations
Center for Drug Evaluation and Research

IND 133193

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ENCLOSURE:

Preliminary Meeting Comments



PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: April 25, 2023, 12:00 PM – 1:00 PM EST
Meeting Location: Video conference

Application Number: IND 133193
Product Name: Selpercatinib
Sponsor Name: Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)

Nicole Drezner, MD, Deputy Division Director (Acting), Division of Oncology 2 (DO2)
Diana Bradford, MD, Cross Disciplinary Team Lead, DO2
Elizabeth Duke, MD, Clinical Reviewer, DO2
Jeanne Fourie Zirkelbach, PhD, Clinical Pharmacology Team Lead, Division of Cancer Pharmacology II (DCP II)
Lauren Price, PharmD, Clinical Pharmacology Reviewer, DCP II
Xing Wang, PhD, Product Quality Team Lead, Division of New Drug Products I
Anup Amatya, PhD, Statistics (Acting) Team Lead, Division of Biometrics (DB V)
Chi Song, PhD, Statistics Reviewer, DB V
Anitha Govada, PhD, Senior Pharmaceutical Quality Assessor, Division of Biopharmaceutics (DB)
Payal Agarwal, PhD, Biopharmaceutics Reviewer, DB
Opeyemi Udoka, PhD, Regulatory Health Project Manager, Division of Regulatory Operations

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the video conference meeting scheduled for April 25, 2023, from 12:00 PM – 1:00 PM EST between Loxo Oncology Inc. and the Division of Oncology 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions

based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

On February 28, 2023, Loxo Oncology Inc. (Lilly) requested a type B meeting to gain agreement with the FDA that the proposed New Drug Application (NDA) submission provides a complete application in support of filing and review of the Retevmo tablet formulation. The meeting was granted on March 2, 2023, as a type B, pre-NDA meeting and the meeting background package was received on March 23, 2023.

Regulatory

As of September 21, 2022, selpercatinib is approved in the U.S. for the following indications:

- Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *rearranged during transfection (RET)* gene fusion, as detected by an FDA-approved test
- Adult and pediatric patients 12 years of age or older with advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation, as detected by an FDA-approved test, who require systemic therapy¹
- Adult and pediatric patients 12 years of age or older with advanced or metastatic thyroid cancer with a *RET* gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)¹
- Adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.¹

The recommended dosage of selpercatinib in adults and pediatric patients 12 years of age or older based on body weight is:

- Less than 50 kg: 120 mg orally twice daily
- 50 kg or greater: 160 mg orally twice daily

The currently approved dosage formulation is a capsule, available in 40 mg and 80 mg strengths. Lilly proposes to submit an NDA in 2023 for a new tablet formulation of selpercatinib in strengths of 40 mg, 80 mg, 120 mg, and 160 mg that will replace the current commercial capsule formulation. Lilly states that the tablets are intended to offer an improved patient experience in terms of the number and size of the dosage units.

On May 24, 2021, FDA issued preliminary comments for a type B meeting request to reach agreement with FDA on the study design and analysis plan for Study J2G-MC-

¹ This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

JZJZ to support bioequivalence (BE) requirements for the approval of the new tablet formulation of selpercatinib. FDA stated that the proposed BE study comparing a single dose of the newly proposed 160 mg selpercatinib tablet and 2 x 80 mg commercially available selpercatinib capsules would be sufficient to support the proposed higher 160 mg tablet strength. However, regarding the 40 mg, 80 mg, and 120 mg tablets strengths, the bioavailability/BE requirements for the proposed lower strengths may be waived if the FDA-provided criteria are met. In addition, FDA stated that the proposed design of the BE study, including the two-stage approach, was acceptable. Lilly did not require further discussion with FDA regarding the topics covered in the briefing document and proposed to cancel the type B meeting scheduled for May 27, 2021.

On March 8, 2022, a type C Chemistry, Manufacturing and Controls (CMC) meeting was held to discuss drug product manufacturing control strategy and a plan for drug substance data in a future NDA for the tablet formulation.

On October 13, 2022, FDA issued preliminary comments for a type B meeting to discuss the planned content of the proposed NDA submission for the Retevmo tablet formulation. Lilly proposed to submit a data-driven pre-NDA meeting when the required data becomes available. The meeting was subsequently cancelled by Lilly after providing comments to FDA's Preliminary Comments on October 19, 2023.

Clinical Pharmacology

Selpercatinib tablets have been evaluated in two clinical trials in healthy volunteers:

Study J2G-MC-JZJZ was a randomized, 2-stage adaptive crossover study of the pharmacokinetics (PK) of selpercatinib after administration of the tablet formulation (1 x 160 mg) vs the capsule formulation (2 x 80 mg) under fasted conditions. Topline data provided in the meeting package show that bioequivalence criteria were met for primary PK parameters ($AUC_{0-t_{last}}$, AUC_{0-inf} , and C_{max}) when comparing the two formulations.

Study J2G-MC-JZPA was a randomized crossover study of the PK of selpercatinib after administration of the tablet formulation (1 x 160 mg) with a high-fat meal vs under fasted conditions. Topline data provided in the meeting package show that a high-fat meal resulted in a 17% decrease in selpercatinib C_{max} , a 5% decrease in selpercatinib AUC, and a delay in T_{max} by approximately 1 to 1.5 hrs relative to the fasted condition.

Clinical

Selpercatinib is an oral small molecule inhibitor of the *RET* receptor tyrosine kinase being evaluated in patients 12 years of age and older with *RET*-altered advanced solid tumors in an international, multi-center, single-arm dose-escalation and expansion study (LIBRETTO-001; NCT03157128) with a primary endpoint of overall response rate.

Lilly does not intend to submit new clinical safety or efficacy data from trials in cancer patients in the proposed NDA for a new tablet formulation of selpercatinib.

SPONSOR QUESTIONS AND FDA RESPONSES

1. Does the FDA agree that the proposed TOC provides a complete non-NME NDA submission package to support the filing and review of the selpercatinib tablet formulation?

FDA Response: Yes, we agree.

2. Does the FDA agree that the clinical data from Studies JZJZ and JZPA are sufficient to support filing and review of the NDA for selpercatinib tablet formulations?

FDA Response: The topline data from Studies -JZJZ and -JZPA appear sufficient to support filing and review of an NDA for selpercatinib tablets. Whether the data support approval of selpercatinib tablets will be a review issue.

3. Does the FDA agree with the proposal for not conducting a gastric acid-reducing agent interaction study with the tablet formulation?

FDA Response: The rationale for not conducting a clinical drug interaction study with selpercatinib tablets and gastric acid reducing agents appears reasonable. Whether the data support the proposed labeling for selpercatinib tablets will be a review issue.

4. Does the FDA agree with the criteria used to identify notable participants from Studies JZJZ and JZPA to select narratives and CRFs to be included in the NDA?

FDA Response: Yes, the proposal appears reasonable. Additional narratives may be requested during the review.

5. Does the FDA agree that a 4-month safety update is not required?

FDA Response: Yes, we agree.

6. Are the submission plans for the format and composition of clinical datasets, data standards, accompanied documentation, and analysis programs adequate to enable FDA review of the proposed NDA?

FDA Response: Yes, the proposed datasets appear reasonable. Include a PDF version of the define file(s).

7. Does the FDA agree with the proposed approach for financial disclosures?

FDA Response: Yes, the proposed approach appears reasonable.

8. Does the FDA agree with the proposal of not providing the OSI documentation?

FDA Response: Yes, the proposal appears reasonable.

9. Does the FDA agree with the proposed approach to labeling?

FDA Response: Yes, the proposal appears reasonable. A final determination of sections of labeling that require revision will be made upon review of the original NDA.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

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

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or

molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

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

For the latest version of the molecular target list, please refer to [FDA.gov](https://www.fda.gov).²

FDARA REQUIREMENTS

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

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to [FDA.gov](https://www.fda.gov).³

² <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

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 Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ websites, which include:

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

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

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

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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).

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	Email address
-----------	--------------	--------------------------------	---------------	---------------

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

			number	
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h⁶ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁷. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁸

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review

⁶ <https://www.fda.gov/media/84223/download>

⁷ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

⁸ <https://www.fda.gov/media/85061/download>

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

- RTOR⁹: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid¹⁰

⁹ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

¹⁰ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EMILY Y PAK
04/21/2023 02:08:54 PM

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Breakthrough Therapy; Other
Meeting Date and Time: October 31, 2022, 12:00 PM – 1:00 PM EST
Meeting Location: Teleconference
Application Number: 133193
Product Name: selpercatinib
Sponsor Name: Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)

Martha Donoghue, MD, Deputy Director, Division of Oncology 2 (DO2)
Diana Bradford, MD, Cross Disciplinary Team Lead, DO2
Elizabeth Duke, MD, Clinical Reviewer, DO2
Jeanne Fourie Zirkelbach, PhD, Clinical Pharmacology Team Lead, Division of Cancer Pharmacology II (DCP II)
Lauren Price, PharmD, Clinical Pharmacology Reviewer, DCP II
Claudia Miller, PhD, Nonclinical Team Lead (Acting), Division of Hematology, Oncology, and Toxicology (DHOT)
Amy Skinner, PhD, Nonclinical Reviewer, DHOT
Xing Wang, PhD, Product Quality Team Lead, Division of New Drug Products I (DNDPI)
Tefsit (Mimi) Bekele, PhD, Product Quality Reviewer, DNDPI
Paresma (Pinky) Patel, PhD, Division Director, Division of New Drug Active Pharmaceutical Ingredient (DNDAPI)
Raymond Frankewich, PhD, Product Quality Reviewer, DNDAPI
Anup Amatya, PhD, Acting Statistics Team Lead, Division of Biometrics (DB V)
Chi Song, PhD, Statistics Reviewer, DB V
Anitha Govada, PhD, Senior Pharmaceutical Quality Assessor, DB
Payal Agarwal, PhD, Biopharmaceutics Reviewer, DB
Emily Pak, PharmD, Regulatory Health Project Manager, Division of Regulatory Operations

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference meeting scheduled for October 31, 2022, from 12:00 PM – 1:00 PM EST between Loxo Oncology Inc. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements,

important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

On September 2, 2022, Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company (Lilly) submitted type B meeting request and briefing package to gain agreement with FDA on the planned content of the proposed new drug application (NDA) submission for the RETEVMO tablet formulation. Lilly intends to submit a data-driven pre-NDA meeting when the required data becomes available. The meeting was granted on September 7, 2022.

Regulatory

As of September 21, 2022, selpercatinib is approved in the U.S. for the following indications:

- Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *rearranged during transfection (RET)* gene fusion, as detected by an FDA-approved test
- Adult and pediatric patients 12 years of age or older with advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation, as detected by an FDA-approved test, who require systemic therapy¹
- Adult pediatric patients 12 years of age or older with advanced or metastatic thyroid cancer with a *RET* gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)¹

¹ This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

- Adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options¹

The recommended dosage of selpercatinib in adults and pediatric patients 12 years of age or older based on body weight is:

- Less than 50 kg: 120 mg orally twice daily
- 50 kg or greater: 160 mg orally twice daily

The currently approved dosage formulation is a capsule, available in 40 mg and 80 mg strengths. Lilly proposes to submit an NDA in 2023 for a new tablet formulation of selpercatinib in strengths of 40 mg, 80 mg, 120 mg, and 160 mg that will replace the current commercial capsule formulation. Lilly states that the tablets are intended to offer an improved patient experience in terms of the number and size of the dosage units.

On May 24, 2021, FDA issued meeting preliminary comments for a type B meeting request to reach agreement with FDA on the study design and analysis plan for Study J2G-MC-JZJZ to support bioequivalence (BE) requirements for the approval of the new tablet formulation of selpercatinib. FDA stated that the proposed BE study comparing a single dose of the newly proposed 160 mg selpercatinib tablet and 2 x 80 mg commercially available selpercatinib capsules, would be sufficient to support the proposed higher 160 mg tablet strength. However, regarding the 40 mg, 80 mg, and 120 mg tablets strengths, the bioavailability/BE requirements for the proposed lower strengths may be waived if the FDA-provided criteria are met. In addition, FDA stated that the proposed design of the BE study, including the two-stage approach, was acceptable. Lilly did not require further discussion with FDA regarding the topics covered in the briefing document and proposed to cancel the type B meeting scheduled for May 27, 2021.

On March 8, 2022, a type C chemistry manufacturing and controls (CMC) meeting was held to discuss drug product manufacturing control strategy and a plan for drug substance data in a future NDA for the tablet formulation.

Clinical Pharmacology

Lilly proposes to submit data from two ongoing studies to support an NDA for the new tablet formulation:

- Study JZJZ: An open-label, randomized, 2-period, 2-formulation, 2-sequence, 2-stage adaptive crossover study in healthy adult participants to evaluate the bioequivalence (BE) of selpercatinib 160 mg new tablet formulation relative to the existing commercially available selpercatinib 160 mg capsule formulation
- Study JZPA: An open-label, randomized, 2-period crossover study to evaluate the effect of food on the pharmacokinetics (PK) of the new tablet formulation of selpercatinib in healthy adult participants

Lilly proposes to submit a biowaiver request for the tablet formulation at the 40 mg, 80 mg, and 120 mg strengths based on the results of the BE study at the 160 mg strength, and similarities of the lower dosage tablet strengths to the 160 mg tablet with regard to manufacturing process, dosage form, proportion of active and inactive ingredients, dissolution profile, and PK linearity in the proposed dosage range.

Clinical

The approvals of selpercatinib, an oral RET kinase inhibitor, were supported by overall response rate (ORR) and duration of response (DOR) efficacy data in 527 patients enrolled in Study LOXO-RET-17001 (LIBRETTO-001), an international, single-arm, dose-escalation and multi-cohort expansion trial in patients with *RET*-altered advanced solid tumors. The efficacy populations included patients with *RET* fusion-positive NSCLC (n = 316), *RET*-mutant medullary thyroid cancer (n = 143), *RET* fusion-positive thyroid cancer (n = 27), and other *RET* fusion-positive solid tumors (n = 41). The evaluation of safety was supported by data from 796 patients with *RET*-altered advanced solid tumors who received 1 or more doses of selpercatinib as of June 15, 2021.

Lilly does not propose to conduct additional nonclinical or clinical studies to support the new tablet formulation of selpercatinib.

SPONSOR QUESTIONS AND FDA RESPONSES

1. Does the FDA agree that the existing nonclinical data package is adequate to support the review and filing of the Retevmo new tablet formulation and no new nonclinical studies are required?

FDA Response: We agree.

2. Does the FDA agree that inclusion of Modules 2.4 (Nonclinical overview), 2.6 (Nonclinical written and tabulated summaries), and Module 4 (Nonclinical study reports) by cross-reference will be sufficient for FDA review (i.e., there are no filing deficiencies)?

FDA Response: We agree.

3. Does the FDA agree that the proposed clinical data package (Modules 2.5, 2.7, and 2.7.1, which includes data from the two studies discussed above) is adequate for FDA review and Modules 2.7.2 (Summary of clinical pharmacology studies), 2.7.3 (Clinical efficacy), and 2.7.4 (Clinical safety) will not be needed in the submission?

FDA Response: No. A Summary of Clinical Safety (SCS) and Summary of Clinical Efficacy (SCE) should be provided in Module 2.7, as required by 21 CFR 314.50 (c)(2)(viii). Alternatively, you may provide documents in Modules 2.7.3 and 2.7.4 cross-referencing the Clinical Overview that contains the elements required in the SCS and SCE.

Confirm that no patients with solid tumors in the ongoing or completed clinical trials of selpercatinib received the tablet formulation.

We note that summary results of Studies J2G-MC-JZJZ and J2G-MC-JZPA were not provided in the Meeting Package. We acknowledge your plan to request a data-driven pre-NDA meeting when data from these studies become available. Additional comments will be provided at the planned pre-NDA meeting upon review of the summary results. The adequacy of the data from these two studies in support of the NDA will be a review issue.

In addition, the capsule formulation of selpercatinib has a clinically relevant drug interaction when coadministered with a proton pump inhibitor (PPI). This interaction is modified by administration of food and the labeling of selpercatinib provides administration instructions to take selpercatinib capsules with food when selpercatinib is coadministered with a PPI. Provide a plan to assess the effects of gastric acid reducing agents (including a PPI) on the PK of the selpercatinib tablet formulation.

We agree with the plan to not submit a new Summary of Clinical Pharmacology Studies.

4. Does the FDA agree with the proposed rationale for the biowaiver request?

FDA Response: Your proposed approach for requesting a biowaiver for Selpercatinib Tablets 40 mg, 80 mg and 120 mg based on the results of the BE study for higher strength (Selpercatinib Tablet vs Capsule, 160 mg) appears reasonable. However, the adequacy of biowaiver request for lower strengths will be determined upon review of the supporting data submission in the NDA. We strongly recommend that you provide the complete dissolution method development and validation report as an IND amendment to allow sufficient time for review and feedback. If you choose to submit the dissolution method development and validation reports under IND as an amendment, inform the OPQ's regulatory business project manager (RBPM) of the submission via E-mail and clearly indicate in the cover letter that you are requesting the Division of Biopharmaceutics/ONDP/OPQ feedback on the acceptability of the proposed dissolution method. FDA will provide feedback approximately three months after receiving the IND amendment.

Refer to the Additional Biopharmaceutics Comments for the general guidance on the dissolution method development and setting of acceptance criterion/criteria for the proposed drug product.

5. Does the FDA agree that the balance of the standard 12 months of drug product stability data may be submitted before the mid-point of the 10-month review cycle?

FDA Response: The drug product stability package should include 12-month stability data at long-term and 6-month data under accelerated storage conditions on at least three primary drug product batches manufactured with multiple drug substance lots. It is acceptable to submit the original NDA with 9 months of primary stability data for three registration batches to be followed by an amendment within 30 days after the NDA is submitted to provide data from the 12-month time points. We cannot commit to evaluate any stability data submitted later than 30 days after submission of the original NDA.

We agree with your proposal to submit 12 months of primary stability data for selpercatinib drug substance, provided that the data is generated for the solid state form that will be used in the proposed tablet dosage form. You indicate on pg. 8 of the briefing document that the new (tablet) formulation will incorporate

(b) (4)

We refer you to the meeting minutes from the pre-NDA CMC meeting held on August 8, 2019, (finalized September 3, 2019) regarding control strategies to support use of the new

(b) (4)

6. Does the FDA agree that the proposed TOC provides a complete NDA submission package to support the filing and review of the Retevmo new tablet formulation?

FDA Response: The proposed approach generally appears acceptable. If needed, additional data may be requested during review of the NDA.

Include all relevant datasets and in-use performance information for the bioanalytical methods used to quantify selpercatinib for Studies J2G-MC-JZJZ and J2G-MC-JZPA.

In the meeting package for the anticipated pre-NDA meeting, provide a comprehensive plan for cross-referencing relevant non-clinical and clinical data which supported prior approvals of selpercatinib in the planned NDA submission.

ADDITIONAL COMMENTS

Biopharmaceutics

7. We have the following general recommendations regarding the dissolution information (method and acceptance criterion/criteria) that should be provided in the submission.

Dissolution Method: Provide the dissolution method development report and method validation report supporting the selection of the proposed dissolution test for evaluating the proposed drug product.

Include the following information in the dissolution method development report:

- a. Solubility data of the drug substance over the physiologic pH range.
- b. Detailed description of the dissolution method being proposed for the evaluation of the product, along with the developmental parameters supporting the selection of the proposed dissolution method as the optimal test for the proposed drug product (e.g., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, media pH, sink conditions, use of sinker and enzyme, if applicable, etc.). If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. The testing conditions associated with each method development study should be clearly specified. The dissolution profiles should be complete and cover at least ^{(b) (4)}% of drug release of the labeled amount or whenever a plateau (i.e., no increase over 3 consecutive timepoints) is reached. The use of at least twelve dosage units per testing variable and sampling time points (e.g., 10, 15, 20, 30, 45, 60, etc. min) is recommended.
- c. A list of the critical material attributes (CMAs), critical formulation variables (CFVs) and critical process parameters (CPPs) affecting dissolution.
- d. Data supporting the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) drug product and the test products that are intentionally manufactured with meaningful variations (i.e. target range $\pm$ 10-20% change to the specified values) for the most relevant critical bioavailability attributes (CBAs) such as critical material attributes, critical formulation variables, and critical process parameters.
- e. Submit the dissolution profile data and similarity testing results obtained with appropriate statistical test (e.g., f_2 values) comparing the test and reference drug products. In addition, if available, submit data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference-target drug product.
- f. Supportive validation data for the dissolution methodology (bench testing) and analytical method used for assaying the dissolution samples (specificity,

precision, accuracy, linearity/range, stability, robustness, etc.). For general recommendations on method validation, refer to the USP Chapters “The Dissolution Procedure: Development and Validation” <1092> and “Validation of Compendial Methods” USP Chapter <1225>.

- g. Complete dissolution multi-point profile data for each variable tested during method development, assessment of discriminating ability, and validation [individual (n=12), mean, RSD, %CV at each time point and mean profiles]. The dissolution data should be reported as the cumulative percentage of drug dissolved (the percentage is based on the drug product's label claim).

Dissolution Acceptance Criterion/Criteria: For the selection of the dissolution acceptance criterion of the proposed drug product, consider the following:

- h. The multi-point dissolution data from the pivotal clinical/PK drug product batches and primary registration batches should be used for the setting of the dissolution acceptance criterion (i.e., sampling time points and limits).
- i. The in vitro dissolution profile should encompass the timeframe over which at least $\frac{(b)}{(4)}\%$ of the drug is dissolved or if incomplete dissolution occurs, where the plateau of drug dissolved is reached (i.e., no increase over 3 consecutive time-points).
- j. The dissolution acceptance criterion should be based on the average in vitro dissolution data of each batch/lot under study, equivalent to USP Stage 2 testing (n = 12).
- k. The selection of the sampling time point should be where $Q = \frac{(b)}{(4)}\%$ dissolution occurs.
- l. Include a detailed discussion of the justification of the proposed dissolution acceptance criterion in the appropriate section of the eCTD.

The adequacy of the proposed dissolution method and acceptance criterion/criteria for the proposed drug product will be made during the NDA review process.

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.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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

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

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

For the latest version of the molecular target list, please refer to [FDA.gov](https://www.fda.gov).²

FDARA REQUIREMENTS

Sponsors planning to submit original applications may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor’s initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD & C Act) for early evaluation in the pediatric

² <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meeting requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.³

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).

ONCOLOGY PILOT PROJECTS

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

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

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

- RTOR⁴: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid⁵

⁴ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

⁵ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EMILY Y PAK
10/13/2022 09:14:04 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 133193
Request Receipt Date	8/16/2018
Product	LOXO-292
Indication	For the treatment of patients with advanced <i>RET</i> -fusion-positive thyroid cancer who require systemic therapy, have progressed following prior treatment, and have no acceptable alternative treatment options.
Drug Class/Mechanism of Action	Small molecule inhibitor of the <i>RET</i> receptor tyrosine kinase
Sponsor	Loxo Oncology, Inc.
ODE/Division	Division of Oncology Products 2
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	10/15/2018

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes, and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

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):

For the treatment of patients with advanced *RET*-fusion-positive thyroid cancer who require systemic therapy, have progressed following prior treatment, and have no acceptable alternative treatment options.

The sponsor originally submitted a breakthrough therapy request which included the following indication:

For the treatment of patients with advanced (b) (4) *RET*-mutant medullary thyroid carcinoma (MTC) who require systemic therapy, have progressed following prior treatment, and have no acceptable alternative treatment options.

DOP2 had noted previously in meetings with the company that patients with (b) (4) and *RET*-mutant MTC represent two distinct patient populations. In a teleconference held on July 18, 2018, DOP2 recommended that the sponsor submit separate breakthrough therapy designation requests for each of these indications. The sponsor agreed, and amended the indication in the initial request to include only (b) (4) and submitted a new request with the indication of *RET*-mutant MTC.

Following review of the data for the (b) (4) patients, it was determined that there was insufficient data to support granting the breakthrough designation request (b) (4) indication. In a teleconference held on August 13, 2018, DOP2 advised the sponsor to provide separate requests (b) (4) including a request for the treatment of patients with *RET*-fusion-positive NSCLC. DOP2 advised that a request for the treatment of patients with (b) (4) or deferred until additional clinical data are available. On August 16, 2018, the sponsor submitted a request for breakthrough designation for *RET*-fusion-positive thyroid cancer. Of note, the data submitted for patients enrolled on LOXO-RET-17001 as a whole (including (b) (4) and patients with MTC) have a data cutoff date of June 14, 2018, while the data for patients with *RET*-fusion-positive thyroid cancers has been updated with a data cutoff date of August 3, 2018.

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

☐ YES ☒ NO

3. Was the BTDR submitted to a PIND?

☐ YES ☒ NO

If “Yes” do not review the BTDR. The sponsor must withdraw the BTDR. BTDR’s cannot be submitted to a PIND.

If 2 above is checked “Yes,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “No”, proceed with below:

4. Consideration of Breakthrough Therapy Criteria:

a. Is the condition serious/life-threatening¹?

☒ YES ☐ NO

If 4a is checked “No,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “Yes”, proceed with below:

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

☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review

☐ Undetermined

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

- i. Only animal/nonclinical data submitted as evidence ☐
- ii. Insufficient clinical data provided to evaluate the BTDR
(e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

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>

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>

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 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 the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTDR Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

6. 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.

7. 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.

- Information regarding the disease and intended population for the proposed indication.
- Disease mechanism (if known) and natural history (if the disease is uncommon).

Disease Background

The RET proto-oncogene encodes for a transmembrane tyrosine kinase receptor involved in multiple cellular processes including cell proliferation, migration, differentiation and neuronal maintenance. RET signaling through binding with glial cell line-derived neurotrophic factor (GDNF) ligands leads to activation of multiple downstream pathways including MAPK and PI3K. Gain of function amplifications/mutations or rearrangements of RET can lead to development of multiple endocrine neoplasia type 2 (MEN2) syndrome. RET mutations occur in approximately 50% of patients with medullary thyroid cancer (MTC) (>90% in hereditary forms of MTC). (Romei, 2018) RET gene fusions have been identified in up to 10 – 20% of patients with papillary thyroid cancer (PTC), 1-2% of non-small cell lung cancers (NSCLC), and less commonly in other tumor types, including colorectal cancer, and breast cancer. (Kato, 2017; Kohno, 2012) There are several approved multi-tyrosine kinase inhibitors (TKI) targeting RET (e.g., vandetanib, cabozantinib, ponatinib), although none are directed solely against RET.

Thyroid Cancer:

Differentiated thyroid cancer includes well-differentiated tumors, poorly differentiated tumors, and undifferentiated tumors. Well-differentiated tumors such as papillary and follicular thyroid cancer are usually curable with total thyroidectomy or lobectomy, followed by postoperative treatment with radioactive iodine (RAI) therapy. Thyroid suppression therapy with supratherapeutic doses of thyroid hormone may be administered to suppress TSH. External beam radiotherapy (EBRT) may be used for unresectable or metastatic disease as palliative treatment or residual RAI-refractory disease. Sorafenib is approved for the treatment of locally recurrent or metastatic, progressive differentiated thyroid carcinoma (DTC) refractory to radioactive iodine. Lenvatinib is approved for patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC. RET mutations carry an unfavorable prognosis in patients with papillary thyroid cancer.

Anaplastic thyroid cancer (ATC) is a more aggressive form of thyroid cancer; all patients are considered to have stage IV disease. Total thyroidectomy is indicated if disease is localized, and EBRT may be used for unresectable disease.

Radioactive iodine is not effective in ATC, and chemotherapy is used (cisplatin and doxorubicin vs. doxorubicin alone), but most patients experience recurrence and may be referred to clinical trials. Trametinib is indicated, in combination with dabrafenib, for the treatment of patients with BRAFV600E-mutant locally advanced or metastatic ATC with no satisfactory locoregional treatment options.

8. 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.

Loxo considers durable objective response rate to be a clinically meaningful endpoint supporting the BTDR. The data for overall response rate in Study LOXO-RET-17001 presented in the BTDR request is based on investigator-assessed response by RECIST 1.1. Overall response rate according to RECIST 1.1, assessed by an independent review committee (IRC) is a primary endpoint of the planned expansion phase for Study LOXO-RET-17001. Key secondary endpoints include duration of response (DOR), central nervous system (CNS) ORR/DOR (by investigator and IRC), progression-free survival (PFS), and overall survival (OS).

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
 - *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
 - *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

DOP2 agrees that demonstration of a meaningful effect size on durable objective response rate according to RECIST would be clinically meaningful and reasonably likely to predict clinical benefit of a drug for patients with advanced *RET*-fusion-positive thyroid cancer who require systemic therapy, have progressed following prior treatment, and have no acceptable alternative treatment options. Demonstration of a significant improvement in PFS in a randomized study would be considered clinical benefit if the magnitude of the treatment effect was large and no evidence of detrimental effects on survival, such PFS effects could be used to support an application for regular approval.

- c. 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.

None.

9. 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:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Table 1: FDA-Approved Available Therapies for Differentiated Thyroid Cancer

Agent	Intended population	Approval	n	ORR (95% Confidence Interval [CI])	Median DOR, mths (95% CI)
Sorafenib	Locally recurrent or metastatic, progressive, RAI-refractory DTC	Regular Primary endpoint: PFS	207	12% (7.6, 16.8)	10 (7.4, 16.6)
Lenvatinib	Locally recurrent or metastatic, progressive, RAI-refractory DTC	Regular Primary endpoint: PFS	261	65% (59, 71)	NA (16.8, NA)

NA= not available; RAI= radioactive iodine; DTC= differentiated thyroid carcinoma

Trametinib is approved in combination with dabrafenib for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer with BRAF V600E mutation and with no satisfactory locoregional treatment option; however, this is not a suitable therapy for patients with RET-fusion-positive anaplastic thyroid cancer. A randomized study of doxorubicin and cisplatin compared with doxorubicin alone in advanced thyroid carcinoma demonstrated a slightly statistically insignificant improvement in overall response rate for patients treated with the combination (26% vs. 17%, $p>0.1$), however there were significantly more complete responses in the combination group. (Shimaoka, 1985) Furthermore, the responses were not centrally confirmed and were based on older response criteria.

There are no approved therapies for RET fusion-positive NSCLC, PTC, or RET fusion-positive solid tumors in general. Sorafenib was approved for the treatment of locally recurrent or metastatic, progressive differentiated thyroid carcinoma (DTC) refractory to radioactive iodine on the basis of a randomized, double-blind, placebo-controlled trial in patients with locally recurrent or metastatic DTC who had progression within 14 months of enrollment. Patients receiving sorafenib demonstrated an improved PFS compared to those receiving placebo (median 10.8 months vs. 5.8 months) with a hazard ratio (HR) of 0.59 (95% CI 0.46 – 0.76). Lenvatinib was approved for patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC on the basis of a randomized, double-blind, placebo-controlled study in patients with RAI-refractory DTC with disease progression within the past 12 months with a primary endpoint of PFS. Patients receiving lenvatinib demonstrated improved progression-free survival (median 18.3 months vs. 3.6 months) with a HR of 0.21 (95% CI 0.16, 0.28).

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

There have been no breakthrough therapy designation requests for other drugs (b) (4) for RET fusion-positive NSCLC or thyroid cancer.

(b) (4)

10. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

LOXO-RET-17001 is a multicenter, first-in-human, global study of LOXO-292 for patients ≥ 12 years with advanced solid tumors harboring RET gene fusions/mutations, RET-mutant MTC, and other cancers. Study LOXO-RET-17001 was initiated in May 2017, and eight dose levels of LOXO-292 (20 mg QD to 240 mg BID) have been explored. According to Loxo, the maximum tolerated dose (MTD) was not reached and 160 mg BID

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

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

was selected for the dose-expansion portion of the study. Loxo states that 52 patients have received LOXO-292 at the 160 mg BID dose.

In June 2018, protocol LOXO-RET-17001 was amended to include expansion cohorts. The primary endpoint is ORR based on RECIST 1.1, assessed by an independent review committee (IRC). Key secondary endpoints include duration of response (DOR), central nervous system (CNS) ORR/DOR (by investigator and IRC), progression-free survival (PFS), and overall survival (OS).

The expansion cohorts will include the following:

- Cohort 1: RET fusion-positive solid tumor progressed after/intolerant to standard first-line therapy
- Cohort 2: RET fusion-positive solid tumor without prior standard first-line therapy.
- Cohort 3: RET-mutant MTC progressed on/intolerant to standard first-line cabozantinib or vandetanib.
- Cohort 4: RET-mutant MTC without prior first-line cabozantinib, vandetanib, or other kinase inhibitor(s) targeting RET
- Cohort 5: Other (e.g., Cohorts 1-4 without measurable disease, MTC not meeting the requirements for Cohorts 3 or 4, other RET-altered solid tumor or other RET alteration/activation).

A total of ~450 patients are planned for this portion of the study across all cohorts. The protocol will allow up to 100 patients in Cohort 1 and Cohort 3. For patients with RET fusion-positive solid tumors, Loxo hypothesizes a true ORR of $\geq 50\%$ for LOXO-292, and estimates that a sample size of 55 patients will provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial confidence interval (CI) about the estimated ORR that exceeds 30%. For patients with RET-mutant MTC, Loxo hypothesizes a true ORR of $\geq 35\%$ with LOXO-292, and estimates that a sample size of 83 patients will provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 20%.

As of a data cutoff date of April 2, 2018, 82 patients have received LOXO-292 on the dose escalation portion of the study, including patients with RET fusion positive tumors (n=49), RET mutated MTC (n=29) and tumors without known RET tumor alterations (n=4). Patients with RET fusion positive tumors included 38 patients with NSCLC, 9 with PTC, and 2 with pancreatic cancer.

As of June 14, 2018, Loxo reports durable responses for evaluable patients with RET fusion positive tumors receiving LOXO-292, with an overall response rate (ORR) of 77% (n=30/39, 5 pending confirmation; 95% CI: 61, 89) by investigator assessment. Responses occurred in patients with NSCLC, including patients with brain metastases (n=23), and thyroid cancer. The response rate in RET-fusion positive NSCLC was 77% (n=23/30, 3 pending confirmation). The sponsor reports that since the data cut-off date, all unconfirmed responses have been confirmed, and 1 patient with pancreatic cancer has experienced an unconfirmed partial response. As of 14 June 2018, responses were ongoing for 29 of the 30 RET fusion-positive solid tumors patients who had a best overall response of at least a confirmed PR; 15 of these first 30 responders were followed for more than 6 months from the onset of response

As of a data cutoff of August 3, 2018, 12 patients with RET-fusion-positive thyroid cancer have been treated, and 10 have had at least one response evaluation (described as evaluable patients). Seven of 12 patients had received both prior RAI and a tyrosine kinase inhibitor. The study has enrolled 10 patients with PTC, 1 patient with ATC, and 1 patient with poorly-differentiated thyroid cancer (PDTC). All responding patients (n=8) received at least one standard of care therapy for their disease, though some patients did not receive all available approved therapies. The therapies for all evaluable patients and all responding patients are outlined in Tables 2 and 3 below. Ten patients have been assessed for response, and 8 have demonstrated a partial response (1 unconfirmed response of 40% decrease in tumor size), with an overall response rate of 80% (95% CI 0.44 – 0.97). The remaining patients who have had a response evaluation (n=2) have a best response of stable disease.

Table 2: Prior therapies among all patients by histology

Histology	N (total =10)	Prior Therapy
Papillary thyroid cancer	8	• Sorafenib alone (n=1) • RAI (n=7) - o RAI + lenvatinib (n=2)

		- o RAI + sorafenib + ≥ 1 investigational therapy (n=3) - o RAI + investigational therapy (n=2)
Poorly differentiated thyroid cancer	1	• Lenvatinib (RAI deferred given large volume of disease)
Anaplastic thyroid cancer	1	• Docetaxel and doxorubicin

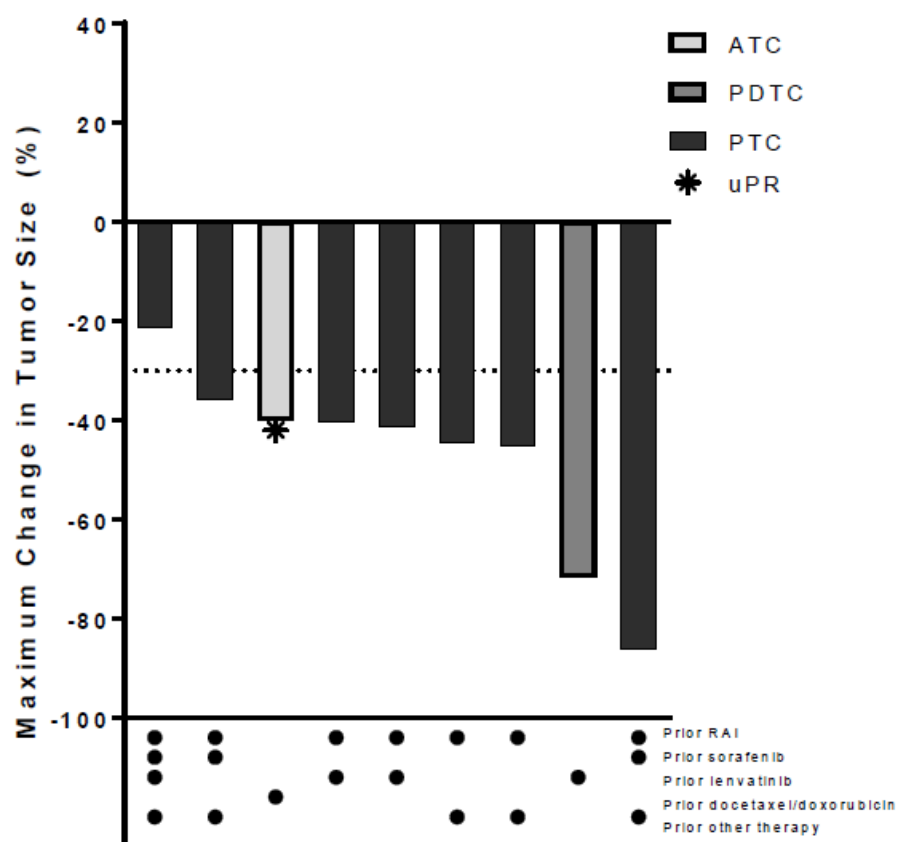
Table 3: Prior therapies among responding patients by histology

Histology	N (total =8)	Prior Therapy
Papillary thyroid cancer	6	• RAI (n=6) - o RAI + lenvatinib or sorafenib (n=4) - o RAI + investigational therapy (n=2)
Poorly differentiated thyroid cancer	1	• Lenvatinib (RAI deferred given large volume of disease)
Anaplastic thyroid cancer	1	• Docetaxel and doxorubicin

For confirmed responders with thyroid cancers (data cutoff August 3, 2018), the median follow-up time from the initial response was 7.2 months (range 4.5 – 10.2 months) from onset of response. Five of 7 confirmed responders with thyroid cancers have been followed for more than 6 months from the onset of response. The figures below are reproduced from the sponsor's breakthrough therapy and meeting package submissions, and demonstrate the responses observed thus far on Study LOXO-RET-17001.

Figure 3

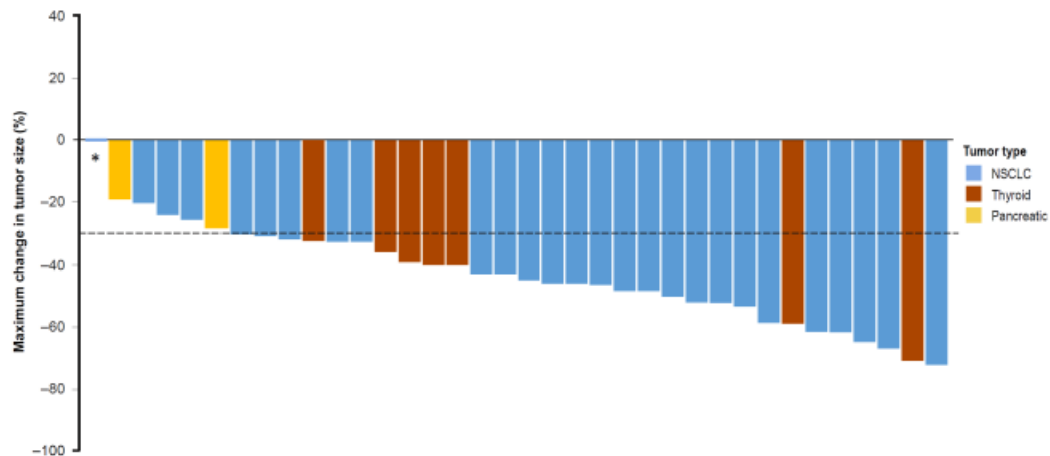
Efficacy of LOXO-292 in RET Fusion-Positive Thyroid Cancer
(Study LOX+O-RET-17001)



Abbreviations: PTC = papillary thyroid cancer (n = 7); PDTC = poorly differentiated thyroid cancer (n = 1); ATC = anaplastic thyroid cancer (n = 1); uPR = unconfirmed partial response (n = 1); RAI = radioactive iodine. Cutoff date: 03 August 2018

Figure 3 Efficacy of LOXO-292 in *RET* fusion-positive cancers
(Study LOXO-RET-17001)

A. Per Tumor Type



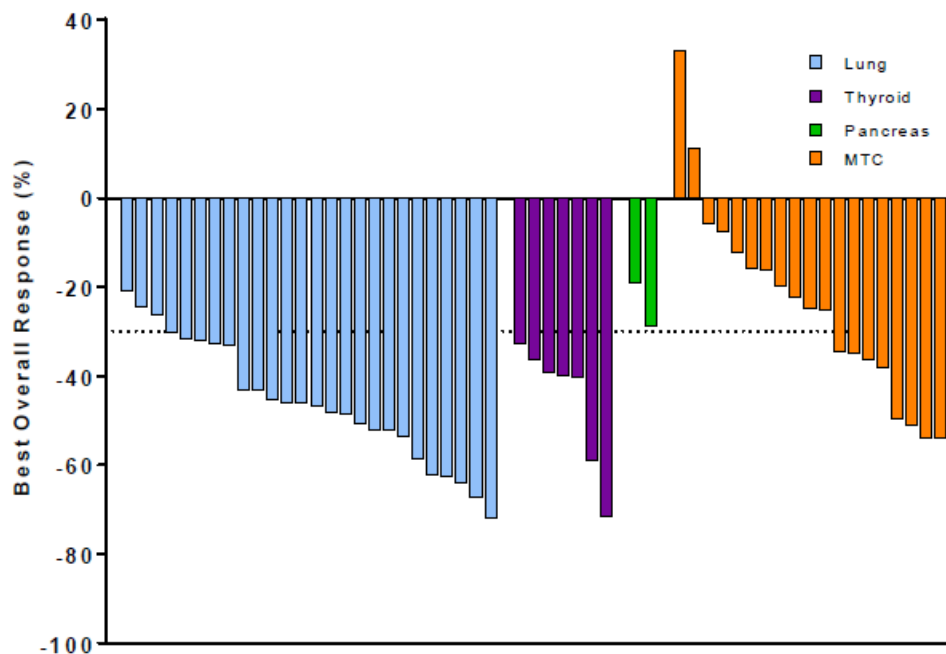
Note: Three patients not displayed due to treatment discontinuation prior to first post-baseline response assessment;

*Denotes patient with 0% maximum change in tumor size

Cutoff date: 02 April 2018.

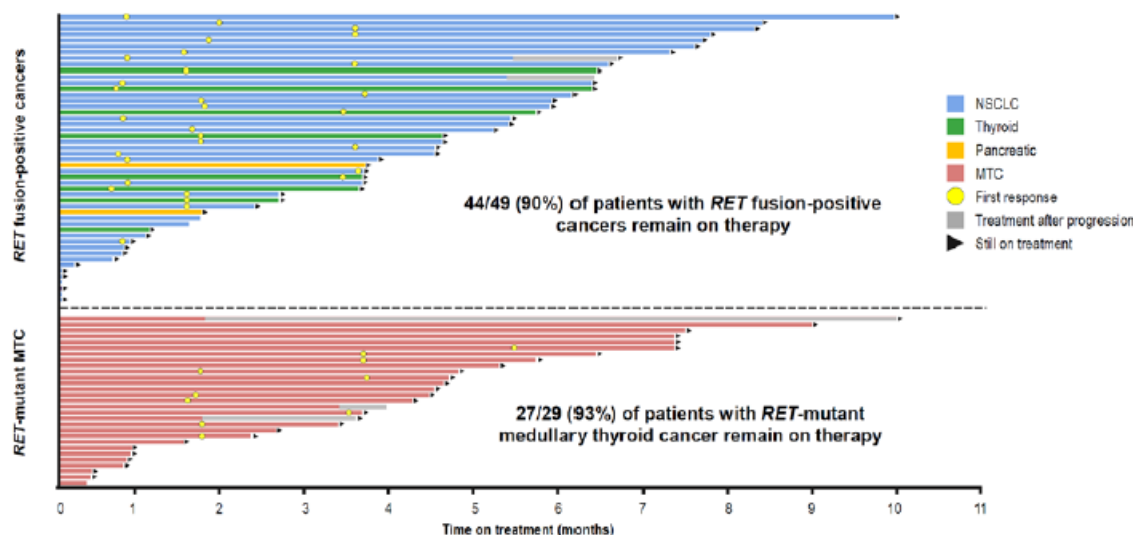
Source: (Drilon, 2018)

Figure 4 Waterfall Plot of Best Overall Response for Patients with Known Activating RET Alterations* (Study LOXO-RET-17001)



*4 patients without known activating RET alterations are not included

Figure 5 Swimmers Plot of Study Treatment Duration for Patients with Known Activating RET Alterations* (Study LOXO-RET-17001)



b. Include any additional relevant information. Consider the following in your response:

- Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.
- Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.
- Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.

Treatment-emergent adverse events (TEAEs) observed in 10% of patients or more included fatigue (20%), diarrhea (16%), constipation (15%), dry mouth (12%), nausea (12%), and dyspnea (11%). TEAEs which were Grade 3 or 4 included dyspnea (1.2%), increased ALT (2.4%), increased AST (1.2%), hypertension (1.2%), and hyponatremia (2.4%). Nine patients have discontinued study drug for disease progression (n=5), death (n=2) or adverse event/physician decision (1 each). Nine patients have discontinued study drug for disease progression (n=5), death (n=2) or adverse event/physician decision (1 each).

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

☒ GRANT :

Provide brief summary of rationale for granting:

The data provided suggest that patients with RET fusion-positive thyroid cancer previously treated with one or more therapies demonstrate durable objective responses to treatment with LOXO-292. Although the patient numbers are small, the majority of patients with a response have maintained the response for > 6 months, and all responders represent patients who have failed one or more prior therapies. The response rate observed in this small number of patients favorably compares to available therapies, and the available data for patients with other RET fusion-positive data who have been treated with LOXO-292 are supportive.

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):

The sponsor has recently met with FDA in an end-of-phase 1 meeting during which feedback on the proposed development program was conveyed. (b) (4)

- b. An expanded access program was also recommended for patients not eligible for the ongoing study. 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.

13. List references, if any:

Kato, S., et al. Ret aberrations in diverse cancers: Next-generation sequencing of 4,871 patients. Clin Cancer Res. 2017; 23(8): 1988-1997.

National Cancer Institute, Thyroid Cancer Treatment (Adult) (PDQ)-Health Professional Version. Updated July 18, 2018. <https://www.cancer.gov/types/thyroid/hp>

Shimaoka K, Schoenfeld DA, DeWys WD, et al.: A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. Cancer 56 (9): 2155-60, 1985.

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 }

Revised 6/12/18/M. Raggio

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DIANA L BRADFORD
10/09/2018

SUZANNE G DEMKO
10/09/2018

STEVEN J LEMERY
10/10/2018

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 133193
Request Receipt Date	07/20/2018
Product	LOXO-292
Indication	For the treatment of patients with advanced <i>RET</i> -mutant medullary thyroid cancer (MTC) who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options.
Drug Class/Mechanism of Action	Small molecule inhibitor of the <i>RET</i> receptor tyrosine kinase
Sponsor	Loxo Oncology, Inc.
ODE/Division	Division of Oncology Products 2
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	09/18/2018

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes, and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

- 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-292 is indicated for the treatment of patients with advanced *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options.
- Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?**
☐ YES ☒ NO
- Was the BTDR submitted to a PIND?**
☐ YES ☒ NO
If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. Consideration of Breakthrough Therapy Criteria:

- a. Is the condition serious/life-threatening¹? ☒ YES ☐ NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

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>

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):
- i. Only animal/nonclinical data submitted as evidence ☐
 - ii. Insufficient clinical data provided to evaluate the BTDR
(e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
 - iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
 - iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
 - v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 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 the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

6. 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.

7. 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.

- Information regarding the disease and intended population for the proposed indication.
- Disease mechanism (if known) and natural history (if the disease is uncommon).

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>

Background

LOXO-292 is a small molecular inhibitor of the RET receptor tyrosine kinase. The RET proto-oncogene encodes for a transmembrane tyrosine kinase receptor involved in multiple cellular processes including cell proliferation, migration, differentiation and neuronal maintenance. RET signaling through binding with glial cell line-derived neurotrophic factor (GDNF) ligands leads to activation of multiple downstream pathways including MAPK and PI3K. There are several approved multi-tyrosine kinase inhibitors (TKI) targeting RET (e.g., vandetanib, cabozantinib, ponatinib), although none are directed solely against RET. Gain of function amplifications, mutations or rearrangements of RET can lead to development of multiple endocrine neoplasia type 2 (MEN2) syndrome. RET mutations occur in approximately 50% of medullary thyroid cancer (MTC) (>90% in hereditary forms of MTC). (Romei, 2018)

Approximately 25% of cases of medullary thyroid cancer are hereditary, and may be part of syndromes such as MEN2A and MEN2B. Medullary thyroid cancer is relatively rare, comprising 3 – 4% of all thyroid cancers. Prognosis is dependent upon the extent of disease at presentation including spread to regional lymph nodes or distant metastases, and the extent of surgical resection. Local control measures including total thyroidectomy are the standard of care for patients with localized disease; external beam radiation has a primarily palliative role. Vandetanib is a multi-tyrosine kinase inhibitor with activity against RET, and is approved for the treatment of patients with symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease based on the demonstration of improved progression-free survival in a randomized, placebo-controlled trial. Cabozantinib is approved for the treatment of patients with progressive, metastatic medullary thyroid cancer.

Relevant Regulatory History

On March 2, 2017, Loxo submitted IND 133193, including Protocol LOXO-RET-17001, (b) (4) The IND went into effect on March 31, 2017.

On November 13, 2017, Loxo submitted a Preliminary Breakthrough Therapy Designation (BTD) request for Loxo-292 (b) (4) This request contained the cover protocol LOXO-RET-17001, entitled “A Phase 1 Study of Oral LOXO 292 in Patients with Advanced Solid Tumors, Including RET Fusion Non-Small Cell Lung Cancer, Medullary Thyroid Cancer and Other Tumors with Increased RET Activity,” and two Single Patient Protocols for patients with RET-dependent cancers.

On November 20, 2017, a teleconference was held between representatives from Loxo and FDA to provide preliminary advice for the BTD request. FDA stated that it was premature for Loxo to request the BTDR.

On April 20, 2018, Loxo submitted a Type B, End-of-Phase 1, meeting request to obtain input from FDA regarding a registrational program which would establish clinical benefit for LOXO-292, acceptability of design elements and proposed changes to the Phase 1/2 Study LOXO-RET-17001, and the acceptability of nonclinical and clinical pharmacology studies and Chemistry, Manufacturing, and Controls (CMC) development to support registration, and input on an accelerated approval pathway.

- Loxo requested FDA’s input on whether the population of (b) (4) and patients with RET-mutant MTC who have failed at least one or more prior therapies, represent populations with unmet medical need. FDA agreed that patients with RET-mutant MTC who have progressed on either cabozantinib or vandetanib and require systemic therapy is a distinct population with unmet medical need. FDA suggested that for (b) (4), Loxo needed to demonstrate that no available therapy is available, or that LOXO-292 has an improved effect on a serious outcome of the condition compared with available therapy. FDA noted that the latter subgroup is primarily driven by results obtained in patients with RET fusion-positive NSCLC.

8. 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.

Loxo considers durable objective response rate to be a clinically meaningful endpoint supporting the BTDR. The data for overall response rate in Study LOXO-RET-17001 presented in the BTDR request is based on investigator-assessed response by RECIST 1.1. Overall response rate according to RECIST 1.1, assessed by an independent review committee (IRC) is a primary endpoint of the planned expansion phase for Study LOXO-RET-17001. Key secondary endpoints include duration of response (DOR), central nervous system (CNS) ORR/DOR (by investigator and IRC), progression-free survival (PFS), and overall survival (OS).

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
 - *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
 - *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

DOP2 agrees that demonstration of a meaningful effect size on durable objective response rate according to RECIST would be clinically meaningful and reasonably likely to predict clinical benefit of a drug in patients with *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options. Demonstration of a significant improvement in PFS in a randomized study would be considered predictive of clinical benefit and if the magnitude of the treatment effect was large in magnitude with no evidence of detrimental effects on survival, such PFS effects could be used to support an application for traditional approval.

- c. 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.

None.

9. 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:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Table 1: Available therapies in Medullary Thyroid Carcinoma

Agent	Intended population	Approval	N	ORR (95% Confidence Interval [CI])	Median DOR, mths (95% CI)
Vandetanib	Symptomatic or progressive, locally advanced or metastatic MTC*	Regular Primary endpoint: PFS	231	44% (CI not provided)	NR
Cabozantinib	Progressive, metastatic MTC*	Regular Primary endpoint: PFS	219	27% (20.8, 32.9)	14.7 (11.1, 19.3)

* Approved regardless of RET status; DOR= duration of response; PFS=progression-free survival

Vandetanib is a multi-tyrosine kinase inhibitor with activity against RET, and is approved for the treatment of patients with symptomatic or progressive medullary thyroid cancer with unresectable locally advanced or metastatic disease based on the demonstration of improved progression-free survival in a randomized, placebo-controlled trial. The results of this study demonstrated a statistically significant improvement in PFS for patients randomized to vandetanib (Hazard Ratio [HR]= 0.35; 95% Confidence Interval [CI] = 0.24-0.53; $p < 0.0001$), with a median PFS in the placebo arm of 16 months and not reached in the vandetanib arm. Cabozantinib is approved for the treatment of patients with progressive, metastatic medullary thyroid cancer. The approval was based on a randomized, placebo-controlled study in patients with progressive metastatic MTC which demonstrated a statistically significant improvement in PFS in patients taking cabozantinib compared to those receiving placebo (HR 0.28 [95% CI: 0.19, 0.40]; $p < 0.0001$), with median PFS times of 11.2 months and 4.0 months in the cabozantinib and placebo arms, respectively.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

There have been no requests for breakthrough therapy designation for medullary thyroid carcinoma. There have been no breakthrough therapy designation requests for (b) (4) RET fusion-positive NSCLC or (b) (4). A preliminary breakthrough designation advice request was submitted by (b) (4) was advised that the data was immature, and that the tumor types represented in the preliminary clinical data presented would not support (b) (4) for a breakthrough therapy designation request.

10. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

LOXO-RET-17001 is a multicenter, first-in-human, global study of LOXO-292 for patients ≥ 12 years with advanced solid tumors harboring RET gene fusions/mutations, RET-mutant MTC, and other cancers. Study LOXO-RET-17001 was initiated in May 2017, and eight dose levels of LOXO-292 (20 mg QD to 240 mg BID) have been explored. According to Loxo, the maximum tolerated dose (MTD) was not reached and 160 mg BID

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

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

was selected for the dose-expansion portion of the study, though dose exploration continues. Loxo states that 52 patients have received LOXO-292 at the 160 mg BID dose.

In June 2018, protocol LOXO-RET-17001 was amended to include expansion cohorts. The primary endpoint is ORR based on RECIST 1.1, assessed by an independent review committee (IRC). Key secondary endpoints include duration of response (DOR), central nervous system (CNS) ORR/DOR (by investigator and IRC), progression-free survival (PFS), and overall survival (OS). Clinical outcomes assessments (COA) are planned to evaluate changes from baseline in disease-related symptoms and health-related quality of life (HRQoL) as measured by EORTC QLQ-C30, QLQ-LC-13 module (NSCLC patients), QLQ-BN-20 (patients with brain metastases), patient bowel diaries (MTC patients), and PedsQL (for ages 12-17 years).

The expansion cohorts will include the following:

- Cohort 1: RET fusion-positive solid tumor progressed after/intolerant to standard first line therapy
- Cohort 2: RET fusion-positive solid tumor without prior standard first-line therapy.
- Cohort 3: RET-mutant MTC progressed on/intolerant to standard first-line cabozantinib or vandetanib.
- Cohort 4: RET-mutant MTC without prior first-line cabozantinib, vandetanib, or other kinase inhibitor(s) targeting RET
- Cohort 5: Other (e.g., Cohorts 1-4 without measurable disease, MTC not meeting the requirements for Cohorts 3 or 4, other RET-altered solid tumor or other RET alteration/activation).

A total of ~450 patients are planned for this portion of the study across all cohorts. The protocol will allow up to 100 patients in Cohort 1 and Cohort 3. For patients with RET fusion-positive solid tumors, Loxo hypothesizes a true ORR of $\geq 50\%$ for LOXO-292, and estimates that a sample size of 55 patients will provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial confidence interval (CI) about the estimated ORR that exceeds 30%. For patients with RET-mutant MTC, Loxo hypothesizes a true ORR of $\geq 35\%$ with LOXO-292, and estimates that a sample size of 83 patients will provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 20%.

As of a data cutoff date of April 2, 2018, 82 patients have received LOXO-292 on the dose escalation portion of the study, including patients with RET fusion positive tumors (n=49) and tumors without known RET tumor alterations (n=4). Updated data was provided with a cutoff date of August 3, 2018 for patients with MTC; a total of 45 patients (43 with measurable disease) with MTC have enrolled. Patients with RET fusion positive tumors included 38 patients with NSCLC, 9 with PTC, and 2 with pancreatic cancer. Most patients (66%) received prior therapy targeting RET. Patients with MTC (n=45) most commonly received prior therapy with either cabozantinib or vandetanib (n=17, 38%), cabozantinib and vandetanib (n=16, 36%), no prior therapy (n=10, 22%), or therapy other than cabozantinib or vandetanib (n=2, 4%).

Loxo reports that for patients with *RET* mutation positive MTC with measurable disease and at least one post-baseline imaging assessment, the best overall response rate (ORR) is 51% (n=23/45, with 8 pending confirmation; 95% CI: 35 – 67). Two patients had a complete response, 13 have confirmed partial responses for a confirmed ORR of 33% (95% CI: 19,48). There were two patients enrolled without measurable disease, one of whom is reported as having a complete response; these patients are included in the above calculations. As of August 3, 2018, there are six patients among the 14 patients with at least one post-response assessment where the is DOR > 6 months (43% of confirmed responses). The median follow-up time was 5.1 months (range 2.7 – 7.7 months) from onset of response. Response rates by prior therapy received are presented in Tables 2 and 3.

Table 2: Responses in Patients with Measurable and Non-Measurable Disease

Prior therapy	N	Number of Responders (ORR)
Cabozantinib or vandetanib*	33	15 (45%)
Cabozantinib and vandetanib	16	9 (56%)
No prior approved therapy**	12	8 (67%)

*Includes 16 patients who received prior treatment with both cabozantinib and vandetanib

**Includes 10 patients with no prior therapy and 2 patients with investigational therapies

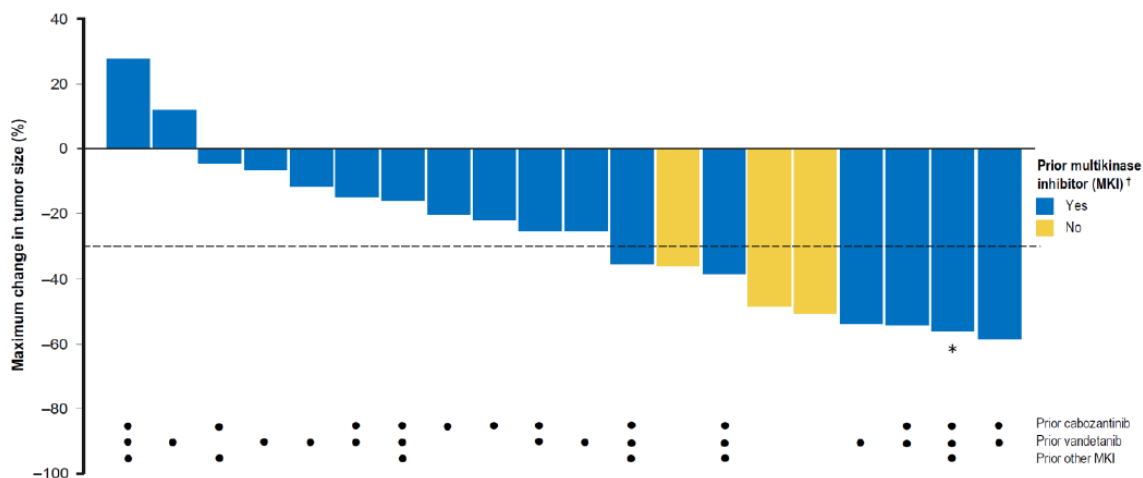
Table 3: Responses in Patients with Measurable Disease Only

Prior therapy	N	Number of Responders (ORR)
Cabozantinib or vandetanib*	31	14 (45%)
Cabozantinib and vandetanib	15	8 (53%)
No prior approved therapy**	12	8 (67%)

*Includes 15 patients who received prior treatment with both cabozantinib and vandetanib

**Includes 10 patients with no prior therapy and 2 patients with investigational therapies

The figures below, reproduced from the sponsor's request for Breakthrough Designation, demonstrate waterfall and swimmers plots from patients on Study LOXO-RET-17001, with a data cutoff of April 2, 2018.

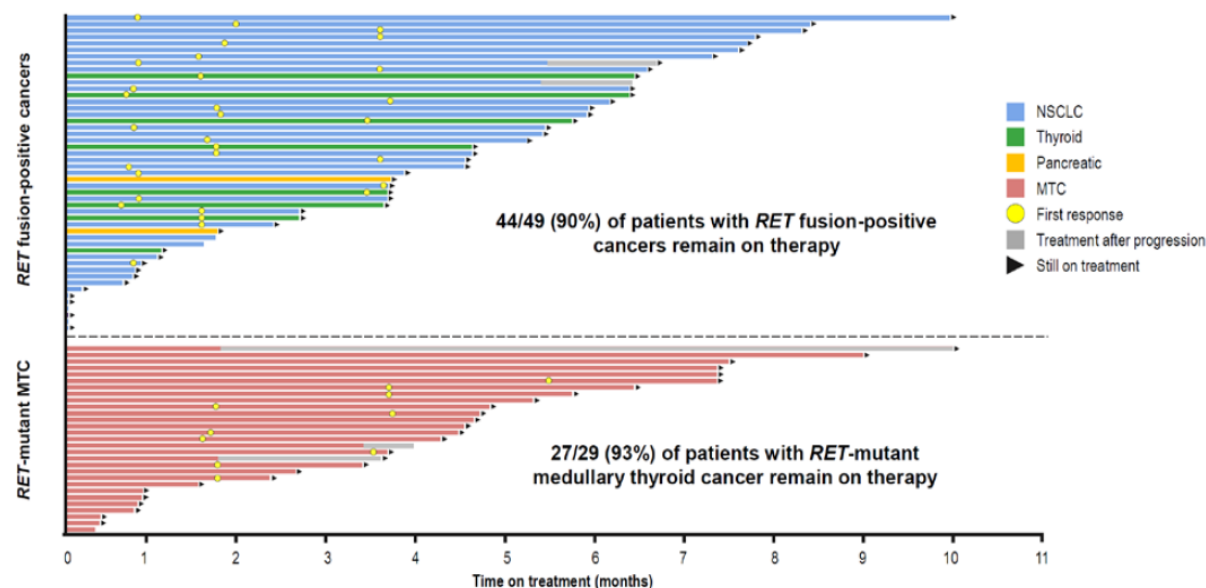
Figure 4 Efficacy of LOXO-292 in *RET*- Mutant MTC (Study LOXO-RET-17001)

Note: Two patient not displayed (one due to treatment discontinuation prior to first post-baseline response assessment; one due to non-measurable disease at baseline (uCR; unconfirmed complete response); †Includes cabozantinib, lenvatinib, pazopanib, RXDX-105, sorafenib, sunitinib, and vandetanib; *CR (complete response)

Cutoff date: 02 April 2018.

Source: (Drilon, 2018)

Figure 5 Swimmers Plot of Study Treatment Duration for Patients with Known Activating RET Alterations* (Study LOXO-RET-17001)



Cutoff date: 02 April 2018.

Source: (Drilon, 2018)

Data as of 4/2/2018.

b. Include any additional relevant information. Consider the following in your response:

- Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.
- Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.
- Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.

Treatment-emergent adverse events (TEAEs) observed in 10% of patients or more included fatigue (20%), diarrhea (16%), constipation (15%), dry mouth (12%), nausea (12%), and dyspnea (11%). TEAEs which were Grade 3 or 4 included dyspnea (1.2%), increased ALT (2.4%), increased AST (1.2%), hypertension (1.2%), and hyponatremia (2.4%). Nine patients have discontinued study drug for disease progression (n=5), death (n=2) or adverse event/physician decision (1 each).

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

☒ GRANT :

Provide brief summary of rationale for granting:

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

The demonstrated response rate in a population without available treatment options is promising, and there is evidence of durable responses. A significant number of responses occurred in patients with no available approved therapies, with 56% of patients previously treated with both cabozantinb and vandetanib demonstrating a response.

☐ 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):

As described above, the sponsor recently met with FDA in an end-of-phase-1 meeting to discuss the development plan.

- 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:

13. List references, if any:

Romei C et al., RET mutation heterogeneity in primary advanced medullary thyroid cancers and their metastases. Oncotarget. 2018 Feb 9; 9(11): 9875 – 9884.

Kato, S., et al. "Ret aberrations in diverse cancers: Next-generation sequencing of 4,871 patients." Clin Cancer Res. 2017; 23(8): 1988-1997.

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}

Revised 6/12/18/M. Raggio

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DIANA L BRADFORD
08/30/2018

SUZANNE G DEMKO
08/30/2018

STEVEN J LEMERY
08/30/2018

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 133193
Request Receipt Date	07/03/2018
Product	LOXO-292
Indication	For the treatment of patients with metastatic <i>RET</i> -fusion-positive non-small cell lung cancer who require systemic therapy, and have progressed following platinum-based chemotherapy and an anti-PD-1 or anti-PD-L1 therapy.
Drug Class/Mechanism of Action	Small molecule inhibitor of the <i>RET</i> receptor tyrosine kinase
Sponsor	Loxo Oncology, Inc.
ODE/Division	Division of Oncology Products 2
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	09/01/2018

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes, and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

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):

For the treatment of patients with advanced *RET*-fusion-positive non-small cell lung cancer who require systemic therapy, have progressed following prior treatment, and have no acceptable alternative treatment options.

The sponsor originally submitted a breakthrough therapy request which included the following indication:

For the treatment of patients with advanced (b) (4) *RET*-mutant medullary thyroid carcinoma (MTC) who require systemic therapy, have progressed following prior treatment, and have no acceptable alternative treatment options.

DOP2 had noted previously in meetings with the company that patients with (b) (4) and *RET*-mutant MTC represent two distinct patient populations. In a teleconference held on July 18, 2018, DOP2 recommended that the sponsor submit separate breakthrough therapy designation requests for each of these indications. The sponsor agreed, and amended the indication in the initial request to include only (b) (4) and submitted a new request with the indication of *RET*-mutant MTC.

Following review of the data for the (b) (4) patients, it was determined that there was insufficient data to support granting the breakthrough designation request (b) (4) indication. In a teleconference held on August 13, 2018, DOP2 advised the sponsor to provide separate requests (b) (4) including a request for the treatment of patients with *RET*-fusion-positive NSCLC. DOP2 advised that a request for the treatment of patients with (b) (4) or deferred until additional clinical data are available.

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

☐ YES ☒ NO

3. Was the BTDR submitted to a PIND?

☐ YES ☒ NO

If “Yes” do not review the BTDR. The sponsor must withdraw the BTDR. BTDR’s cannot be submitted to a PIND.

If 2 above is checked “Yes,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “No”, proceed with below:

4. Consideration of Breakthrough Therapy Criteria:

a. Is the condition serious/life-threatening¹?

☒ YES ☐ NO

If 4a is checked “No,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “Yes”, proceed with below:

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

☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review

☐ Undetermined

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

- i. Only animal/nonclinical data submitted as evidence ☐
- ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 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 the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTDR Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

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>

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>

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.

7. 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.

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

Disease Background

The RET proto-oncogene encodes for a transmembrane tyrosine kinase receptor involved in multiple cellular processes including cell proliferation, migration, differentiation and neuronal maintenance. RET signaling through binding with glial cell line-derived neurotrophic factor (GDNF) ligands leads to activation of multiple downstream pathways including MAPK and PI3K. Gain of function amplifications/mutations or rearrangements of RET can lead to development of multiple endocrine neoplasia type 2 (MEN2) syndrome. RET mutations occur in approximately 50% of patients with medullary thyroid cancer (MTC) (>90% in hereditary forms of MTC). (Romei, 2018) RET gene fusions have been identified in up to 10 – 20% of patients with papillary thyroid cancer (PTC), 1-2% of non-small cell lung cancers (NSCLC), and less commonly in other tumor types, including colorectal cancer, and breast cancer. (Kato, 2017; Kohno, 2012) There are several approved multi-tyrosine kinase inhibitors (TKI) targeting RET (e.g., vandetanib, cabozantinib, ponatinib), although none are directed solely against RET.

Non-Small Cell Lung Cancer:

There will approximately be 230,000 new cases of lung cancer and 154,000 deaths from lung cancer in the US in 2018 (NCI, 2018). Of these, 85-90% are NSCLC and approximately 80% of patients have locally advanced or metastatic disease at diagnosis; approximately 18% of all patients diagnosed with lung cancer will survive 5 years, with much lower survival rates for patients with metastatic disease at diagnosis. Treatment with platinum doublet-based chemotherapy leads to a median overall survival (OS) of approximately 10 months and a median progression-free survival (PFS) of approximately 5 months; in patients who have tumors with PD-L1 expression $\geq 50\%$, treatment with pembrolizumab, the only PD-1/PD-L1 inhibitor approved as monotherapy in the first line setting for patients with metastatic NSCLC, leads to a median PFS of approximately 10 months. (Scagliotti, 2008; Reck, 2016) Recently presented data suggest that RET-fusion positive NSCLCs demonstrate significantly lower tumor mutational burden compared to all NSCLCs (3.3 M/Mb vs. 5.7M/Mb). (Sabari, 2018) In this analysis, patients with RET fusion-positive NSCLC who were treated with anti-PD-1 or anti PD-L1 therapy did not demonstrate an improved survival compared to those patients who were not treated with anti-PD-1/PD-L1 therapy.

Relevant Regulatory History

On March 2, 2017, Loxo submitted IND 133193, including Protocol LOXO-RET-17001, (b) (4)
The IND went into effect on March 31, 2017.

On November 13, 2017, Loxo submitted a Preliminary Breakthrough Therapy Designation (BTD) request for Loxo-292 (b) (4). This request contained the cover protocol LOXO-RET-17001, entitled "A Phase 1 Study of Oral LOXO 292 in Patients with Advanced Solid Tumors, Including RET Fusion

Non-Small Cell Lung Cancer, Medullary Thyroid Cancer and Other Tumors with Increased RET Activity,” and two Single Patient Protocols for patients with RET-dependent cancers.

On November 20, 2017, a teleconference was held between representatives from Loxo and FDA to provide preliminary advice for the BTDR request. FDA stated that it was premature for Loxo to request the BTDR.

On April 20, 2018, Loxo submitted a Type B, End-of-Phase 1, meeting request to obtain input from FDA regarding a registrational program which would establish clinical benefit for LOXO-292, acceptability of design elements and proposed changes to the Phase 1/2 Study LOXO-RET-17001, and the acceptability of nonclinical and clinical pharmacology studies and Chemistry, Manufacturing, and Controls (CMC) development to support registration, and input on an accelerated approval pathway.

- Loxo requested FDA’s input on whether the population of (b) (4) and patients with RET-mutant MTC who have failed at least one or more prior therapies, represent populations with unmet medical need. FDA agreed that patients with RET-mutant MTC who have progressed on either cabozantinib or vandetanib and require systemic therapy is a distinct population with unmet medical need. FDA suggested that for (b) (4), Loxo needed to demonstrate that no available therapy is available, or that LOXO-292 has an improved effect on a serious outcome of the condition compared with available therapy. FDA noted that the latter subgroup is primarily driven by results obtained in patients with RET fusion-positive NSCLC.

8. 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.

Loxo considers durable objective response rate to be a clinically meaningful endpoint supporting the BTDR. The data for overall response rate in Study LOXO-RET-17001 presented in the BTDR request is based on investigator-assessed response by RECIST 1.1. Overall response rate according to RECIST 1.1, assessed by an independent review committee (IRC) is a primary endpoint of the planned expansion phase for Study LOXO-RET-17001. Key secondary endpoints include duration of response (DOR), central nervous system (CNS) ORR/DOR (by investigator and IRC), progression-free survival (PFS), and overall survival (OS).

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
 - *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
 - *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
 - *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

DOP2 agrees that demonstration of a meaningful effect size on durable objective response rate according to RECIST would be clinically meaningful and reasonably likely to predict clinical benefit of a drug for patients with advanced *RET*-fusion-positive NSCLC who require systemic therapy, have progressed following prior treatment, and have no acceptable alternative treatment options. Demonstration of a statistically significant improvement in overall survival or of a statistically significant and clinically meaningful improvement in PFS of sufficient magnitude to be considered direct evidence of clinical benefit could be used to support an application for traditional approval.

- c. 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.

None.

9. 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:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Table 1: Available therapies for NSCLC, 2nd line

Regimen	Intended population	Approval	n	ORR (95% Confidence Interval [CI])	Median DOR, mths (95% CI)
Docetaxel	NSCLC after platinum therapy failure	Regular Primary endpoint: OS ¹	104 (TAX317)	5.5% (1.1, 15.1)	Not provided
			373 (TAX320)	5.7% (2.3, 11.3)	Not provided
Docetaxel +Ramacirumab	NSCLC after platinum therapy failure	Regular Primary endpoint: OS ²	628	23% (20, 26)	Not provided
Pemetrexed	NSCLC (excluding squamous cell histology)	Regular Primary endpoint: OS ³	283	8.5% (5.2, 11.7)	Not provided
Nivolumab	NSCLC after platinum therapy failure	Regular Primary endpoint: OS	286 (non-squamous)	19% (15, 24)	17 (8.4, NR)
			135 (squamous)	20% (14, 28)	NR (9.8, NR)
Atezolizumab	NSCLC after platinum therapy failure	Regular Primary endpoint: OS	425	14% (11, 17)	16.3 (10.0, NE)
Pembrolizumab	NSCLC, PD-L1 ≥1%	Regular Primary endpoint: OS	344	18% (14, 23)	NR (0.7, 20.1)

¹ The TAX317, TAX320 studies are cited in product labeling as studies used to support approval. TAX 317 demonstrated improved effect on survival. The REVEL study randomized patients to receive docetaxel or docetaxel +ramicirumab. Data for the control arm (n=625) demonstrated an ORR of 14% (DOR not provided).

² Data used to support approval included a median OS of 10.5 mo (95%CI: 9.5, 11.2 mo) for docetaxel + ramicurimab, vs 9.1 mo (95% CI: 8.4, 10.0) placebo +docetaxel, HR 0.86 (0.75, 0.98).

³ Data used to support approval included a median OS of 8.3 mo (95%CI: 7.0 – 9.4) for pemetrexed vs. 7.9 mo (95%CI: 6.3 – 9.2) , HR 0.99 (0.82 – 1.20) for docetaxel.

DOR= duration of response; OS= overall survival; NE= not estimable; NR= not reached

There are no approved therapies for RET fusion-positive NSCLC

(b) (4)

9. A brief description of any drugs being studied for the same indication, or very similar indication, that

requested breakthrough therapy designation³.

There have been no breakthrough therapy designation requests (b) (4) for *RET* fusion-positive NSCLC. A preliminary breakthrough designation advice request was submitted by (b) (4) (b) (4) was advised that the data were immature and that the tumor types represented in the preliminary clinical data presented would not support a (b) (4) for a breakthrough therapy designation request.

Nivolumab was granted breakthrough therapy designation for the treatment of advanced or metastatic nonsquamous NSCLC with progression on or after platinum-based chemotherapy. Pembrolizumab was granted breakthrough designation for the treatment of patients w/EGFR mutation-negative, ALK rearrangement-negative NSCLC whose disease has progressed on or following platinum-based chemotherapy. Atezolizumab was granted breakthrough therapy designation for the treatment of patients with PD-L1 positive non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy.

10. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

LOXO-RET-17001 is a multicenter, first-in-human, global study of LOXO-292 for patients ≥ 12 years with advanced solid tumors harboring *RET* gene fusions/mutations, *RET*-mutant MTC, and other cancers. Study LOXO-RET-17001 was initiated in May 2017, and eight dose levels of LOXO-292 (20 mg QD to 240 mg BID) have been explored. According to Loxo, the maximum tolerated dose (MTD) was not reached and 160 mg BID was selected for the dose-expansion portion of the study. Loxo states that 52 patients have received LOXO-292 at the 160 mg BID dose.

In June 2018, protocol LOXO-RET-17001 was amended to include expansion cohorts. The primary endpoint will be ORR based on RECIST 1.1, assessed by an independent review committee (IRC). Key secondary endpoints include duration of response (DOR), central nervous system (CNS) ORR/DOR (by investigator and IRC), progression-free survival (PFS), and overall survival (OS). Clinical outcomes assessments (COA) are planned to evaluate changes from baseline in disease-related symptoms and health-related quality of life (HRQoL) as measured by EORTC QLQ-C30, QLQ-LC-13 module (NSCLC patients), QLQ-BN-20 (patients with brain metastases), patient bowel diaries (MTC patients), and PedsQL (for ages 12-17 years).

The expansion cohorts will include the following:

- Cohort 1: *RET* fusion-positive solid tumor progressed after/intolerant to standard first-line therapy
- Cohort 2: *RET* fusion-positive solid tumor without prior standard first-line therapy.
- Cohort 3: *RET*-mutant MTC progressed on/intolerant to standard first-line cabozantinib or vandetanib.
- Cohort 4: *RET*-mutant MTC without prior first-line cabozantinib, vandetanib, or other kinase inhibitor(s) targeting *RET*
- Cohort 5: Other (e.g., Cohorts 1-4 without measurable disease, MTC not meeting the requirements for Cohorts 3 or 4, other *RET*-altered solid tumor or other *RET* alteration/activation).

A total of ~450 patients are planned for this portion of the study across all cohorts. The protocol will allow up to 100 patients in Cohort 1 and Cohort 3. For patients with *RET* fusion-positive solid tumors, Loxo hypothesizes a true ORR of $\geq 50\%$ for LOXO-292, and estimates that a sample size of 55 patients will provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial confidence interval (CI) about the estimated ORR

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

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

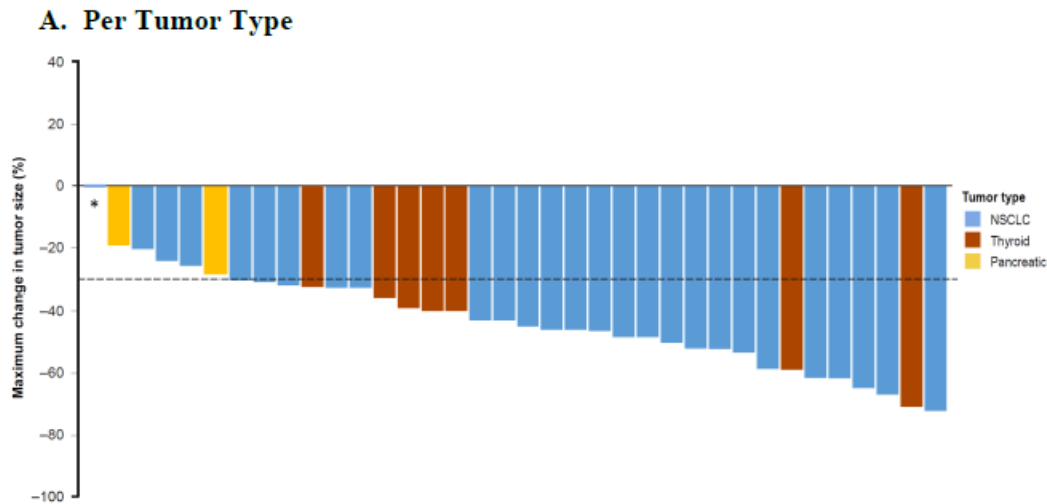
that exceeds 30%. For patients with RET-mutant MTC, Loxo hypothesizes a true ORR of $\geq 35\%$ with LOXO-292, and estimates that a sample size of 83 patients will provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 20%. As of the data cutoff date of April 2, 2018, 82 patients have received LOXO-292 on the dose escalation portion of the study, including 49 patients with RET fusion positive tumors, 29 patients with RET mutated MTC and four patients with tumors without known RET tumor alterations. Patients with RET fusion positive tumors included 38 patients with NSCLC, 9 with PTC, and 2 with pancreatic cancer.

Loxo reports durable responses for 39 evaluable patients with RET fusion positive tumors receiving LOXO-292, with a confirmed overall response rate (ORR) of 77% ; 95% CI: 61, 89) was identified by investigator assessment. As of June 14, 2018, responses were ongoing for 29 of the 30 responding patients with *RET* fusion-positive solid tumors patients; 15 responders had durable responses of more than 6 months from the onset of response. Responses occurred in patients with NSCLC, including patients with brain metastases (n=23) and in patients with PTC (n=7).

Of the patients with NSCLC enrolled, 35 (92%) had prior therapy. Fifteen (39%) had only prior chemotherapy (1 – 3+ lines) and 2 had only prior immunotherapy. Sixteen (42%) had prior chemotherapy and immunotherapy. The confirmed overall response rate (ORR) in the 30 “evaluable” patients with RET-fusion positive NSCLC was 77% (95% CI: 58, 90). For the 23 responders with NSCLC, 18 had durable responses of more than 6 months from the onset of response. In the 12 evaluable patients who were previously treated with both chemotherapy and immunotherapy, the ORR was 75% (95% CI: 46, 95). Eight of nine responders previously treated with both chemotherapy and immunotherapy demonstrated responses > 6 months (range 6.5 – 11.2 months).

The figures below are reproduced from the sponsor’s breakthrough therapy and meeting package submissions, and demonstrate the responses observed thus far on Study LOXO-RET-17001.

Figure 3 Efficacy of LOXO-292 in *RET* fusion-positive cancers
(Study LOXO-RET-17001)



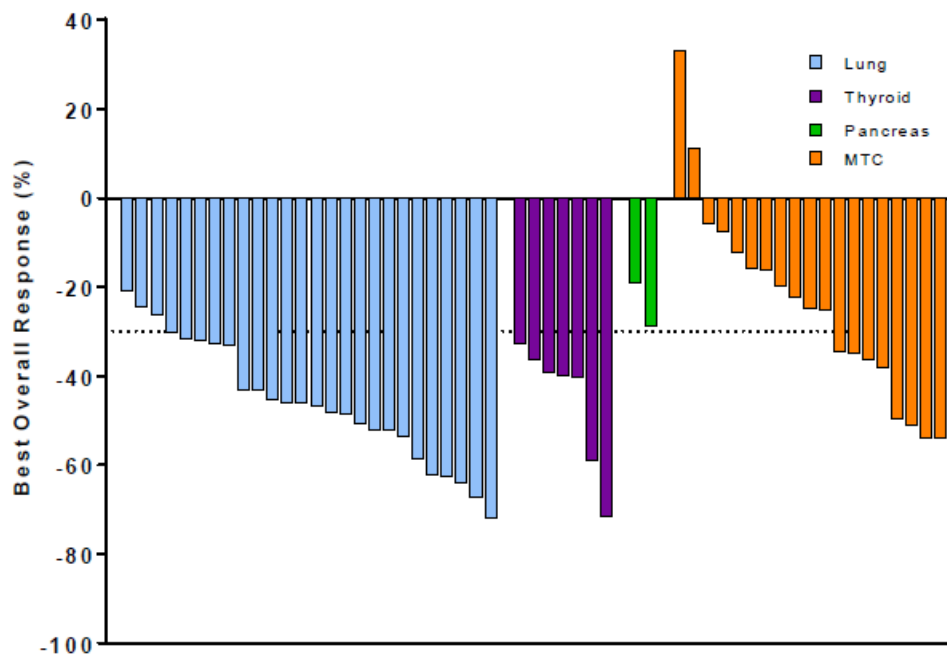
Note: Three patients not displayed due to treatment discontinuation prior to first post-baseline response assessment;

*Denotes patient with 0% maximum change in tumor size

Cutoff date: 02 April 2018.

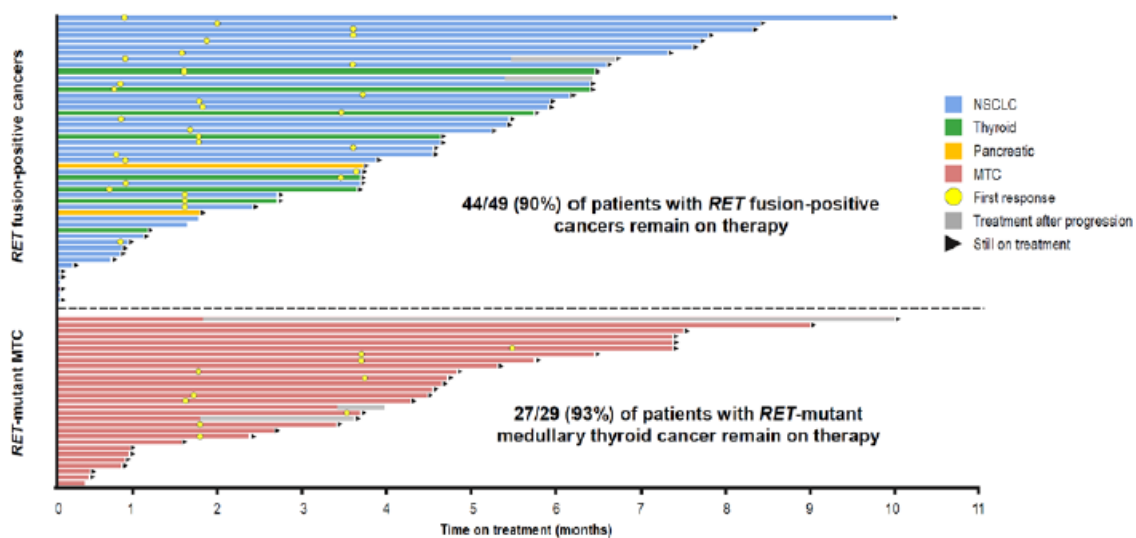
Source: (Drilon, 2018)

Figure 4 Waterfall Plot of Best Overall Response for Patients with Known Activating RET Alterations* (Study LOXO-RET-17001)



*4 patients without known activating RET alterations are not included

Figure 5 Swimmers Plot of Study Treatment Duration for Patients with Known Activating RET Alterations* (Study LOXO-RET-17001)



Cutoff date: 02 April 2018.

Source: (Drilon, 2018)

Data as of 4/2/2018.

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness .*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

Treatment-emergent adverse events (TEAEs) observed in 10% of patients or more included fatigue (20%), diarrhea (16%), constipation (15%), dry mouth (12%), nausea (12%), and dyspnea (11%). TEAEs which were Grade 3 or 4 included dyspnea (1.2%), increased ALT (2.4%), increased AST (1.2%), hypertension (1.2%), and hyponatremia (2.4%). Nine patients have discontinued study drug for disease progression (n=5), death (n=2) or adverse event/physician decision (1 each). Nine patients have discontinued study drug for disease progression (n=5), death (n=2) or adverse event/physician decision (1 each).

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

☒ GRANT :

Provide brief summary of rationale for granting:

The data provided suggest that patients with RET fusion-positive NSCLC previously treated with one or more therapies who received LOXO-292 achieved a higher response rate than would be achieved with available therapy for 2 or 3-line FDA-approved treatment and that these responses can be durable . (b) (4)

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:

- 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):
- 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:

The sponsor has recently met with FDA in an End-of-Phase 1 meeting during which feedback on the proposed development program was conveyed. (b) (4)

13. List references, if any:

Kato, S., et al. Ret aberrations in diverse cancers: Next-generation sequencing of 4,871 patients. Clin Cancer Res. 2017; **23**(8): 1988-1997.

Kohno, T., et al. Kif5b-ret fusions in lung adenocarcinoma. Nat Med 2012; **18**(3): 375-377.

National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER). Accessed July 24, 2018. <https://seer.cancer.gov/statfacts/html/lungb.html>

Scagliotti GV et al, Phase III Study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. J Clin Oncol, 2008, 26: 3543-3551.

Reck M et al, Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. NEJM, 2016, 375(19): 1823-1833.

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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}

Revised 6/12/18/M. Raggio

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DIANA L BRADFORD
08/30/2018

ERIN A LARKINS
08/30/2018

STEVEN J LEMERY
08/30/2018