CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213246Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 133193

MEETING MINUTES

Loxo Oncology, Inc.
Attention: Elaine Fashana
Executive Director, Regulatory Affairs
701 Gateway Boulevard, Suite 420
South San Francisco, CA 94080

Dear Ms. Fashana:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for selpercatinib (LOXO-292).

We also refer to the meeting between representatives of your firm and the FDA on November 25, 2019. The purpose of the meeting was to discuss the content and format of the planned new drug application (NDA) for selpercatinib relying on the safety and efficacy results from specific cohorts from the ongoing clinical trial Study LOXO-RET-17001 entitled, "A Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumors, Including RET Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors with RET Activation (LIBRETTO-001)," for the proposed indications of the treatment of patients with:

- metastatic RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy and have progressed following platinum-based chemotherapy;
- RET-mutant medullary thyroid cancer (MTC) who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options; and
- advanced RET fusion-positive thyroid cancer who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options.

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

If you have any questions, call me at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Meredith Libeg
Senior Regulatory Health Project Manager
Division of Regulatory Operations-Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	Monday, November 25, 2019; 9:00 AM – 10:30 AM (ET)
Meeting Location:	White Oak Building 22, Conference Room: 1313
Application Number:	IND 133193
Product Name:	selpercatinib
Indication:	metastatic RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy and have progressed following platinum-based chemotherapy; RET-mutant medullary thyroid cancer (MTC) who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options; and advanced RET fusion-positive thyroid cancer who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options
Sponsor Name:	Loxo Oncology, Inc. (Loxo)
Meeting Chair:	Suzanne Demko
Meeting Recorder:	Meredith Libeg

FDA ATTENDEES

Harpreet Singh, M.D.	Division Director (Acting), DO2
Suzanne Demko, PA-C	Clinical Team Leader, OOD/DO2
Diana Bradford, M.D.	Clinical Reviewer, OOD/DO2
Erin Larkins, M.D.	Clinical Team Leader, OOD/DO2
Yuan-Li Shen, Ph.D.	Statistical Team Leader, DBV/OB
Pallavi Roy, Ph.D.	Statistical Reviewer, DBV/OB
Edwin Chow, Ph.D.	Clinical Pharmacology Reviewer, DCPV/OCP
Emily Wearne, Ph.D.	Nonclinical Reviewer, DHOT
Francisca Reyes Turcu, Ph.D.	Scientific Reviewer, CDRH/OIR/DMGP/MPCB
Reena Philip, Ph.D.	Director, CDRH/OIR/DMGP
Meredith Libeg	Senior RPM, ORO – DO2

SPONSOR ATTENDEES

Nisha Nanda, Ph.D.&	Chief Development Officer
Elaine Fashana&	Executive Director, Regulatory Affairs
Katie Cairati, M.S.&	Head, Regulatory Affairs
Michael Rothenberg, M.D., Ph.D.	Vice President, Clinical Development
Jennifer Kherani, M.D.&	Sr. Medical Director
Xin Huang, Ph.D.&	Sr. Director, Biostatistics
Edward Zhu, Ph.D.&	Clinical Scientist
Yassine Labiad, M.S., R.A.C.&	Director, Regulatory Affairs Program Management, CDx
Jacob Van Naarden&	Chief Operating Officer
Joshua Bilenker, M.D.&	Chief Executive Officer, Sr. Vice President, Oncology Research and Early Phase Development
Symantha Melemed, Ph.D.	Global Product Team Leader 2

(b) (4)

BACKGROUND

Meeting Purpose

The goal of the meeting is to obtain FDA feedback on the proposed the content and format of the planned new drug application (NDA) under the provisions of 21 CFR 314 Subpart H for selpercatinib relying on the safety and efficacy results from specific cohorts from ongoing Study LOXO-RET-17001 entitled, “A Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumors, Including RET Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors with RET Activation (LIBRETTO-001),” for the proposed indications of the treatment of patients with:

- metastatic RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy and have progressed following platinum-based chemotherapy;
- RET-mutant medullary thyroid cancer (MTC) who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options; and
- advanced RET fusion-positive thyroid cancer who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options.

The proposed confirmatory studies to verify the clinical benefit are:

- Protocol J2G-MC-JZJB, entitled “A Multicenter, Randomized, Open-label, Phase 3 Trial Comparing LOXO-292 to Physicians Choice of Cabozantinib or Vandetanib in Patients with Progressive, Advanced, Kinase Inhibitor Naïve, RET-Mutant Medullary Thyroid Cancer (LIBRETTO-531),” being conducted under IND 144696, held by Lilly, of which LOXO is a wholly owned subsidiary.
- (b) (4)

Regulatory

See meeting minutes issued August 13, 2019 for a full regulatory history.

On August 8, 2019, a pre-NDA CMC only meeting was held to obtain guidance on chemistry, manufacturing, and controls (CMC) aspects of the content and format of the planned New Drug Application for LOXO-292.

On August 13, 2019, FDA issues WRO relating to the clinical content and format of the planned New Drug Application for LOXO-292. FDA provided guidance on the content and format of a proposed NDA. FDA agreed that the Statistical Analysis Plans (SAPs) for the Summary of Clinical Efficacy (SCE) for the proposed *RET*-mutant MTC indication and for the proposed *RET* fusion-positive NSCLC indication were acceptable. FDA requested specific analyses in the Integrated Summary of Efficacy, including analyses of overall response rate (ORR) and duration of response (DOR) by baseline demographic and disease characteristics and RET gene fusion partner in patients with NSCLC. FDA requested additional details regarding the statistical analysis plan for the Summary of Clinical Safety (SCS, Module 2.7.4). Specifically, FDA requested that Loxo provide the number of patients to be included in each safety dataset, including the number of patients who initiated selpercatinib at 160 mg twice a day (BID), and a description of Loxo’s proposed approach for aggregating preferred terms under composite terms.

Orphan designation

- Selpercatinib does not have orphan designation for these development program; however, applications are currently under review with Orphan Products Development (OOPD). Additionally, agreed iPSPs are currently under review with the division.

Expedited programs

- On August 30, 2018, selpercatinib received Breakthrough Therapy designation (BTD) for "the treatment of patients with metastatic RET fusion-positive NSCLC who require systemic therapy and have progressed following platinum-based chemotherapy and an anti-PD-1 or anti-PD-L1 therapy."
- On August 31, 2018, selpercatinib received BTD for LOXO-292 for "the treatment of patients with *RET*-mutant MTC who require systemic therapy, have progressed following prior treatment, and have no acceptable alternative treatment options."

Clinical Pharmacology

In response to FDA's request (WRO issued on August 13, 2019, to evaluate the impact of BCRP inhibitors on the pharmacokinetic [PK] of selpercatinib), Loxo provided the following rationales to justify that the significant of BCRP inhibitor on the PK of selpercatinib is unlikely:

- Oral bioavailability of selpercatinib is 73%.
- Selpercatinib is a substrate for the transporters P-gp and BCRP in vitro.
- The minimal effect of a P-gp inhibitor was observed in a clinical drug interaction trial (LOXO-RET-18014) in which exposure of selpercatinib was increased only minimally by co-administration of the P-gp inhibitor rifampin (increase of approximately 6.5% and 19% in AUC0-24 and C_{max}, respectively).
- The in vitro and clinical DDI results suggest that there is unlikely to be a significant impact of a BCRP inhibitor on the PK of selpercatinib.

Nonclinical

Selpercatinib is an orally available small molecule inhibitor of the RET receptor tyrosine kinase. Loxo plans to submit 3-month repeat-dose toxicology studies in rats and minipigs; safety pharmacology, phototoxicity, and genotoxicity studies; an embryo-fetal development study in rats; as well as in vitro and in vivo pharmacology studies supporting the mechanism of action of selpercatinib, and ADME studies to support the planned NDA. As previously discussed, Loxo plans to submit a fertility and early embryonic development study after initiation of the review cycle. If approved, FDA agreed that Loxo can submit carcinogenicity studies for LOXO-292 in rats and mice as post-marketing requirements.

Clinical

The NDA for selpercatinib (LOXO-292) will include efficacy and safety data from a single, pivotal study, Study LIBRETTO-001, to support indications in RET fusion positive NSCLC and RET-mutant MTC. Study LIBRETTO-001 is an ongoing multicenter, single-arm, dose-finding and activity-estimating study of selpercatinib for patients ≥ 12 years old with advanced solid tumors harboring *RET* gene fusions/mutations. The primary endpoint for the expansion component is ORR based on RECIST 1.1, assessed by an independent review committee (IRC). Key secondary endpoints include DOR, central nervous system (CNS) ORR and DOR (by investigator and IRC), progression-free survival (PFS), and overall survival (OS). Clinical outcomes assessments (COA) will 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).

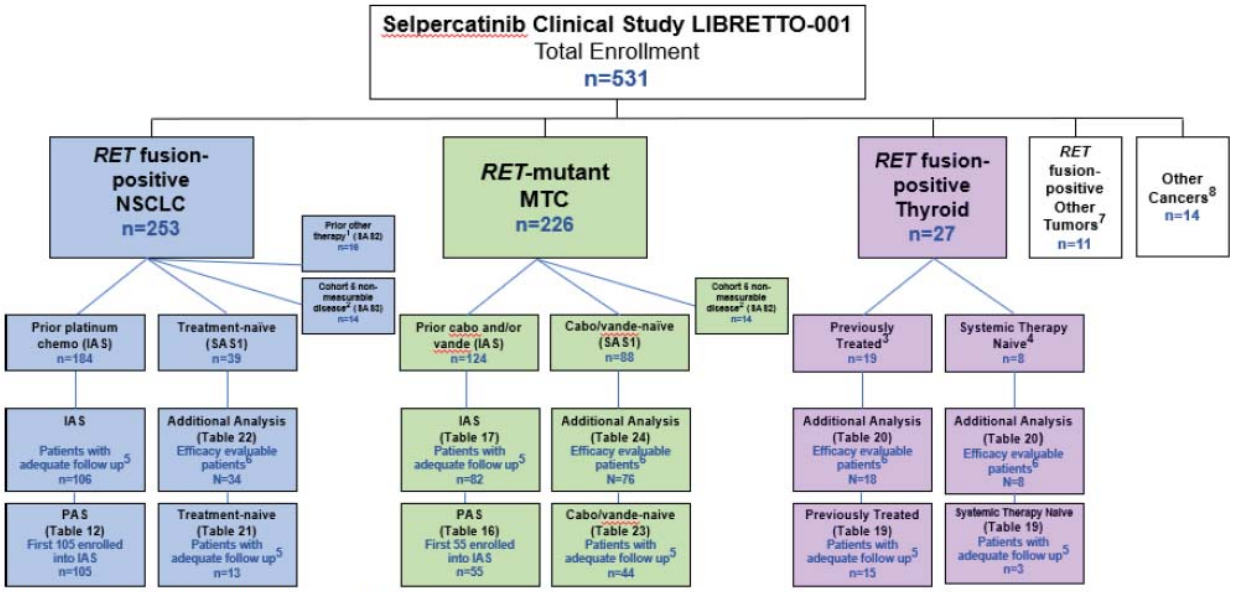
The activity-estimating cohorts in Study LIBRETTO-001 are:

- Cohort 1: *RET*-fusion-positive solid tumor progressed on or intolerant to ≥ 1 prior standard first-line therapy.
- Cohort 2: *RET*-fusion-positive solid tumor without prior standard first-line therapy.
- Cohort 3: *RET*-mutant MTC progressed on or intolerant to ≥ 1 prior standard first-line cabozantinib and/or vandetanib.
- Cohort 4: *RET*-mutant MTC without prior standard first-line cabozantinib or vandetanib or other kinase inhibitors(s) with anti-RET activity.
- Cohort 5: Cohorts 1-4 without measurable disease; MTC not meeting the requirements for Cohorts 3 or 4; MTC syndrome spectrum cancers (e.g., MTC, pheochromocytoma) or poorly differentiated thyroid cancers with other RET alteration/activation may be allowed with prior LOXO approval; cfDNA positive for a RET gene alteration not known to be present in a tumor sample.

Proposed NDA

Loxo has provided a schema with the multiple efficacy analysis population:
Figure 3, copied from page 48 of the meeting package, provides the numbers of patients to be included in the original NDA

Figure 3 **Selpercatinib Enrollment and Analysis Populations**



1. Prior systemic therapy other than platinum-based chemotherapy
2. Patients without measurable disease who were enrolled into Phase 1 dose expansion Cohort 5 (per protocol version 4.0 or earlier) or Phase 2 Cohort 5 (per protocol version 5.0 and later)
3. Previously treated RET fusion-positive thyroid cancer defined as ≥ 1 prior systemic therapy in addition to radioactive iodine if indicated
4. Systemic therapy naïve RET fusion-positive thyroid cancer defined as 0 prior systemic therapy other than radioactive iodine if indicated
5. Adequate follow up defined as ≥ 6 months from 1st dose to data cutoff of 17 June 2019, per SCE SAPs
6. Efficacy evaluable defined as at least 1 evaluable post baseline tumor assessment, or discontinued treatment prior to first post baseline tumor assessment
7. RET fusion-positive Other Tumors: pancreatic cancer, rectal neuroendocrine cancer, salivary gland cancer, carcinoid, colon, small intestine, and xanthogranuloma.
8. Other solid tumors that do not fit the other disease cohorts. Please see section 12.2 Summary of Clinical Data for more details.

Proposed Clinical Data Package to Support the Indication for NSCLC:

The primary efficacy endpoint will be ORR based on RECIST v1.1 as determined by an IRC in the primary analysis set (PAS), defined as the first 105 patients with RET fusion positive NSCLC consecutively enrolled on Study LIBRETTO-001 as of April 10, 2019, who meet the following criteria:

- Have evidence of a protocol defined and definitive RET fusion as identified by a documented CLIA-certified (or equivalent ex-US) molecular pathology report. Patients with an additional oncogenic driver mutation will be included in the NSCLC PAS.
- Have measurable disease by RECIST v1.1 (with the exception of patients without measurable disease who were included in the dose escalation phase, who will be included in the PAS).
- Have received one or more lines of prior platinum-based chemotherapy
- Have received one or more doses of selpercatinib.
- Responders have been followed for at least 6 months from the first dose of selpercatinib to the data cutoff date of June 17, 2019.

As of the June 17, 2019 data cutoff, ORR in the RET fusion-positive NSCLC PAS was 61.9% (65/105; 95% confidence interval [CI]: 51.9, 71.2) by IRC, and the median DOR by IRC was 12.5 months (95% CI: 10.3, NE), with 17/65 (26%) events observed.

Treatment-Naïve RET-Fusion NSCLC

Loxo proposes that the data from Study LIBRETTO-001 may support approval of selpercatinib in patients with NSCLC who are treatment naïve. As of the data cut-off date of June 17, 2019, a total of 39 treatment-naïve patients with RET fusion-positive NSCLC had been treated with selpercatinib. Of these, 13 had follow-up time of at least 6 months from first dose of selpercatinib. In these 13 patients, the ORR by both IRC and investigator assessment was 92.3% (12/13; 95% CI: 64.0, 99.8). The median DOR by IRC was not reached (95% CI: 6.4, NE), with 3/12 (25%) events observed.

The proposed December 16, 2019 data cutoff date for the 60-day update will provide an additional 6 months of follow-up, at which time all 39 treatment-naïve patients with RET fusion-positive NSCLC will have been evaluated for response by IRC and followed for at least 6 months from first dose. An additional analysis is included in this briefing book for 34 of the 39 patients with at least one post baseline evaluable disease assessment (or discontinued treatment prior to first post-baseline scan). The confirmed ORR in these 34 patients was 64.7% (22/34; 95% CI: 46.5, 80.3) by investigator assessment, and there are an additional 7 partial responses (PRs) pending confirmation.

Table 3, copied from page 32 of the meeting package, provides the numbers of patients to be included in the original NDA and 60-day update.

Table 3 **Number of patients with adequate follow-up to be included in the original NDA and 60-Day Update**

	Original NDA (n)	60-Day Update (n)
SCE: *RET* fusion-positive NSCLC		
Primary Analysis Set (PAS)[1]	105	105
Integrated Analysis Set (IAS)[2]	106	184
Treatment-naïve NSCLC (SAS1)[2]	13	39
Treated with other therapy NSCLC (SAS2)[2]	12	16
Non-measurable disease NSCLC (SAS3)[2]	5	14
Fusion-positive Thyroid Analysis Set[2, 3]	18	27
Fusion-positive Other Solid Tumors[2]	6	11
SCE: *RET*-mutant MTC		
Primary Analysis Set (PAS)[1]	55	55
Integrated Analysis Set (IAS)[2]	82	124
Cabo/Vande-naïve MTC (SAS1)[2]	44	88
Non-measurable disease MTC (SAS2)[2]	6	14
Fusion-positive Thyroid Analysis Set[2, 3]	18	27

[1] Primary Analysis Set (PAS) is a subset of the Integrated Analysis Set (IAS); SCE = Summary of Clinical Efficacy

[2] Includes all patients in the analysis set who have the opportunity to be followed for at least 6 months from the first dose of selpercatinib to the data cutoff date (per *RET* fusion-positive NSCLC and *RET*-mutant MTC SCE SAPs)

[3] The Fusion-positive Thyroid Analysis Set is the same dataset that is planned to be presented in both SCEs

Proposed Clinical Data Package to support the indication for RET-mutant MTC

The primary efficacy endpoint will be ORR based on RECIST v1.1 as determined by an IRC in the PAS, defined as the first 55 patients with *RET*-mutant MTC enrolled on Study LIBRETTO-001 who meet the following criteria:

- Have evidence of a protocol defined and definitive *RET* mutation as identified by a documented CLIA-certified (or equivalent ex-US) molecular pathology report. Patients with an additional oncogenic driver mutation will be included in the MTC PAS.
- Have measurable disease by RECIST v1.1. Patients without measurable disease who were included dose escalation phase will be included in the PAS.
- Have received one or more lines of prior therapy (cabozantinib or vandetanib).
- Have received one or more doses of selpercatinib.

Based on a data cut-off date of June 17, 2019, 90% of patients in the PAS will have at least 6 months of follow-up from the date of onset of the initial response as determined by the investigator. The ORR for the RET-mutant MTC PAS was 63.6% (35/55; 95% CI: 49.6, 76.2) by IRC. The median DOR by IRC was not reached (95% CI: NE, NE), with

4/35 (11%) events observed. Sixteen patients (45.7% of responders) have been in response for ≥ 6 to <12 months, and six patients (6/35, 17.1%) have been in response for ≥ 12 months. Three patients experienced a complete response (3/55, 5.5%) and the remainder of responders experienced a PR (32/55, 58.2%).

The RET-mutant MTC IAS will include all patients who have received 1 or more lines of prior therapy of cabozantinib and/or vandetanib who have enrolled in the Phase 1 and Phase 2 portions of the LIBRETTO-001 study meeting the PAS eligibility criteria as of the June 17, 2019 data cutoff (n 124). As of the data cutoff, 82 patients had adequate follow-up time (at least 6 months from first dose) to be evaluated for efficacy as defined in the RET-mutant MTC SCE SAP. The ORR in these patients was 58.5%. Two supplemental analysis sets (SAS, SAS1 and SAS2) will include 1) patients who did not have prior exposure to cabozantinib or vandetanib and 2) who did not have measurable disease, respectively, but otherwise meet the criteria outlined in the PAS population. Loxo proposes to submit an amendment containing updated duration of response information using the data cut-off date of June 17, 2019, for the MTC PAS by Day 60 following submission of the original NDA.

Treatment-Naïve RET-Mutant MTC

Loxo proposes that the data from Study LIBRETTO-001 may support approval of selpercatinib in patients with MTC who are naïve to treatment with cabozantinib and vandetanib. As of the June 17, 2019 data cutoff, 88 cabozantinib/vandetanib-naïve RET-mutant MTC patients had been treated with selpercatinib and 44 had been followed for at least 6 months from the first dose. For these patients, the ORR by IRC was 70.5% (31/44; 95% CI: 54.8, 83.2). The median DOR by IRC was not reached (95% CI: NE, NE), with 2/31 (6.5%) events observed. Three (9.7%) of the responding patients experienced a response lasting ≥ 12 months by IRC assessment. Loxo notes that 92% of these cabozantinib/vandetanib-naïve patients experienced progression within 14 months prior to enrollment and compares the response rate in patients who are cabozantinib and vandetanib-naïve to the response rates observed in the randomized studies of cabozantinib (27%) and vandetanib (44%) used to support approval of these products. At the time of the December 16, 2019 data cut-off, Loxo states that all 88 cabozantinib/vandetanib-naïve patients with RET-mutant MTC will have been evaluated for response by IRC and followed for at least 6 months from the first dose of selpercatinib. In the meeting package, Loxo provides an analysis of the 76 of these 88 patients with at least one post-baseline scan (or who discontinued treatment prior to a baseline scan). The ORR in these patients is 47.4% (36/76) by investigator assessment and excludes 9 patients with PRs pending confirmation. Among all cabozantinib/vandetanib-naïve patients with MTC who had at least 1 evaluable post baseline tumor assessment, or discontinued treatment prior to first post baseline tumor assessment as of the initial data cutoff (n=76), the ORR was 51.3% by IRC.

RET-Fusion-Positive Thyroid Cancer

The sponsor proposes to submit data to support consideration of approval of selpercatinib in patients with *RET* fusion-positive thyroid cancer who require systemic therapy. As of the June 17, 2019 data cutoff, 27 patients with *RET* fusion-positive thyroid cancer had been treated with selpercatinib, with 19 patients having received a prior systemic therapy other than radioactive iodine (RAI). Histology for these 19 patients included papillary (n 13), poorly differentiated (n 3), anaplastic (n 2), and Hurthle cell (n 1). Fifteen patients had been followed for at least 6 months from the first dose of selpercatinib and were considered evaluable. The sponsor reports an ORR of 86.7% (13/15; 95% CI: 59.5, 98.3) by IRC. The median DOR by IRC was not reached (95% CI: 7.6, NE), with 3/13 (23%) events observed. Four patients (4/13, 30%) have been in response for ≥ 12 months by IRC. With the 60-day update, based on a December 16, 2019 data cutoff, all 27 patients with *RET* fusion-positive thyroid cancer will be evaluable for a response and followed for at least 6 months from first dose. The sponsor states that, of the three patients with *RET* fusion-positive thyroid cancer who are systemic therapy naïve and have adequate follow-up time were all responders (3/3, 100%).

Safety

The safety analysis will be inclusive of all patients enrolled and treated in the LIBRETTO-001 study with doses ranging from 200 mg QD to 240 mg BID as of June 17, 2019 (n 531). This analysis set includes patients with and without documented RET alterations. A total of 439 patients, including 195 with RET-mutant MTC and 208 with RET fusion-positive NSCLC, were treated at a starting dose of 160 mg BID (recommend Phase 2 dose [RP2D]). The RET fusion-positive NSCLC Safety Analysis Set (n 253) includes all patients with documented RET fusion-positive NSCLC who were enrolled in LIBRETTO-001 and received one or more doses of selpercatinib at starting doses ranging from 200 mg QD to 240 mg BID as of the June 17, 2019 data cutoff date. The RET-mutant MTC Safety Analysis Set (n 226) includes all patients with documented RET-mutant MTC who were enrolled in LIBRETTO-001 and received one or more doses of selpercatinib at starting doses ranging from 200 mg QD to 240 mg BID as of the June 17, 2019 data cutoff date. Four hundred forty-one of 531 patients (83.1%) continue to receive selpercatinib. The most common reason for treatment discontinuation across all analysis sets was disease progression (87%) followed by adverse event (AE) (3.6%). AEs leading to treatment discontinuation all occurred at a frequency of <1%. Most treated patients (97.7%) experienced at least one treatment-emergent AE (TEAE) during the study. Approximately half of patients (51%) had at least one Grade 3-4 TEAE. Serious AEs (SAEs) occurred in 30.3% of patients (6.2% assessed as related to selpercatinib) and 15 patients experienced a fatal TEAE (none assessed as related to selpercatinib). The most common TEAEs (occurring in ≥20%) in the overall safety population were dry mouth (32%), diarrhea (31%), hypertension (29%), AST increase (28%), ALT increase

(26%), fatigue (24%), and constipation (22%). The most common SAEs were ALT increase, AST increase, and pneumonia (2.1% each); dyspnea (1.7%); and hyponatremia (1.5%). Loxo has provided tables of AEs leading to treatment discontinuation, a comparison of common AEs in patients with NSCLC and MTC, and a description of the proposed approach for aggregating preferred terms under composite terms.

60-Day Update:

Loxo proposes to submit a 60-day update including updated safety and efficacy data with a data cutoff of December 16, 2019. This will include an updated safety analysis set (n=650 compared to n=531 for the original data cutoff) and an updated efficacy analysis for all patients treated on or before the original NDA data cutoff date.

Companion Diagnostic:

DISCUSSION

Clinical:

1.& *Background: See pages 26 to 30 and Section 12.1 and 12.2 of the Briefing Document*.

As discussed and agreed during the Type B - Breakthrough Therapy Multidisciplinary (BTD) meetings (RET fusion NSCLC; minutes dated 28 Jan 2019, Reference ID 4381836; RET-mutant MTC; minutes dated 04 Jan 2019, Reference ID 4371585), the NDA will be structured around two primary analysis sets to support Agency review of the following indications:

1. *Selpercatinib is indicated for the treatment of patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy and have progressed following platinum-based chemotherapy.*
2. *Selpercatinib is indicated for the treatment of patients with RET-mutant medullary thyroid cancer (MTC) who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options.*

In addition, as discussed during the Type B - BTD Meetings referenced above, the Sponsor will also be submitting data for patients with RET fusion-positive thyroid cancer, treatment-naïve RET fusion-positive NSCLC and cabozantinib/ vandetanib-naïve RET-mutant MTC. These data sets could potentially support the following alternate indications, with #2 and #3 below subsuming those cited above:

1. *Selpercatinib is indicated for the treatment* (b) (4)
2. *Selpercatinib is indicated for the treatment of patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy*
3. *Selpercatinib is indicated for the treatment of patients with RET-mutant medullary thyroid cancer (MTC) who require systemic therapy*

Given the strength of the data summarized below, does the Agency

a. **agree that the PAS data support subpart H approval for selpercatinib in patients with previously treated RET fusion-positive NSCLC and MTC, and**
b. **wish to consider the broader and additional indication(s) as a review issue?**

FDA Response: FDA agrees that the PAS data is adequate to support the filing of an NDA for the proposed indications in patients with previously treated RET fusion-positive NSCLC and RET-mutant MTC. Whether broader and/or additional indications are supported by the submitted data will be determined during the review of the NDA.

Loxo's emailed response of November 24, 2019: Loxo acknowledged FDA's advice.

Discussion during the meeting on November 25, 2019: No discussion occurred during the meeting.

2.& *Background: See pages 30 to 31 Section 12.1 and 12.2 of the Briefing Document*.

Does the Agency agree that the safety database from the LIBRETTO-001 study is adequate to support the review of safety for selpercatinib?

FDA Response: Yes. FDA agrees the safety data set consisting of 531 patients enrolled in LIBRETTO-001 and treated with at least one dose of selpercatinib as of a June 17, 2019 data cutoff date, including the 439 patients treated at 160 mg BID (RP2D) is adequate to support the review of overall safety for selpercatinib.

Loxo's emailed response of November 24, 2019: Loxo acknowledged FDA's advice.

Discussion during the meeting on November 25, 2019: No discussion occurred during the meeting.

3.& *Background: See pages 31 to 32 and Section 12.1 and 12.2 of the Briefing Document*.

The Sponsor proposes a data cutoff date of 16 December 2019 to support the submission of the Day 60 Safety Update Report, in the form of an addendum to the Summary of Clinical Safety (SCS), an efficacy update in the form of an addenda to the both Summaries of Clinical Efficacy (SCEs), and an updated draft USPI. Does the Agency agree?

FDA Response: FDA agrees with Loxo's proposal to submit the Day 60 update including approximately 650 patients in the safety analysis set and with an updated efficacy analysis in which the patients included in the PAS will not change.

Loxo's emailed response of November 24, 2019: Loxo acknowledged FDA's advice.

Discussion during the meeting on November 25, 2019: No discussion occurred during the meeting.

Clinical Pharmacology

4. *Background: See page 33 and Section 12.1 and 12.2 of the Briefing Document*.

Does the Agency agree that the combined in vitro and in vivo clinical pharmacology results suggest there is unlikely to be any significant impact of a BCRP inhibitor on the PK of selpercatinib and that the plan for no further studies is appropriate for the NDA?

FDA Response: FDA acknowledges Loxo's rationale to suggest that BCRP inhibitors are unlikely to impact the PK of selpercatinib based on in vitro and in vivo clinical pharmacology results. The plan not to conduct any further studies appears acceptable; however, a final determination on the adequacy of the data to support the conclusion will be determined at the time of NDA review.

Loxo's emailed response of November 24, 2019: Loxo acknowledged FDA's advice.

Discussion during the meeting on November 25, 2019: No discussion occurred during the meeting.

Device

5. *Background: See pages 33 to 34 and Section 12.3 of the Briefing Document*.

Does FDA agree with the CDx development and submission plans presented here?

FDA Response: In the absence of a companion diagnostic with demonstrated analytical and clinical performance for clinically relevant RET variants observed in the trial for this therapeutic indication, your proposal to decouple the submission of the drug and device marketing applications may lead to poorly defined target populations post-approval due to the variability across tests (e.g., specific RET variants the test is capable of detecting and sensitivity for such variants) and potential poor performance of locally implemented tests (e.g., false positives/false negatives). You have not provided a satisfactory explanation for the proposed delay in having an FDA approved companion diagnostic for each of the indications.

In section 12.2.3.1.1 of the meeting (pre-NDA) briefing package, you indicated that NSCLC cancer patients with a RET fusion co-occurring with another oncogenic driver were enrolled in LIBRETTO-001. Please provide information regarding the additional co-occurring oncogenic driver mutations to include the specific co-occurring mutations of interest that were evaluated and the number of

patients with the co-occurring mutations in total and per variant. Please provide this information as well as the prevalence of the co-occurring driver mutations to allow the Agency to assess the complete biomarker status of the population evaluated in LIBRETTO-001.

Loxo's emailed response of November 24, 2019:

Explanation for decoupling the NDA and PMA submissions
Decoupling the NDA and PMA submissions accelerated the development of selpercatinib in patients with RET-altered thyroid cancers and NSCLC, populations with high unmet need. With this response, we provide an overview of the companion diagnostic development program alongside key regulatory interactions and ongoing validation work conducted in collaboration with CDx partners (b) (4)

The selpercatinib development program has moved very quickly. The first patient was dosed in May 2017, and we are now in the process of submitting an NDA approximately 2.5 years later. From the outset, in the interest of enrollment, the Sponsor chose to utilize local assays to identify patients. We respected local testing practices and patient referral patterns, rather than ask investigators to accommodate a central assay. We received investigator feedback that to do so would impose demands on scarce tissue samples and cause screening delays, thus creating disincentives for enrollment. We believe the merit of this decision - to use local testing - is manifest in the very robust enrollment of a rare patient population. As of 17 June 2019, 531 patients have been enrolled, based on results from >40 discrete local tests.

In parallel, we quickly launched a companion diagnostic program knowing that protocol- mandated tissue collection would enable the development and validation of a PMA-ready CDx. Relying on draft FDA guidance, "Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product," dated July 2016, we believed the Agency would prioritize the public health benefit of earlier commercial access to selpercatinib, so long as we demonstrated good faith due diligence in bringing a CDx forward.

(b) (4)

(b) (4)

The Sponsor acknowledges the Agency's concern that decoupling the NDA and CDx timelines, "…may lead to poorly defined target populations post-approval due to the variability across tests (e.g., specific RET variants the test is capable of detecting and sensitivity for such variants) and potential poor performance of locally implemented tests (e.g., false positives/false negatives)." The Sponsor believes, however, that the LIBRETTO-001 clinical data themselves provide evidence to significantly mitigate this concern.

Local tests were performed in accredited laboratories (e.g. CLIA/CAP). Tables 1 and 2 illustrate 1) the diversity of LDTs employed; and 2) the consistency of anti-tumor activity for selpercatinib in NSCLC and MTC, independent of assay method. The validation plans for the (b) (4) CDx assays are

structured to ensure that our very favorable real-world results will be maintained as these new assays are approved and enter routine clinical use.

Table 1: Summary of Local LDT for RET Fusion Detection and ORR for NSCLC Patients in the Primary Analysis Set

Laboratory	Test	n	INV ORR
(b) (4)		25	64% (16/25)
		11	72.7% (8/11)
		7	85.7% (6/7)
		6	66.7% (4/6)
		4	100% (4/4)
		4	50% (2/4)
		3	66.7% (2/3)
		3	66.7% (2/3)
		2	50% (1/2)
		2	50% (1/2)
		2	100% (2/2)
		2	100% (2/2)
		2	100% (2/2)
		2	50% (1/2)
		2	100% (2/2)
		28	57% (16/28)

(b) (4)

(b) (4)

Table 2: Summary of Local LDT for RET Mutation Detection and ORR for MTC Patients in the Primary Analysis Set

Laboratory	Test	N	INV ORR
(b) (4)		13	61.5% (8/13)
		7	28.6% (2/7)
		4	50% (2/4)
		4	75% (3/4)
		3	66.7% (2/3)
		2	50% (1/2)
		2	100% (2/2)
		2	100% (2/2)
		18	50% (9/18)

(b) (4)

(b) (4)

Co-occurring oncogenic driver mutations
In LIBRETTO-001, four of the 184 RET fusion-positive NSCLC patients in the IAS (which is inclusive of the PAS) were enrolled with a co-occurring putative NSCLC oncogenic driver. Two were included among the PAS and 2 were included in the IAS only. Among these 4, there were 3 PIK3CA mutations – E545K (2) and H1047L(1). The fourth patient exhibited an L858R EGFR driver mutation albeit in a metachronous lung cancer that had been cured with surgery. One of 3 patients with PIK3CA mutations had a confirmed PR with the other two in SD (tumor reduction) and still on study. The patient with the metachronous EGFR cancer had a confirmed PR.

Our results are consistent with multiple published studies indicating that it is very rare for patients to exhibit a co-occurring oncogenic driver alongside an activating *RET* alteration (Stransky, et al. 2014, Takeuchi, et al. 2012, Wang, et al. 2012 TCGA, et al. 2014, Yoshihara, et al. 2015, Kato et al. 2016, Ji et al. 2015).

Discussion during the meeting on November 25, 2019: Loxo plans to submit a more detailed submission timeline for their companion diagnostic. FDA reiterated their concerns regarding the timing of the clinical submission in relationship to the CDx submission, however, FDA acknowledged that Loxo and (b) (4) are putting forth a concerted effort to accelerate the timeline for a CDx submission. The timing of the NDA submission (clinical) is at Loxo's discretion.

Loxo will also submit supportive information on co-occurring oncogenic driver mutations in all patients, including those in the intent-to-treat population, as well as those treated in their expanded access program.

Regulatory

6. *Background: See pages 32 to 30 and Appendix 1 of the Briefing Document*.

Would the Agency like to have an application orientation meeting with the Sponsor after the submission of the NDA to outline the major components of the NDA?

FDA Response: An application orientation will most likely be requested; however, a formal decision will be made upon receipt of the marketing application.

Loxo's emailed response of November 24, 2019: Loxo acknowledged FDA's advice.

Discussion during the meeting on November 25, 2019: No discussion occurred during the meeting.

7.& *Background: See pages 32 to 30 and Appendix 1 of the Briefing Document*.

As described in Table 1: LOXO-292: Key Global Regulatory Interactions, at the request of FDA on 16 August 2019, an initial Pediatric Study Plan (iPSP/full waiver) for "treatment of patients with metastatic RET fusion positive non-small cell lung cancer (NSCLC), who require systemic therapy and who have progressed following platinum-based chemotherapy and an anti-PD-1 or anti-PD-L1 therapy" was submitted on 30 August 2019. An iPSP for "treatment of patients with RET-mutant medullary thyroid cancer (MTC) who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options" was submitted on 30 August 2019. Both are currently under review and FDA feedback has not been received to date.

If we do not have an agreed-to PSP at the time of NDA submission, does the Agency agree that the NDA will be accepted for filing?

FDA Response: FDA defers to future correspondence regarding the iPSPs for MTC and NSCLC. FDA anticipates that an agreement will be reached regarding the iPSP prior to the filing of the NDA and does not intend to refuse to file the NDA based on the lack of an agreed iPSP, if applicable.

Loxo's emailed response of November 24, 2019: Loxo acknowledged FDA's advice.

Discussion during the meeting on November 25, 2019: No discussion occurred during the meeting.

Additional comments:

Clinical

8.& The Oncology Center for Excellence has developed an Assessment Aid to facilitate FDA's assessment of NDA/BLA applications (including supplements). The Assessment Aid is based on the FDA Multidisciplinary Review template with most sections divided into two parts, clearly delineated to emphasize ownership of each position as either the Applicant's position or the FDA's position. The applicant fills in their positions in the relevant sections; these should be

concise and only include critical information (e.g., should generally be no longer than 100 pages).

FDA would like to offer you the use of the Assessment Aid for the NDA for selpercatinib. If you choose to participate, FDA would expect receipt of the completed Assessment Aid as part of the complete NDA package. An Assessment Aid intended to address multiple indications should contain clearly delineated subsections to address the evaluations of efficacy and safety in each intended population.

FDA would like to discuss the use of the Assessment Aid during the November 25, 2019 meeting. Included with the meeting minutes is the FDA website describing this program.

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

Loxo's emailed response of November 24, 2019: Thank you for the offer to use the Assessment Aid. We look forward to further discussion and details regarding this topic at the meeting.

Discussion during the meeting on November 25, 2019: Loxo will review the assessment aid template and instructions. They will inform FDA if they choice to utilize this review tool prior to the formal submission of the NDA. FDA agreed that it is acceptable to submit the assessment aid within 30 days of the NDA submission. FDA also agreed that the 60 day safety update maybe submitted as an addendum to the assessment aid.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. There was no discussion on the contents of a complete application. As a result, you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or

deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

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.

FDA acknowledges receipt of the February 25, 2019, iPSP for LOXO-292 for treatment of advanced solid tumors including RET-fusion positive solid tumors, MTC and other tumors with RET activation, our Written Response letter requesting revisions to the iPSP issued May 24, 2019, and your July 19, 2019, amendment containing a revised iPSP. We further refer to your two August 30, 2019, amendments containing iPSPs for LOXO-292:

- treatment of adult and pediatric patients with, RET-mutant medullary thyroid cancer (MTC) who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options.

- For the treatment of patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) , who require systemic therapy and who have progressed following platinum-based chemotherapy and an anti-PD-1 or anti-PD-L1 therapy

These submissions are under review and additional comments will be provided under separate cover.

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.[1]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and Pregnancy and Lactation Labeling Final Rule[3] 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

[1] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[2] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[3] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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

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.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[4]

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

- RTOR[5]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid[6]

[4] https://www.fda.gov/media/85061/download
[5] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[6] 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/

MEREDITH LIBEG
12/25/2019 11:48:38 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 *RET*-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 *RET* 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 (Breakthough 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 *RET*-fusion-positive (b) (4) and *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 *RET*-fusion-positive (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 *RET*-fusion-positive (b) (4) and submitted a new request with the indication of *RET*-mutant MTC.

(b) (4) 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 all *RET*-fusion-positive (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-threatening[1])? ☒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 adequeate and sufficiently complete to permit a substantive review?

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

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

[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 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).*

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 BTD request is based on investigator-assesed 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 ith 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 designation[3].

There have been no breakthrough therapy designation requests for other drugs for (b) (4) nor for *RET* fusion-positive NSCLC or thyroid cancer.

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 design[4], 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 ≥ 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 ≥ 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)

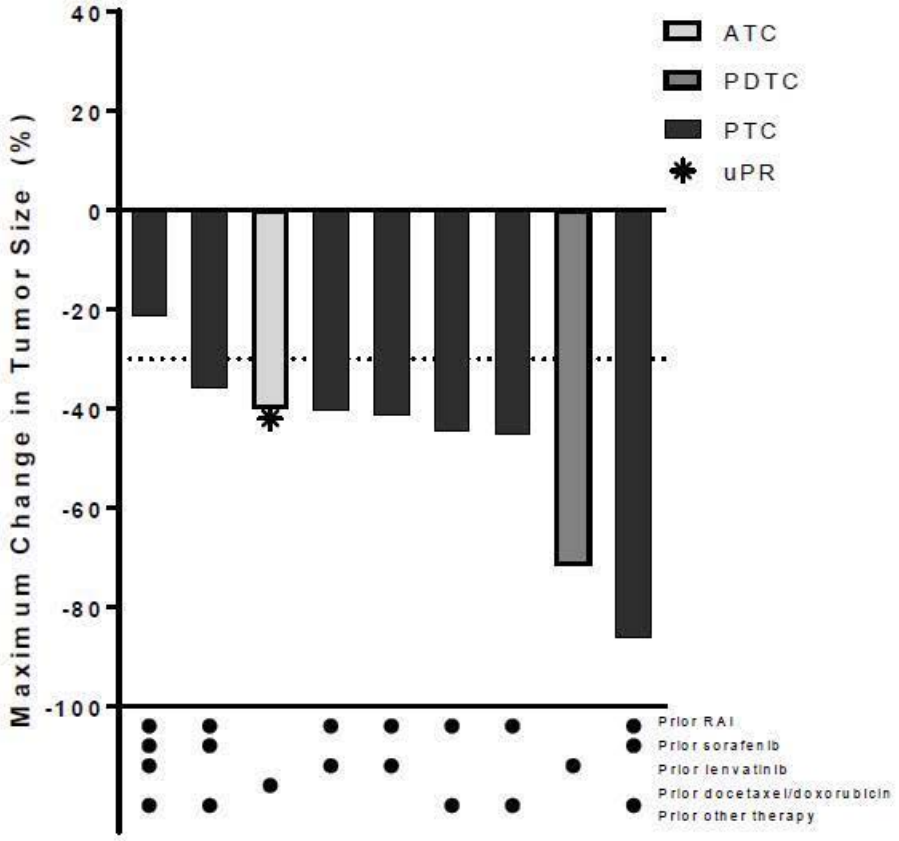
		○ RAI + sorafenib + ≥1 investigational therapy (n=3) ○ RAI + investigational therapy (n=2)
Poorly differentiated thyroid cancer	1	• Lenvatinib (RAI deferred given large volume of disease)
Anaplastic thyroid cancer	1	• Docetaxel and doxorubicin

Table 3: Prior therapies among responding patients by histology

Histology	N (total =8)	Prior Therapy
Papillary thyroid cancer	6	• RAI (n=6) ○ RAI + lenvatinib or sorafenib (n=4) ○ 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.

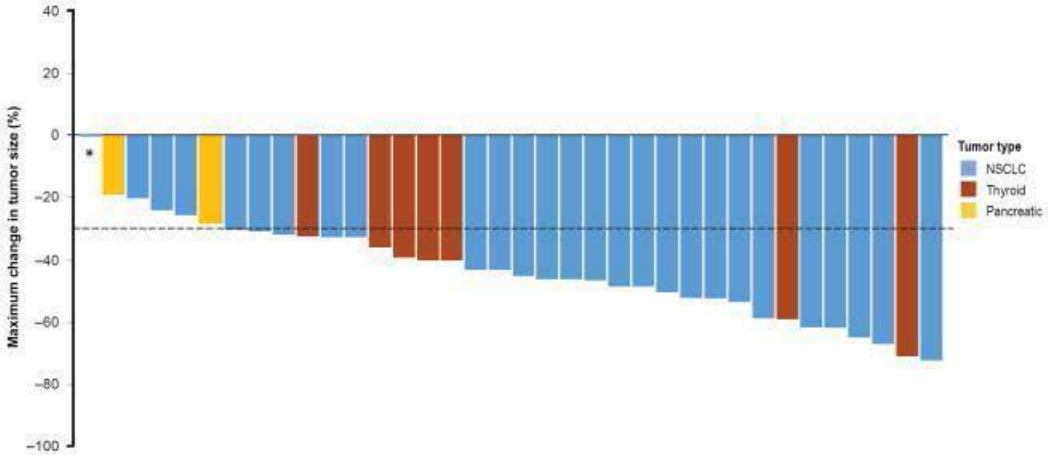
Figure 3 **Efficacy of LOXO-292 in RET Fusion-Positive Thyroid Cancer (Study LOX+O-RET-17001)**



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

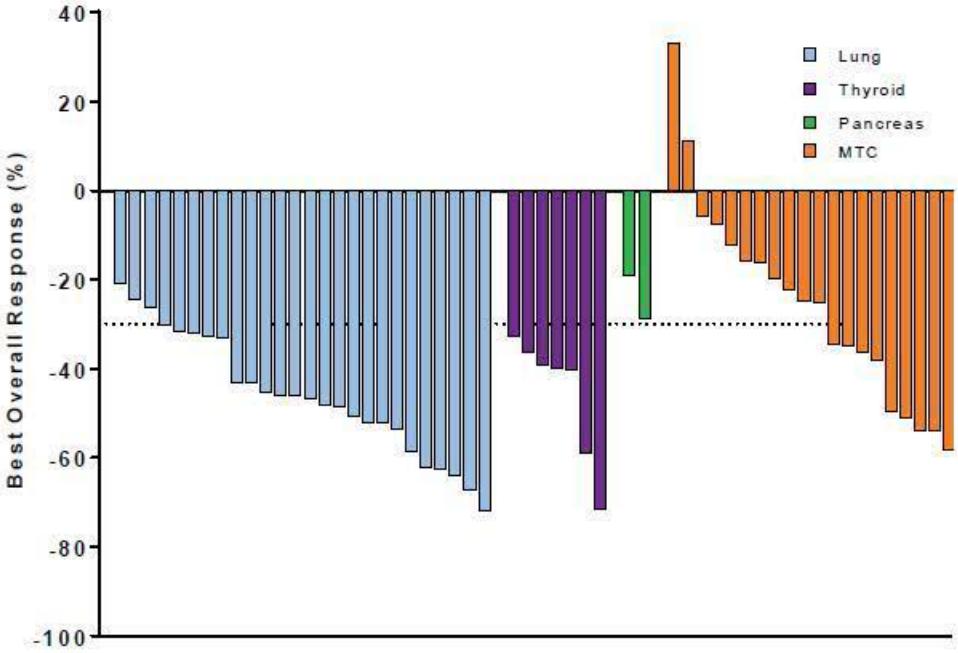


Note: Three patients not displayed due to treatment discontinuation prior to first post-baseline response assessment;
*Denotes patient with 0% maximum change in tumor size

Cutoff date: 02 April 2018.

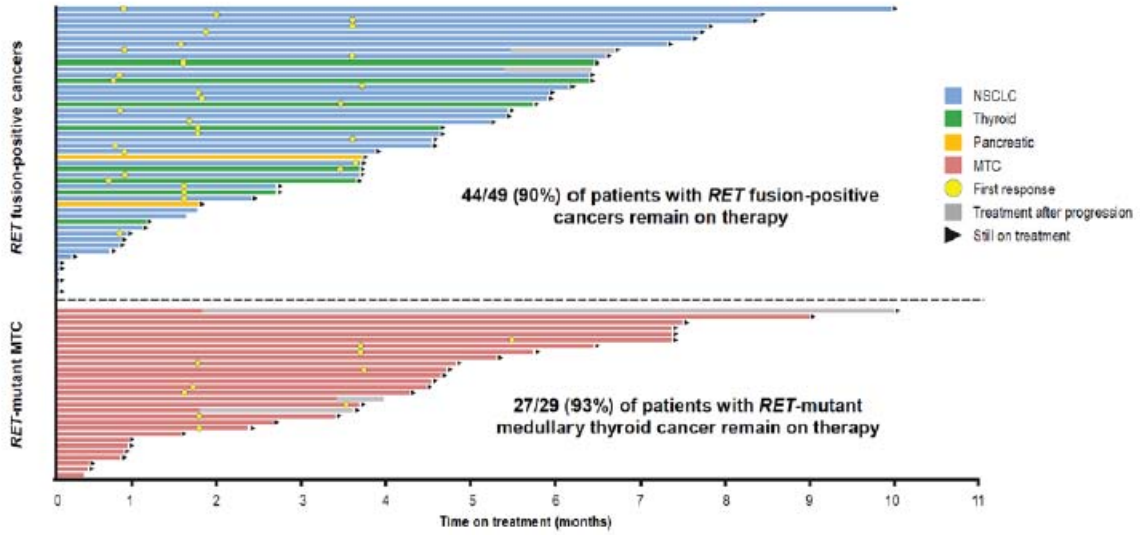
Source: (Drilon, 2018)

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)**



Cutoff date: 02 April 2018.
Source: (Drilon, 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%), increasd 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) [redacted]

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	07/03/2018
Product	LOXO-292
Indication	For the treatment of patients with metastatic *RET*-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 *RET* 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 (Breakthough 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 (b) (4) *RET*-fusion-positive non-small cell lung cancer who require systemic therapy, have progressed following (b) (4)

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

For the treatment of patients with advanced *RET*-fusion-positive (b) (4) and *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 *RET*-fusion-positive (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 *RET*-fusion-positive (b) (4) and submitted a new request with the indication of *RET*-mutant MTC.

(b) (4)

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-threatening[1])? ☒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 adequeate and sufficiently complete to permit a substantive review?

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

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

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)

---

[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 ≥ 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, entitled "A Phase 1 Study of Oral LOXO-292 in Adult Patients with Advanced Solid Tumors Harboring RET Alterations." 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 [redacted] (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 RET fusion-positive solid tumors 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 RET fusion-positive solid tumors, 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 BTD request is based on investigator-assesed 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 +ramicurimab. 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 or RET fusion-positive solid tumors in general.

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

requested breakthrough therapy designation[3].

There have been no breakthrough therapy designation requests for *RET* fusion-positive (b) (4) nor for *RET* fusion-positive NSCLC. (b) (4)

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 rearrangment-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 design[4], 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 ≥ 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 ≥ 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.

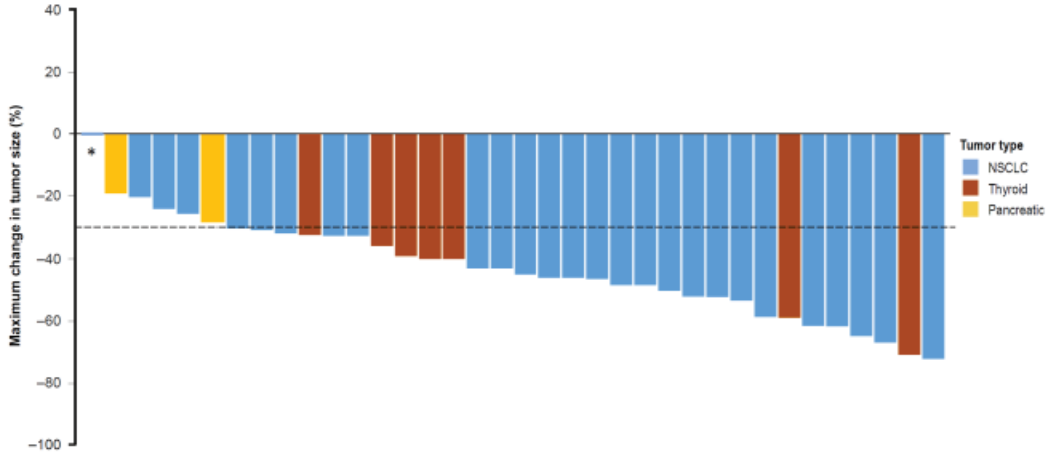
Loxo reports durable responses for 39 evaluable patients with RET fusion positive tumors receiving LOXO-292, with a confirmed overall response rate (ORR) of 77% ; 95% CI: 61, 89) was identified by investigator assessment. As of June 14, 2018, responses were ongoing for 29 of the 30 responding patients 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.

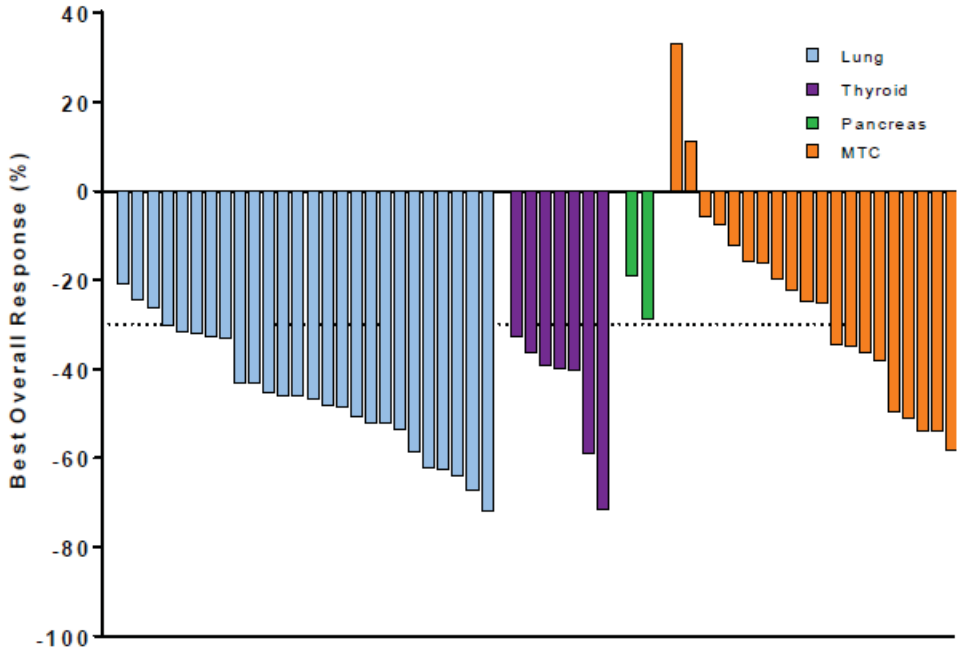
Figure 3 Efficacy of LOXO-292 in *RET* fusion-positive cancers (Study LOXO-RET-17001)

A. Per Tumor Type



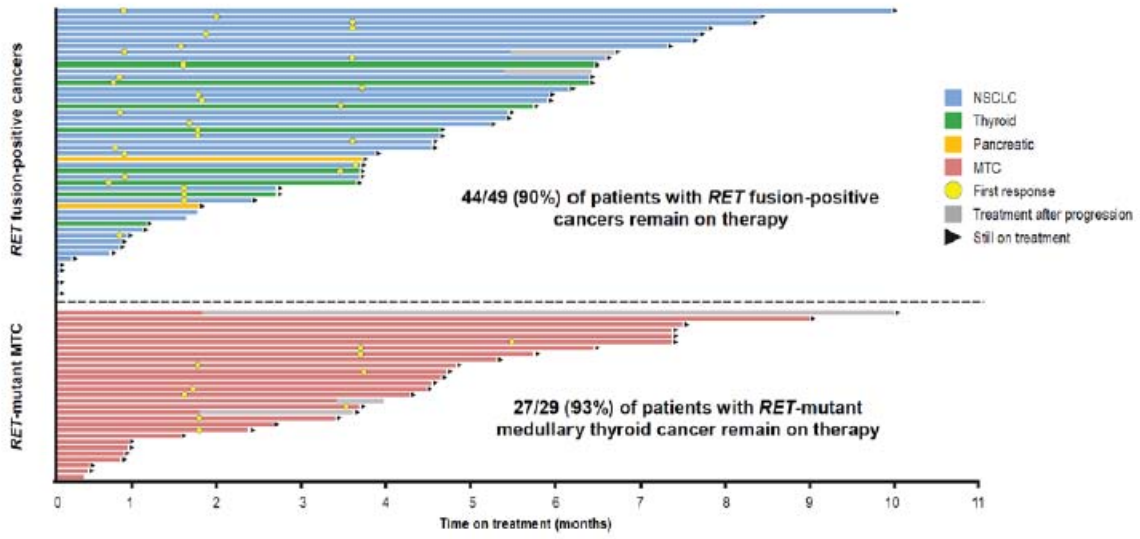
Note: Three patients not displayed due to treatment discontinuation prior to first post-baseline response assessment;
*Denotes patient with 0% maximum change in tumor size
Cutoff date: 02 April 2018.
Source: (Drilon, 2018)

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)**



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%), increasd 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:

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

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

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 plust gemcitabline with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cel 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.

Sabari JK, et al, RET-rearranged lung cancers: immunophenotyped and response to immunotherapy. J Clin Oncol 36, 2018 (suppl; abstr 9034).

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

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 *RET*-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 *RET* 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 (Breakthough 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):**
   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.

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-threatening[1]? ☒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 adequeate and sufficiently complete to permit a substantive review?

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

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

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 exent 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, entitled "A Phase 1 Study of Oral LOXO-292 in Adult Patients with Advanced Solid Tumors Harboring RET Alterations." 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 RET fusion-positive solid tumors 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 RET fusion-positive solid tumors, 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 BTD request is based on investigator-assesed 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 designation[3].

There have been no requests for breakthrough therapy designation for medullary thyroid carcinoma. There have been no breakthrough therapy designation requests for *RET* fusion-positive (b) (4) nor in *RET* fusion-positive NSCLC or papillary thyroid cancer (PTC). (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 design[4], 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 ≥ 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 ≥ 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

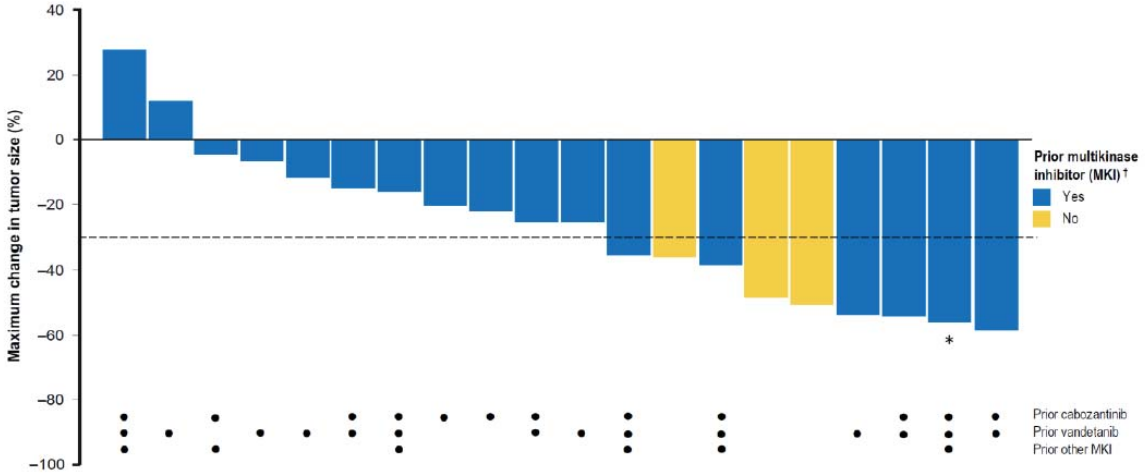
Table 3: Responses in Patients with Measurable Disease Only

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

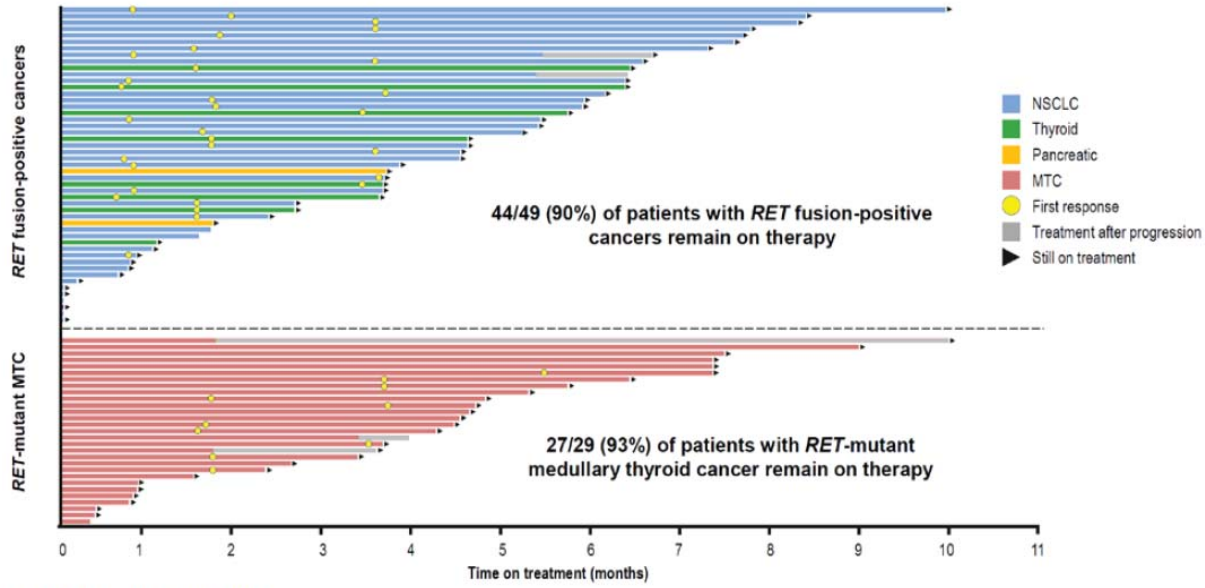
The figures below, reproduced from the sponsor's request for Breakthrough Designation, demonstrate waterfall and swimmers plots from patients on Study LOXO-RET-17001, with a data cutoff of April 2, 2018.

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