CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213246Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

[FDA will complete this section.]

Application Type	NME
Application Number(s)	213246
Priority or Standard	Priority
Submit Date(s)	December 4, 2019
Received Date(s)	December 4, 2019
PDUFA Goal Date	August 4, 2020
Division/Office	Division of Oncology 2/Office of Oncologic Diseases
Review Completion Date	May 8, 2020
Established Name	Selpercatinib
(Proposed) Trade Name	Retevmo
Pharmacologic Class	Kinase inhibitor
Code name	LOXO-292
Applicant	Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company
Dosing form	Capsule
Dosing Regimen	The proposed dosing regimen is 160 mg orally twice daily for patients ≥ 50 kg and 120 mg orally twice daily for patients < 50 kg until disease progression or unacceptable toxicity.
Applicant Proposed Indication(s)/Population(s)	• Metastatic RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy, • RET-mutant medullary thyroid cancer (MTC) who require systemic therapy, or • Advanced RET fusion-positive thyroid cancer who require systemic therapy (b) (4)
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	• Adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)

	• Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy • Adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

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Reviewers of Multi-Disciplinary Review and Evaluation

[FDA will complete this section.]

Regulatory Project Manager	Autumn Zack-Taylor
Pharmacology/Toxicology Reviewer(s)	Amy Skinner
Pharmacology/Toxicology Team Leader(s)	Whitney Helms
Office of Clinical Pharmacology Reviewer(s)	Lauren Price, Rosane Charlab Orbach, Yangbing Li, Ying-Hong Wang
Office of Clinical Pharmacology Team Leader(s)	Jeanne Fourie-Zirkelbach, Michael Pacanowski, Jiang Liu, Xinyuan Zhang
Clinical Reviewer	Diana Bradford
Clinical Team Leader	Suzanne Demko & Erin Larkins
Safety Analyst (if applicable)	Min Wang
Statistical Reviewer	Sirisha Mushti
Statistical Team Leader	Lisa Rodriguez
Cross-Disciplinary Team Leader	Diana Bradford (acting)
Division Director (DHOT)	John Leighton
Division Director (OCP)	Nam Atiqur Rahman
Division Director (OB/DBV)	Shenghui Tang (acting)
Division Director (OOD)	Harpreet Singh
Office Director (or designated signatory authority)	Marc Theoret

Additional Reviewers of Application

OPQ	Xing Wang (ATL)
Microbiology	
OPDP	Nazia Fatima
OSI	Michele Fedowitz
OSE/DEPI	Steven Bird
OSE/DMEPA	Janine Stewart
OSE/DRISK	Mei Yean Chen
Other	

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Appears this way on original

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine amino transferase
AST	aspartate amino transferase
ATA	American Thyroid Association
ATC	anaplastic thyroid cancer
AUC	area under the curve
BLA	biologics license application
BID	twice a day
BMI	body mass index
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSA	body surface area
BTD	Breakthrough Designation
CAP	College of American Pathologists
CBER	Center for Biologics Evaluation and Research
CCDC6	Coiled-coil domain-containing protein 6
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CT	computed tomography
CV	coefficient of variation
CYP3A4	cytochrome P450 3A4
DLT	dose limiting toxicity

DMC	data monitoring committee
DOR	duration of response
DTC	differentiated thyroid cancer
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FISH	Fluorescence In Situ Hybridization
FTC	follicular thyroid cancer
GCP	good clinical practice
GDNF	glial cell-line derived neurotrophic factor
GFLs	GDNF family ligands
GFR	GDNF family receptor-alpha
GI	gastrointestinal
GLP	good laboratory practice
GM	geometric mean
GRMP	good review management practice
HCl	hydrogen chloride
hERG	human Ether-a-go-go related gene
HR	hazard ratio
IAS	integrated analysis set
IC	inhibitory concentration
ICI	immune checkpoint inhibitor
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRC	independent review committee
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
JAK-STAT	Janus Kinase-Signal Transducer and Activator of Transcription
KIF5B	Kinesin Familty Member 5B
LOXO-292	selpercatinib (investigational product)
LPS	Lansky Performance Score
LTFU	Long-term Follow-up
MAPK	Mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEN	multiple endocrine neoplasia

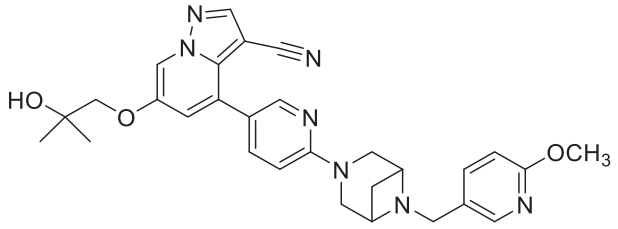
mITT	modified intent to treat
MKI	multikinase inhibitor
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NE	not evaluable
NGS	next generation sequencing
NME	new molecular entity
NOAEL	no observed adverse effect level
NR	not reached
NSCLC	non-small cell lung cancer
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSAS	overall safety analysis set
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAS	primary analysis set
PBPK	physiologically-based pharmacokinetic
PBRER	Periodic Benefit-Risk Evaluation Report
PCR	polymerase chain reaction
PD	pharmacodynamics
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PDTC	poorly differentiated thyroid cancer
PFS	progression free survival
P-gp	P-glycoprotein
PI	prescribing information
PI3K	phosphatidylinositol-3-kinase
PK	pharmacokinetics
PKA	protein kinase A
PKC	protein kinase C
PMC	postmarketing commitment
PMR	postmarketing requirement
PopPK	population PK
PP	per protocol
PPI	patient package insert
PPI	proton pump inhibitor
PR	partial response
PREA	Pediatric Research Equity Act

PRO	patient reported outcome
PSUR	Periodic Safety Update report
PTC	papillary thyroid cancer
QC	quality control
QD	once daily
QLQ-C30	Quality of Life Questionnaire-Core 30
QTc	corrected QT interval
RAI	radioactive iodine
RANO	Response Assessment in Neuro-Oncology Criteria
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
RET	Rearranged during transfection
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SAS	supplemental analysis set
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SFU	Safety Follow-up
SGE	special government employee
SOC	standard of care
SPP	single patient protocol
SRC	Safety Review Committee
TEAE	treatment emergent adverse event
TPS	tumor proportion scores
TSH	thyroid-stimulating hormone
USPI	United States prescribing information

1 Executive Summary

1.1 Product Introduction

On December 4, 2019, Loxo Oncology (Loxo) submitted original New Drug Application (NDA) 213246 under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) seeking approval of selpercatinib (Retevmo) for the treatment of patients with metastatic RET fusion-positive non- small cell lung cancer (NSCLC) (b) (4) and for the treatment of RET mutant MTC who require systemic therapy, (b) (4) . Selpercatinib (also known as LOXO-292) is an inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase as well as VEFGR1 and VEGFR3. Gene rearrangements (fusions) and mutations in RET have the potential to be oncogenic drivers and have been observed in a variety of tumors types, with fusions observed in non-small cell lung cancer (NSCLC) and thyroid cancer and mutations observed in medullary thyroid cancer. Selpercatinib is being developed as an anti-cancer agent for the treatment of patients with RET mutant MTC, RET fusion-positive NSCLC, and RET fusion-positive thyroid cancer. The molecular formula for selpercatinib is: $C_{29}H_{31}N_7O_3$ and the molecular weight is 525.61 g/mol. The chemical name is 6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. Selpercatinib has the following chemical structure:



Source: Product Labeling, Section 11

Selpercatinib is a new molecular entity; selpercatinib has not been previously marketed in the U.S. and has not been approved for any indication by FDA.

1.2 Conclusions on the Substantial Evidence of Effectiveness

In the opinion of the review team, the submitted evidence meets the statutory evidentiary standard for accelerated approval. The recommendation for accelerated approval is based on the results from a single multicenter, single-arm, open-label, first-in-human, dose escalation and expansion study (LIBRETTO-001) which enrolled patients with advanced solid tumors with a

RET fusion or mutation as detected by a CLIA-certified (or equivalent) laboratory. This study enrolled patients with three primary tumor types which form the basis of this application: patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC), patients with advanced or metastatic *RET* mutant medullary thyroid cancer (MTC), and patients with *RET* fusion-positive thyroid cancer. The primary efficacy populations for each tumor type included patients with a documented RET mutation or fusion, measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, sufficient follow-up to make a determination of efficacy and safety, and who received at least one dose of selpercatinib. The primary efficacy populations for each tumor type included 105 patients with *RET* fusion-positive NSCLC previously treated with platinum chemotherapy, 39 patients with *RET* fusion-positive NSCLC who were naïve to systemic therapy, 55 patients with *RET* mutant MTC previously treated with cabozantinib or vandetanib, 88 patients with *RET* mutant MTC who were naïve to systemic therapy, and 27 patients with *RET* fusion-positive thyroid cancer who were radioactive iodine (RAI)-refractory (if appropriate for their tumor histology). The analysis of efficacy in each tumor type demonstrated a large, clinically meaningful, and durable overall response rate (ORR) per blinded independent central review (BICR).

<u>RET fusion-positive NSCLC</u>
The confirmed ORR in patients with metastatic, treatment-naïve RET fusion-positive NSCLC (n=39) per BICR was 84.6% (95% CI: 69.5%, 94.1%), with 42.4%, 12.1%, and 3% of the 33 responders having observed DOR of of 6 – 12, 12 – 18, and ≥18 months, respectively. Since only 3% of patients had an observed DOR of ≥ 18 months and follow-up is short, the estimated median DOR may not be a reliable estimate of the true median DOR; therefore, the estimated median DOR will not be included in product labeling. The lower limit of the 95% CI for ORR with selpercatinib (69.5) in the treatment naïve patients excludes the ORR observed in clinical trials of other therapies approved for the first-line treatment of an unselected population of patients with NSCLC or non-squamous NSCLC (i.e., chemotherapy plus anti-PD-(L)1 antibody, ORR 48% to 58%). In 105 patients with metastatic RET fusion-positive NSCLC (the primary analysis set, or PAS), the ORR per BICR was 63.8% (95% CI: 53.9%, 73.0%) and with 44.8%, 29.9%, and 4.5% of responders having observed DOR of 6 – 12, 12 – 18, and ≥18 months, respectively. The lower limit of the 95% CI for ORR for selpercatinib in the treatment of platinum-treated patient (59.8%) excludes the ORR observed in clinical trials of approved therapies for second-line treatment of an unselected population of patients with NSCLC (i.e., ramucirumab plus docetaxel, ORR 23%).

Assessment of the anti-tumor activity of selpercatinib in the CNS was pre-specified in the plan for analysis specifically as descriptive analyses of intracranial ORR (IC-ORR) and IC-DOR as secondary endpoints. The PAS in NSCLC (n=105) included 11 patients with measurable CNS metastases at baseline per BICR and who had not received radiation to the brain within 2 months of first dose of selpercatinib; 10 of these patients had confirmed IC response (ORR 90.9%). Given the limited number of patients, the point estimate for these results needs to be interpreted with caution; however, the results do support a conclusion that selpercatinib has

anti-tumor activity in the CNS in patients with RET fusion-positive NSCLC with brain metastases. Given the rarity of RET fusion-positive NSCLC and the magnitude of the response observed in LIBRETTO-001, a randomized trial may not be feasible. The review team considers that the ORR, which is large in magnitude, along with the observed duration of responses, in patients treated with selpercatinb is sufficient to establish clinical benefit in the genetically defined (RET fusion-positive), rare subgroup of patients with metastatic NSCLC. Data from additional patients with NSCLC (treatment naïve and platinum-treated) including overall response rate and duration of response, will be required as a post-marketing requirement to confirm clinical benefit.

RET mutant MTC

Confirmed ORR per BICR in patients 12 years of age and older with advanced or metastatic RET mutant MTC who are naïve to cabozantinib and vandetanib was 72.7% (95% CI: 62.2%, 81.7%), with 37.5%, 20.3%, and 3.1% of responders having observed DOR of 6 – 12, 12 – 18, and ≥18 months, respectively. The lower bound of the 95% CI for ORR in this population excludes that of available therapy (i.e., vandetanib, ORR 45%) for a biomarker-unselected population with MTC. In patients who had previously received an approved therapy (cabozantinib, vandetanib, or both, n=55), the ORR per BICR was 69.1% (95% CI: 55.2%, 80.9%) with 21.2%, 36.8%, and 18.4% of responders having an observed DOR of of 6 – 12, 12 – 18, and ≥18 months, respectively. These patients have no approved therapies, and there are no approved therapies specifically for RET mutant MTC. The review team considers that the ORR, which is large in magnitude, along with the observed duration of responses, in patients treated with selpercatinb is sufficient to establish clinical benefit in the genetically defined subgroup of patients with advanced or metastatic *RET*-mutant MTC. Data from additional patients with treatment-naïve MTC will be required as a post-marketing requirement to confirm clinical benefit.

RET fusion-positive thyroid cancer

Patients ages 12 years of age and older with advanced *RET* fusion-positive thyroid cancer included patients who were RAI-refractory (if appropriate), and patients who were RAI refractory and had received a subsequent systemic therapy (hereafter referred to as "previously treated") and patients who had received RAI alone. The 19 patients who were previously treated demonstrated an ORR 78.9% (95% CI: 54.4%, 93.9%), with 40%, 26.7%, and 20% of responders having an observed DOR of 6 – 12, 12 – 18, and ≥18 months, respectively. Among 8 patients with *RET* fusion-positive thyroid cancer who had received RAI but not a subsequent therapy, 100% (95% CI 63%, 100%) demonstrated a response, with 62.5% and 12.5% of patients demonstrating an observed DOR of 6 – 12 and 12 – 18 months, respectively. Though there were few patients with histologic subtypes other than papillary thyroid cancer (n=6), responses were observed in patients across histologic subtypes of thyroid cancer, including poorly-differentiated thyroid cancer and anaplastic thyroid cancer. Both lenvatinib and sorafenib are approved in patients with differentiated thyroid cancer who are RAI-refractory, but there are no approved therapies in the second-line post-RAI setting or for RET fusion-positive thyroid cancers specifically. The response rate in this rare molecularly-defined subset of patients compares favorably to the response rates observed in studies of lenvatinib

(65%) and sorafenib (12%) for a broader population of patients with RAI-refractory differentiated thyroid cancer, regardless of *RET* mutation status. The review team considered that the evidence of efficacy in *RET* fusion-positive thyroid cancer is supported by the comparably high, durable response rates observed in response to selpercatinib in the other *RET*-driven cancers described in the application. Data from additional patients to confirm clinical benefit will be required as a post-marketing requirement.

1.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Metastatic NSCLC is a life-threatening condition with poor survival. The 5-year survival for this population is less than 5%. The incidence of *RET* gene fusions in metastatic NSCLC is 1-2%. There are no approved treatments for RET mutant NSCLC. Treatment options for patients with *RET* fusion-positive NSCLC include regimens used for first-line systemic therapy an unselected population of patients with NSCLC or non-squamous NSCLC (i.e., chemotherapy and/or anti-PD-(L)1 antibody). The highest ORRs, 48% and 58%, have been reported for platinum-based chemotherapy plus pembrolizumab (regardless of histology) and platinum-based chemotherapy plus atezolizumab and bevacizumab (non-squamous NSCLC), respectively. In the second line, there are several therapeutic options for the general population of patients with metastatic NSCLC with a maximum ORR of 23% (ramucirumab/docetaxel).

Advanced or metastatic *RET* mutation-positive MTC is a life-threatening condition; although prolonged survival is possible in patients with limited disease, patients with advanced, progressive disease have poor survival. Five-year relative survival for patients with stage IV disease is approximately 28%. Treatment options for patients with RET mutation-positive MTC include therapies for patients with advanced or metastatic, progressive or symptomatic MTC, the TKIs cabozantinib and vandetanib. Both these products inhibit *RET* in addition to other kinases, but are not approved solely for the treatment of patients with RET mutations. The ORRs for vandetanib and cabozantinib as evaluated in the studies to support approval were 45% and 28%, respectively.

Patients with metastatic *RET* fusion-positive DTC that is refractory to RAI, and patients with RET fusion-positive anaplastic thyroid cancer face an unmet medical need. Treatment options for patients with RET fusion-positive thyroid cancer include radioactive iodine (if appropriate based on the underlying histology), lenvatinib and sorafenib for patients with DTC that is RAI-refractory, and doxorubicin (approved for thyroid carcinoma). The ORR demonstrated in the studies supporting the approvals of lenvatinib and sorafenib in patients with RAI-refractory DTC were 65% and 12%, respectively.

Selpercatinib is an inhibitor of the RET receptor tyrosine kinase. The proposed dosing regimen is 160 mg orally twice daily for patients ≥ 50 kg and 120 mg orally twice daily for patients < 50 kg until disease progression or unacceptable toxicity. Loxo's proposed indications for selpercatinib are for the treatment of 1) adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC), 2) patients ≥ 12

years old with *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy and 3) patients ≥ 12 years old with advanced *RET* fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine refractory (if radioactive iodine is appropriate).

The primary efficacy data supporting this NDA are from a single multicenter, single-arm, open-label, first-in-human, dose escalation and expansion study (LIBRETTO-001). The analysis populations for each disease type included patients who demonstrated a protocol-defined *RET* fusion or mutation identified based on a CLIA-certified (or equivalent) test with measurable disease per RECIST v 1.1, received one or more doses of selpercatinib, and had been followed for ≥ 6 months from the first dose of selpercatinib at the time of the original data cut-off.

RET fusion-positive NSCLC

The confirmed ORR in patients with metastatic, treatment-naïve *RET* fusion-positive NSCLC (n=39) per BICR was 84.6% (95% CI: 69.5%, 94.1%), with 42.4%, 12.1%, and 3% of the 33 responders having observed DOR of of 6 – 12, 12 – 18, and ≥18 months, respectively. Since only 3% of patients had an observed DOR of ≥ 18 months and follow-up is short, the estimated median DOR may not be a reliable estimate of the true median DOR; therefore, the estimated median DOR will not be included in product labeling. The lower limit of the 95% CI for ORR with selpercatinib (69.5) in the treatment naïve patients excludes the ORR observed in clinical trials of other therapies approved for the first-line treatment of an unselected population of patients with NSCLC or non-squamous NSCLC (i.e., chemotherapy plus anti-PD-(L)1 antibody, ORR 48% to 58%). In 105 patients with metastatic *RET* fusion-positive NSCLC (the primary analysis set, or PAS), the ORR per BICR was 63.8% (95% CI: 53.9%, 73.0%) and with 44.8%, 29.9%, and 4.5% of responders having observed DOR of 6 – 12, 12 – 18, and ≥18 months, respectively. The lower limit of the 95% CI for ORR for selpercatinib in the treatment of platinum-treated patient (59.8%) excludes the ORR observed in clinical trials of approved therapies for second-line treatment of an unselected population of patients with NSCLC (i.e., ramucirumab plus docetaxel, ORR 23%).

Assessment of the anti-tumor activity of selpercatinib in the CNS was pre-specified in the plan for analysis as descriptive analyses of intracranial ORR (IC-ORR) and IC-DOR as secondary endpoints. The PAS in NSCLC (n=105) included 11 patients with measurable CNS metastases at baseline per BICR and who had not received radiation to the brain within 2 months of first dose of selpercatinib; 10 of these patients had confirmed IC response (ORR 90.9%). Given the limited number of patients, the point estimate for these results needs to be interpreted with caution; however, the results do support a conclusion that selpercatinib has anti-tumor activity in the CNS in patients with RET fusion-positive NSCLC with brain metastases. Given the rarity of RET fusion-positive NSCLC and the magnitude of the response observed in LIBRETTO-001, a randomized trial may not be feasible. The review team considers that the ORR, which is large in magnitude, along with the observed duration of responses, in patients treated with selpercatinb is sufficient to establish clinical benefit in the genetically defined (*RET* fusion-positive), rare

subgroup of patients with metastatic NSCLC. Data from additional patients with NSCLC (treatment naïve and platinum-treated) including overall response rate and duration of response, will be required as a post-marketing requirement to confirm clinical benefit.

RET mutant MTC

Confirmed ORR per BICR in patients with advanced or metastatic *RET* mutant MTC who are naïve to cabozantinib and vandetanib was 72.7% (95% CI: 62.2%, 81.7%), with 37.5%, 20.3%, and 3.1% of responders having observed DOR of 6 – 12, 12 – 18, and ≥18 months, respectively. The lower bound of the 95% CI for ORR in this population excludes that of available therapy (i.e., vandetanib, ORR 45%) for a biomarker unselected population with MTC. In patients who had previously received an approved therapy (cabozantinib, vandetanib, or both, n=55), the ORR per BICR was 69.1% (95% CI: 55.2%, 80.9%) with 21.2%, 36.8%, and 18.4% of responders having an observed DOR of of 6 – 12, 12 – 18, and ≥18 months, respectively. These patients have no approved therapies, and there are no approved therapies specifically for *RET* mutant MTC. The review team considers that the ORR, which is large in magnitude, along with the observed duration of responses, in patients treated with selpercatinib is sufficient to establish clinical benefit in the genetically defined subgroup of patients with advanced or metastatic MTC. Data from additional patients with treatment-naïve MTC will be required as a post-marketing requirement to confirm clinical benefit.

RET fusion-positive thyroid cancer

Patients with RET fusion-positive thyroid cancer included patients who had received radioactive iodine (if appropriate based on histology) and a subsequent systemic therapy demonstrated an ORR 78.9% (95% CI: 54.4%, 93.9%), with 40%, 26.7%, and 20% of responders having an observed DOR of 6 – 12, 12 – 18, and ≥18 months, respectively. The majority of patients in the efficacy population (n=21) had papillary thyroid cacner, but responses were observed in patients across histologic subtypes of thyroid cancer, including poorly-differentiated thyroid cancer, Hurthle cell histology, and anaplastic thyroid cancer. Both lenvatinib and sorafenib are approved in patients with differentiated thyroid cancer who are RAI-refractory, but there are no approved therapies in the second-line post-RAI setting or for *RET* fusion-positive thyroid cancers specifically. Among 8 patients with *RET* fusion-positive thyroid cancer who had received RAI but not a subsequent therapy, 100% (95% CI 63%, 100%) demonstrated a response, with 62.5% and 12.5% of patients demonstrating an observed DOR of 6 – 12 and 12 – 18 months, respectively. The results are supported by the comparably high, durable response rates observed in response to selpercatinib in the other *RET* -driven cancers described in the application. Data from additional patients to confirm clinical benefit will be required as a post-marketing requirement.

The safety of selpercatinib was evaluated in patients ≥ 12 years of age enrolled in a single multicenter, single-arm, open-label, first-in-human, dose escalation and expansion study (LIBRETTO-001, NCT03157128). Patients in the Phase 1 dose escalation and expansion phase were required to have progressed on or to be intolerant to available therapies, have no standard or curative therapy available, be unlikely to tolerate

or derive significant clinical benefit from standard of care therapy (in the opinion of the investigator), or have declined standard therapy. Patients in the Phase 2 portion were either naïve to approved therapies, or had failed available approved therapy and were enrolled in separate cohorts according to prior therapy and disease type (*RET* fusion-positive tumors vs. *RET* mutation-positive MTC).

The population characteristics were: median age 59 years (range: 15 to 92 years); 52% were male; and 69% were White, 22% were Asian, 5% were Hispanic/Latino, and 3% were Black. The most common tumors were NSCLC (47%), MTC (43%), and non-medullary thyroid carcinoma (5%). Most patients (95%) received at least one dose of the recommended dose of 160 mg BID (86.8% of patients received 160 mg BID as the starting dose). Although assessment of a causal relationship between selpercatinib and adverse events (AEs) was somewhat limited in the context of the single arm design of trials providing safety data, AEs observed in patients treated with selpercatinib were consistent with the mechanism of action (multiple kinase inhibition) and toxicities observed in preclinical studies with selpercatinib. The most common adverse reactions (≥ 20%) in order of decreasing frequency were dry mouth, diarrhea, hypertension, fatigue, edema, AST increased, ALT increased, rash, constipation, headache, nausea, and abdominal pain. The most common laboratory abnormalities (≥ 20%) worsening from baseline were AST increased, ALT increased, glucose increased, white cell count decreased, calcium decreased, albumin decreased, creatinine increased, alkaline phosphatase increased, platelets decreased, total cholesterol increased, sodium decreased, magnesium decreased, potassium increased, bilirubin decreased, and glucose decreased. The primary serious risks of selpercatinib are hepatotoxicity, QT prolongation, hypertension, hemorrhagic events, and hypersensitivity reactions. These adverse reactions largely appear manageable and reversible with dose modification or discontinuation of selpercatinib and are adequately addressed in product labeling. Given the occurrence of rare but serious (including fatal) bleeding events, a Warning has been included in the product label.

Increased AST of any grade occurred in 51% of patients and increased ALT of any grade occurred in 45%. Grade 3 to 4 increased AST or ALT occurred in 7.5% and 9.1% of patients, respectively. Among the 697 patients who received selpercatinib across the clinical trials, 15% of patients with at least one post-baseline ECG assessment experienced QTc interval prolongation of >60 ms after starting selpercatinib and 5.6% had a QTc interval >500 ms. (b) (4) Monitoring guidelines for QT prolongation are included in the Warning. Hypertension occurred in 35% of patients, including (b) (4)% of patients with Grade 3 hypertension and 0.1% with Grade 4 hypertension. The package insert will include language in Warnings and Precautions to describe this risk. Hemorrhagic events of any Grade occurred in approximately 15% of patients. Severe including fatal hemorrhagic events occurred in 2.3% of patients who received selpercatinib with 0.4% of patients experiencing a fatal hemorrhagic event. Hypersensitivity occurred in 4.3% of patients receiving selpercatinib , including a Grade 3

event in 1.6%. Guidelines for treatment and gradual reintroduction of selpercatinib are included in the product label. A Warning has also been included regarding the potential for impaired wound healing as a class effect of drugs that inhibit VEGF.

Preclinical studies demonstrated significant physeal hypertrophy and tooth dysplasia in 4-week general toxicology studies. In the adolescent patients studied in LIBRETTO-001, and in limited data provided from compassionate use experience in pediatric patients, there have been no specific safety signals identified for pediatric or adolescent patients, but additional study is needed. The Applicant has committed to a post-marketing requirement (PMRs) for the conduct of additional studies to further characterize the safety profile of selpercatinib in adolescents, specifically with regards to growth and development.
The adverse reaction profile is acceptable when assessed in the context of clinical benefit observed (ORR of 69 – 100% observed across indications, with at least half of the responses durable for ≥6 months) and the life-threatening nature of metastatic NSCLC, advanced or metastatic MTC and advanced or metastatic thyroid cancer.

The clinical review team determined that it is in the best interest of U.S. patients to approve selpercatinib before one or more companion diagnostic assays are ready for PMA submission. Since a PMA for an in vitro companion diagnostic device was not submitted for contemporaneous approval with this NDA, the approved labeling will state that there is no FDA-approved for detection of RET fusions or mutations for selecting patients for treatment with selpercatinib. The Applicant has agreed to a post-marketing commitment (PMC) to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect RET fusions and mutations for identifying patients who may benefit from selpercatinib.

In the opinion of the review team, the submitted evidence meets the statutory evidentiary standard for accelerated approval. The rarity of RET fusion-positive NSCLC would render the conduct of a randomized study difficult, and in light of the marked overall response rate in metastatic RET fusion-positive NSCLC (85%), a randomized study will not be required by FDA. The review team considers that the ORR, which is large in magnitude, along with the observed duration of responses, in patients treated with selpercatinib is sufficient to establish clinical benefit in the genetically defined, rare subgroup of patients with RET fusion-positive metastatic NSCLC.

The review team concludes that the submitted evidence meets the statutory evidentiary standard for accelerated approval in patients with advanced RET mutant-MTC who require systemic therapy. The studies used to support the approval of cabozantinib and vandetanib in advanced or metastatic MTC included patients with RET mutations, and these products inhibit RET in addition to other kinases. Although the durable responses and observed safety profile in patients with advanced MTC treated with selpercatinib demonstrates evidence of clinical

benefit and an advantage over available therapy, a randomized study will be required to confirm this benefit in light of existing products for this population which have demonstrated an improvement in progression-free survival (PFS).

Finally, the review team concludes that the submitted evidence meets the statutory evidentiary standard for accelerated approval in patients with advanced RET fusion-positive thyroid cancer who are RAI-refractory (if RAI is appropriate). Although most patients with differentiated thyroid cancer have an excellent prognosis, those who have exhausted radioactive iodine have poor survival, and there are no approved treatment options specifically for patients with *RET* fusions. Patients with poorly differentiated thyroid cancer, and patients with anaplastic thyroid cancer without BRAF V600 mutations have limited treatment options. Given the observation of partial responses in all histologic subtypes of *RET* fusion-positive thyroid cancer studied, the review team considered that an indication which encompassed multiple histologic subtypes of thyroid cancer with *RET* fusions was appropriate. Though the population of patients supporting an approval for this indication is limited, the review team considered that the substantial durable ORR was further supported by the robust evidence of activity of selpercatinib in other *RET*-altered tumors. The clinical benefit of selpercatinib in this population will be confirmed in a post-marketing study.

Based on these results, the potential for clinical benefit outweighs the risks of selpercatinib identified during review of this NDA. The review team's regulatory recommendation is to grant selpercatinib accelerated approval for the following indications:

- for the treatment of adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC).
- for the treatment of patients ≥ 12 years old with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy.
- for the treatment of patients ≥ 12 years old with advanced *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer is the leading cause of cancer-related deaths worldwide and in the US. Non-small cell lung cancer accounts for 80% -85% of lung cancer patients and adenocarcinoma is the most common histological subtype. The majority of patients present with locally advanced or metastatic disease at the time of diagnosis, which is generally considered incurable. The incidence of RET gene fusions in metastatic NSCLC is 1-2%. The 5-year survival for patients with metastatic NSCLC is less than 5%; there is no randomized trial data available regarding survival specifically for patients with ROS1-positive metastatic NSCLC. • MTC Medullary thyroid cancer accounts for 3 – 4% of all thyroid cancers. The majority of patients with MTC have a *RET* mutation, including at least 50% of sporadic cases and 90% of familial cases. Although overall survival for patients with MTC is 86% at 5 years, five-year relative survival for patients with stage IV disease is approximately 28%. • Thyroid *RET* fusions can occur in non-medullary thyroid cancer of multiple histologies including differentiated thyroid cancers (DTC, including papillary, follicular, and Hurthle cell subtypes) and anaplastic thyroid cancer. RET rearrangements are identified in 5 – 10% of papillary thyroid carcinomas and are more commonly detected in children than adults. Up to 30% of patients with DTC experience recurrence. In patients with distant metastases, 5-year survival is 50%, regardless of tumor histology. Anaplastic thyroid cancer (ATC) is a more aggressive form of thyroid cancer; all patients are	Metastatic RET fusion-positive NSCLC is a life-threatening condition with poor survival. Advanced or metastatic RET mutation-positive MTC is a life-threatening condition; although prolonged survival is possible in patients with limited disease, patients with advanced, progressive disease have poor survival. Patients with metastatic RET fusion-positive DTC that is refractory to RAI and have progressed following systemic therapy, and patients with RET fusion-positive anaplastic thyroid cancer face an unmet medical need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	considered to have stage IV disease. Patients with ATC have a median survival of 5 months and a 1-year survival rate of 20%.	
Current Treatment Options	• NSCLC Treatment options for patients with RET fusion-positive NSCLC include regimens used for first-line systemic therapy of an unselected population of patients with NSCLC or non-squamous NSCLC (i.e., chemotherapy and/or anti-PD-(L)1 antibody). The highest ORRs, 48% and 58%, have been reported for platinum-based chemotherapy plus pembrolizumab (regardless of histology) and platinum-based chemotherapy plus atezolizumab and bevacizumab (non-squamous NSCLC), respectively. In the second line, there are several therapeutic options for the general population of patients with metastatic NSCLC with a maximum ORR of 23% (ramucirumab/docetaxel). • RET mutation-positive MTC Treatment options for patients with RET mutation-positive MTC include therapies for patients with advanced or metastatic, progressive or symptomatic MTC, the TKIs cabozantinib and vandetanib. Both these products inhibit RET in addition to other kinases, but are not approved solely for the treatment of patients with RET mutations. The ORRs for vandetanib and cabozantinib as evaluated in the studies to support approval were 45% and 28%, respectively (see table 2.2 for details). • RET fusion-positive thyroid cancer Treatment options for patients with RET fusion-positive thyroid	There are no FDA-approved treatments specifically for RET fusion-positive or mutation-positive cancers. Patients with the RET-driven cancers considered in this application are treated with the standard of care for patients with their tumor type, regardless of RET mutation.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cancer include radioactive iodine (if appropriate based on the underlying histology), lenvatinib and sorafenib for patients with DTC that is RAI-refractory, and doxorubicin (approved for thyroid carcinoma). The ORR demonstrated in the studies supporting the approvals of lenvatinib and sorafenib in patients with RAI-refractory DTC were 65% and 12%, respectively.	
Benefit	• The primary efficacy data supporting this NDA are from a single multicenter, single-arm, open-label, first-in-human, dose escalation and expansion study (LIBRETTO-001). The analysis populations for each disease type and the efficacy results are presented below. • Metastatic RET fusion-positive NSCLC **Efficacy Population (1st line):** The first 39 patients enrolled on LIBRETTO-001 with treatment-naïve NSCLC who demonstrated a protocol-defined *RET* fusion identified based on a CLIA-certified (or equivalent) test with measurable disease per RECIST v 1.1, and received one or more doses of selpercatinib. **Efficacy Results (1 st line):** The confirmed ORR in patients with metastatic, treatment-naïve RET fusion-positive NSCLC (n=39) per BICR was 84.6% (95% CI: 69.5%, 94.1%), with 42.4%, 12.1%, and 3% of the 33 responders having observed DOR of of 6 – 12, 12 – 18, and ≥18 months, respectively. **Efficacy Population (2nd line):** The first 105 patients with NSCLC previously treated with platinum chemotherapy enrolled on LIBRETTO-001 who demonstrated a protocol-defined *RET* fusion identified based on a CLIA-certified (or equivalent) test with measurable disease per RECIST v 1.1, and received one or more doses	NSCLC For patients with metastatic *RET* fusion-positive NSCLC who have not received prior systemic therapy, the overall response rate is clearly superior to that provided by available, non-targeted therapy. Though the efficacy population of treatment-naïve metastatic NSCLC in LIBRETTO-001 is limited in size (n=39), the significant ORR and durability of these responses in this molecularly-defined population is sufficient evidence to establish clinical benefit. Patients previously treated with platinum chemotherapy also demonstrate durable ORRs with selpercatinib which is substantially superior to the ORR demonstrated with other second-line therapies. Therefore, there is evidence of clinical benefit of selpercatinib in patients with metastatic *RET* fusion-positive NSCLC regardless of line of therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of selpercatinib. **Efficacy Results (2nd line):** The confirmed ORR per BICR was 63.8% (95% CI: 53.9%, 73.0%) and with 44.8%, 29.9%, and 4.5% of responders having observed DOR of 6 – 12, 12 – 18, and ≥18 months, respectively. • Advanced or metastatic RET mutant MTC who require systemic therapy **Efficacy Population, 1st line:** The first 88 patients enrolled on LIBRETTO-001 with cabozantinib and vandetanib-naïve MTC who demonstrated a protocol-defined *RET* mutation identified based on a CLIA-certified (or equivalent) test with measurable disease per RECIST v 1.1, and received one or more doses of selpercatinib. **Efficacy Results, 1st line:** The confirmed ORR per BICR was 72.7% (95% CI: 62.2%, 81.7%), with 37.5%, 20.3%, and 3.1% of responders having observed DOR of 6 – 12, 12 – 18, and ≥18 months, respectively. **Efficacy Population, 2nd line:** The first 55 patients enrolled on LIBRETTO-001 MTC who were previously treated with cabozantinib, vandetanib or both, who demonstrated a protocol-defined *RET* mutation identified based on a CLIA-certified (or equivalent) test with measurable disease per RECIST v 1.1, and received one or more doses of selpercatinib. **Efficacy Results, 2nd line:** The ORR per BICR was 69.1% (95% CI: 55.2%, 80.9%) with 21.2%, 36.8%, and 18.4% of responders having an observed DOR of of 6 – 12, 12 – 18, and ≥18 months, respectively.	While the point estimate of the results of the descriptive analyses of IC-ORR and IC-DOR need to be interpreted with caution given the limited number of patients, the results do support a conclusion that selpercatinib has anti- tumor activity in the CNS in patients with RET fusion-positive NSCLC with brain metastases. MTC For patients with advanced or metastatic *RET* mutant MTC who have not received prior treatment with an approved TKI and require systemic therapy, the overall response rate observed in study LIBRETTO-001 appears to demonstrate an advantage over available therapy. Patients with advanced or metastatic *RET* mutant MTC who have received prior approved therapy (cabozantinib, vandetanib, or both) also demonstrate evidence of clinical benefit in the form of durable ORR; these patients have no available therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Advanced RET fusion-positive thyroid cancer who require systemic therapy and are RAI-refractory **Efficacy Population:** Nineteen patients with *RET* fusion-positive thyroid cancers who demonstrated a protocol-defined *RET* fusion identified based on a CLIA-certified (or equivalent) test and received one or more doses of selpercatinib. An additional eight patients were RAI-refractory and had not received subsequent therapy. **Efficacy Results, 1st line post RAI:** the ORR per BICR was 100% (95% CI 63%, 100%), with 62.5% and 12.5% of patients demonstrating an observed DOR of 6 – 12 and 12 – 18 months, respectively. **Efficacy Results, 2nd line post RAI:** ORR 78.9% (95% CI: 54.4%, 93.9%), with 40%, 26.7%, and 20% of responders having an observed DOR of 6 – 12, 12 – 18, and ≥18 months, respectively.	RET fusion-positive thyroid cancer The rarity of RET fusion-positive thyroid cancer renders the conduct of a randomized trial not feasible. The review team considers that the ORR, which is large in magnitude, along with the observed duration of responses, in patients treated with selpercatinib is sufficient to establish clinical benefit in the genetically defined, rare subgroup of patients with advanced RET fusion-positive thyroid cancer are RAI-refractory (if appropriate), and in patients who are RAI-refractory and have received a subsequent systemic therapy. Patients with DTC who have not received subsequent systemic therapy following RAI are eligible to receive lenvatinib and sorafenib; however, the ORR for selpercatinib in this population represents a substantial improvement over these therapies despite the limited number of patients. Given the efficacy of selpercatinib in patients with the indications described above, the rarity of these patient populations and the availability of non- companion diagnostic testing, the clinical review team determined that it is in the best interest of U.S. patients to

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		approve selpercatinib before one or more companion diagnostic assays are ready for PMA submission. Since a PMA for an in vitro companion diagnostic device was not submitted for contemporaneous approval with this NDA, approved labeling will state that there is no FDA-approved for detection of RET fusions or mutations for selecting patients for treatment with selpercatinib. The Applicant has agreed to a post-marketing commitment (PMC) to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect RET gene fusions and mutations for identifying patients who may benefit from selpercatinib.
Risk and Risk Management	• The safety population included 702 patients, including 65% who were exposed for 6 months or longer and 34% who were exposed for greater than one year. 95% of patients in the safety population had received at least one dose of RETEVMO at the indicated dose of 160 mg orally twice daily. • Hepatotoxicity, hypertension, QT interval prolongation, hemorrhagic events, hypersensitivity are the primary safety risks with selperatcinib and are described in Section 5 of the product label. The risk of impaired wound healing has been identified in products that inhibit the VEGF pathway, and guidance regarding holding selpercatinib for planned surgical procedures will also be included in Section 5.	While selpercatinib can cause severe toxicities, these safety concerns are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in product labeling. Selpercatinib will be prescribed by oncologists who know how to monitor, identify, and manage such toxicities. The review team did not believe a Risk Evaluation and Mitigation Strategy (REMS) was warranted to ensure the safe use of the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The most common adverse reactions (≥ 20%) were dry mouth, diarrhea, hypertension, fatigue, edema, rash, constipation, headache, nausea, and abdominal pain. • Serious adverse reactions occurred in 33% of patients who received RETEVMO. The most common serious adverse reaction (in ≥ 2% of patients) was pneumonia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in > 1 patient included sepsis, cardiac arrest, and respiratory failure (n = 3).	product given the information included in the product label.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application, include: Descriptive analyses of health-related quality of life (HRQoL).				Section 8.2.7 These evaluations were exploratory and not intended to inform a claim of safety or efficacy.
	X	Clinical outcome assessment (COA) data, such as			
			X	Patient reported outcome (PRO)	
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			

	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.		

X _____

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:

RET is a receptor tyrosine kinase (RTK) critical to development of the enteric nervous system and kidney. Postnatally, RET contributes to the maintenance of neural, neuroendocrine, hematopoietic and male germ cell tissues (Mulligan 2014). [Module 2.5.1.1 (NSCLC)]

The RET receptors are transmembrane glycoproteins. Normal RET activation is initiated by the binding of one of four glial cell-line derived neurotropic factor (GDNF) family ligands (GFLs). In contrast to other RTKs, RET does not bind directly to its ligands, but instead depends on the activity of the GDNF family receptor-α (GFRα) RET co-receptors. GFL-bound, GFRα-mediated RET dimerization leads to RET kinase-mediated auto-phosphorylation of tyrosine residues in the RET intracellular domain, the recruitment of key signaling adaptors and the activation of several downstream signal transduction pathways involved in cellular proliferation, including Mitogen-Activated Protein Kinase (MAPK), Phosphatidylinositol-3-Kinase (PI3K), Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT), Protein Kinase A (PKA) and Protein Kinase C (PKC). [Module 2.5.1.1 (NSCLC)]

Genetic alterations in *RET* have been implicated in the pathogenesis of several human cancers. *RET* can become oncogenically activate by two primary mechanisms: (1) chromosomal rearrangements, producing cytoplasmically localized oncogenic hybrid proteins that fuse the RET kinase domain with a partner protein dimerization domain (e.g., CCDC6/PTC1, KIF5B, NCOA4/PTC3), thus endowing the kinase with ligand-independent, constitutive activity; and (2) point mutations and indels which directly or indirectly activate the kinase.
[Module 2.5.1.1 (NSCLC)]

RET gene fusions have been identified in 1-2% of non-small cell lung cancers (NSCLC), 6% of papillary and poorly differentiated thyroid cancers (PTC, PDTC) and rarely in multiple other tumor types (Ballerini, Struski et al. 2012, Kohno, Ichikawa et al. 2012, Lipson, Capelletti et al. 2012, Takeuchi, Soda et al. 2012, Bossi, Carlomagno et al. 2014, Cancer Genome Atlas Research 2014, Stransky, Cerami et al. 2014, Le Rolle, Klempner et al. 2015, Yoshihara, Wang et al. 2015, Kato, Subbiah et al. 2016, Landa, Ibrahimpasic et al. 2016, Paratala, Chung et al. 2018). *RET* point mutations and indels are present in most medullary thyroid cancers (MTCs), including both hereditary (i.e. Multiple Endocrine Neoplasia [MEN] and other familial MTC syndromes) and sporadic cases (Ji, Oh et al. 2015, Heilmann, Subbiah et al. 2016). [Module 2.5.1.1 (NSCLC)]

RET alterations appear to be bona fide cancer drivers. In patient tumor samples, they almost always appear mutually exclusive of other known validated oncogenic drivers such as EGFR, ALK, ROS1, NTRK, BRAF and RAS. RET alterations cause transformation in vitro and in vivo. They also display the hallmark feature of oncogene addiction—their inhibition in RET-altered, patient-derived cancer models leads to tumor cell death (Takahashi, Ritz et al. 1985, Michiels, Chappuis et al. 1997, Acton, Velthuyzen et al. 2000, Gilbert-Sirieix, Ripoche et al. 2010, Matsubara, Kanai et al. 2012, Duan, Hao et al. 2014, Saito, Ishigame et al. 2014, Stransky, Cerami et al. 2014). [Module 2.5.1.1 (NSCLC)]

Currently, there are no RET-directed therapies approved for patients with advanced, metastatic *RET* fusion-positive NSCLC, *RET* fusion-positive thyroid cancer or *RET*-mutant MTC. Patients are treated with the approved stand of care for these cancers, irrespective of the presence of a known *RET* alteration. These regimens have limited efficacy and are associated with significant toxicity. For patients who cannot tolerate these treatments, or for those whose disease has progressed following treatment with these agents, there are no available therapies associated with clinical benefit. These patients therefore represent a population who have a significant unmet medical need. [Module 2.5.6 (NSCLC); Module 2.5.6 (MTC)]

The FDA's Assessment:

FDA has the following additional points for discussion regarding the specific conditions considered for approval, namely *RET* fusion-positive NSCLC, *RET*-mutant MTC and *RET* fusion-positive thyroid cancer.

RET fusion-positive NSCLC

There were an estimated 228,150 new cases of lung and bronchial cancers and 142,670 deaths due to lung cancer estimated to occur in the US in 2019. (NCI SEER, 2019) NSCLC accounts for 80% of lung cancers and adenocarcinoma is the most common histological subtype. (NCI PDQ, 2019) The majority of patients present with locally advanced or metastatic disease at the time of diagnosis, which is generally considered incurable. The anticipated 5-year survival for patients with clinical stage IIIB NSCLC is approximately 26% and is less than 5% for patients who present with clinical stage IV disease. (Rami-Porta, 2017) As the Applicant notes above, *RET* gene fusions have been identified in 1-2% of patients with NSCLC. *RET* fusions in NSCLC are associated with younger age (≤ 60 years of age) and minimal or no prior tobacco exposure. (Drilon, 2018)

RET mutant Medullary Thyroid Cancer

Medullary thyroid cancer accounts for 3 – 4% of all thyroid cancers and is associated with familial syndromes (MEN2A, MEN2B and familial MTC) in 25% of cases. (Raue, 2015) The majority of patients with MTC have a *RET* mutation; approximately 50% of sporadic cases carry a somatic *RET* mutation and at least 90% of familial cases have an identifiable germline

mutation. (Thomas, 2019; NCCN, 2019) Sporadic disease typically occurs in the 4th – 6th decades of life, but hereditary disease may occur in very young children. Overall survival for patients with MTC is 86% at 5 years and 65% at 10 years, with prognosis dependent upon the extent of disease at diagnosis and extent of surgical resection. (NCI PDQ, 2019) Five-year relative survival for patients with stage IV disease is approximately 28%. (NCCN, 2019)

RET fusion-positive Thyroid Cancer

There will be an estimated 52,890 new cases of thyroid cancer and 2,180 deaths from thyroid cancer in the United Stated in 2020; the 5-year relative survival across subtypes is 98%. (American Cancer Society, 2020) Differentiated thyroid carcinoma (DTC) includes the histologic subtypes of papillary, follicular and Hurthle cell carcinoma. DTC can occur in children and adolescents, and accounts for 1.4% of all pediatric malignancies; most cases of DTC which occur in children are papillary thyroid carcinomas (Verberg, 2017) RET rearrangements are identified in 5 – 10% of papillary thyroid carcinomas and are more commonly detected in children than adults. (Drilon, 2018) RET rearrangements in papillary thyroid cancer are associated with prior exposure to radiation. Localized 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 for patients at high risk of persistent disease or disease recurrence after total thyroidectomy (e.g., patients with gross extrathyroidal disease, tumor > 4 cm, or based on postoperative thyroglobulin levels). Up to 30% of patients may have recurrence of disease. (NCCN, 2019) Prognostic factors include age, completeness of resection, presence of metastasis and tumor size. In patients with distant metastases, 5-year survival is 50%, regardless of tumor histology. (NCCN, 2019) Although children often present with more advanced disease and experience more recurrences compared to adults, they have a favorable long-term survival (90% at two years). (NCCN, 2019)

Poorly differentiated thyroid cancer is a rare subset of thyroid cancer which comprises 2 – 3% of thyroid malignancies in North America carries an intermediate prognosis compared to differentiated thyroid cancers and anaplastic thyroid cancer. (Sanders, 2007) Anaplastic thyroid cancer (ATC) is a more aggressive form of thyroid cancer; all patients are considered to have stage IV disease. Patients with ATC have a median survival of 5 months and a 1-year survival rate of 20%. (Smallridge, 2012)

2.2 Analysis of Current Treatment OptionsThe Applicants Position:

RET fusion-positive NSCLC [Module 2.5 (NSCLC)]

Table 2.1 provides a tabulated summary of results for current treatment options for NSCLC.

First-Line Treatment

In NSCLC, platinum-based chemotherapy was long the standard of care, delivering objective response rates (ORRs) of ~20-30%, median PFS of ~4–8 months and overall survival < 12 months (Soria, Tan et al. 2017; Gandhi 2018). While anti-VEGF therapies were approved for the first-line treatment of NSCLC, they did not dramatically alter the treated natural history of the disease (USPI for AVASTIN). In the last five years, however, PD-1/PD-L1-directed monoclonal antibodies have favourably altered patient management in the first-line setting. For example, in patients with metastatic nonsquamous NSCLC without EGFR or ALK alterations, the phase III KEYNOTE-189 trial established that pembrolizumab plus chemotherapy (vs chemotherapy alone) provided longer overall survival (OS), progression-free survival (PFS) and higher ORRs. Effects were most profound in patients with higher PD-L1 tumor proportion scores (TPS), though effects were seen even among the TPS < 1% group, with a hazard ratio (HR) for OS of 0.52, HR for PFS of 0.63, and an ORR of 32.3% versus 14.3%.

Extrapolating the relevance of large Phase 3 trials such as KEYNOTE-189 to targeted therapies for oncogenically driven NSCLC can be problematic, however. Most large PD-1/PD-L1-directed antibody programs excluded patients positive for EGFR and ALK alterations—populations most biologically relevant to RET and other activating oncogenic events. Further, patients with *RET* fusion positive NSCLC comprised a very rare subset of these large datasets, such that it is unknown whether they enjoyed comparable clinical benefit to the overall population. Since the long-term durable efficacy of the PD-1/PD-L1-directed antibodies appears largely restricted to a small subset of 10–20% of patients, it will be crucial to confirm efficacy of this class in the *RET*-defined subset, and to rule out harm, in this population of interest.

The unmet need argument for selpercatinib in the first-line setting largely resembles the enrollment rationale for these patients in LOXO-RET-17001: 1) a willingness to extrapolate from biologic first principles (i.e. experience in EGFR, ALK and ROS1 tumors) to conclude that targeted therapies are the therapy of choice in affirmatively identified patients; 2) an awareness that PD-1/PD-L1-directed antibodies are approved therapies in the second-line and thus remain a treatment option; 3) the ability to detect rapid benefit or lack of benefit in patients directed to selpercatinib in the first-line, providing an opportunity to change therapies quickly; 4) concern that PD-1/PD-L1-directed antibodies have limited to no efficacy in genetically defined patients (see below); 5) support from published care pathways, such as NCCN guidelines, which explicitly include *RET* among *EGFR, ALK, ROS1, NTRK,* and *BRAF* as an

actionable biomarker appropriate for first-line intervention with targeted therapy (NCCN, 2019); 6) the observation that selpercatinib generates a very high response rate of meaningful duration; 7) the observation that the safety profile of selpercatinib is generally favourable, and different than those reported for chemotherapy+anti-PD-1/PD-L1 regimens. As of November 2019, 53 treatment-naïve patients have been enrolled in LOXO-RET-17001.

In June 2017, FDA issued a line-agnostic approval for dabrafenib and trametinib in patients with metastatic NSCLC with BRAF V600E mutation. However, this approval pre-dated positive results from KEYNOTE 189. In March 2016 and August 2019, FDA issued line-agnostic approvals for crizotinib and entrectinib, respectively, in patients with metastatic NSCLC with ROS1 fusions. In the case of selpercatinib, the Agency must consider the above arguments in assessing the implications of foregoing chemotherapy+anti-PD1/PD-L1 therapy for selpercatinib in the first line. The Sponsor believes an affirmative decision would improve access to this important therapy and that emerging data will continue to suggest lack of benefit for anti-PD-1/PD-L1 agents in the setting of *RET* fusion-positive NSCLC, as per recent reports:

- In the multicenter IMMUNOTARGET tumor registry, for 16 *RET* fusion-positive NSCLC patients treated with immune checkpoint inhibitors (ICIs) (95% second-line or later), the ORR and median PFS were 6% and 2.1 months, respectively, among the lowest of any driver alteration-positive subset of NSCLC patients analyzed (Mazieres, Drilon et al. 2019).

- Similar results were observed in a single institution retrospective study of 74 *RET* fusion-positive NSCLC patients treated with ICIs (median line of therapy ICI was administered = 2; range: 1, 7), who were notable for low tumor mutational burden, 0/13 tumor responses (for whom response data was available) to immunotherapy and median PFS 3.4 months on the ICI (Offin, Guo et al. 2019).

- *RET* fusion tumors, like other single-gene driver oncogenic kinase alterations, tend to have low mutational burden and low neo antigen production (Borghaei, Paz-Ares et al. 2015; Rizvi, Hellman et al. 2015; Gainor, Shaw et al. 2016; Herbst, Baas et al. 2016).

A line-agnostic approval for selpercatinib would not only provide an important treatment option for patients with *RET* fusion-positive NSCLC, it would also reinforce the important public health message that tumor genomic profiling is an important behavior in the newly diagnosed setting.

Second-Line and Beyond

For NSCLC patients without single-gene driver oncogenic kinase alterations, second-line systemic therapies include single agent chemotherapy (e.g. docetaxel, pemetrexed) and single agent anti-PD-1/-PD-L1 agents that result in ORRs of ~5%–25%, median PFS of ~3–5 months and OS 2–15.4 months (Herbst, Baas et al. 2016; Borghaei, Paz-Ares et al. 2015, Rittmeyer, Barlesi et al. 2017). While anti-PD-1/-PD-L1 immune checkpoint inhibitors such as nivolumab, pembrolizumab, and atezolizumab are approved for use in patients with *EGFR* and *ALK* genomic alterations, subgroup analysis indicated decreased benefit for NSCLC patients harboring these alterations; the prescribing information for these agents recommend their use after progression on FDA-approved targeted EGFR/ALK therapies.

Sponsor-Agency agreement around the data supporting this NDA reflects the clear unmet need argument in the second line and beyond for selpercatinib in *RET* fusion NSCLC.

Table 2.1 Summary of Current Treatment Options for Advanced/Metastatic NSCLC

Regimen	Trial Design	Patient number N = Total	ORR (%); (95% CI)	mPFS (months); (95% CI)	mOS (months); (95% CI)	Histology/ Biomarker	Name of Trial (Reference)
Non-small cell lung cancer (irrespective of RET-fusion status)							
First Line							
Platinum doublet	Platinum doublet vs Single-agent platinum	57 trials	Odds Ratio: 0.42 (0.37–0.47) p < 0.001		Median survival Ratio: 0.83 (0.79-0.89); p < 0.001		(Delbaldo et al. JAMA 2004; 292(4):470)
Bevacizumab Paclitaxel/ Carboplatin	Bevacizumab Paclitaxel/ Carboplatin vs Paclitaxel/ Carboplatin	N = 878 444 vs 434			12.3 vs 10.3 HR: 0.80 (0.68-0.94) p = 0.013	Non-squamous	Study E4599 (USPI for AVASTIN®)
Pembrolizumab/ Pemetrexed/ Carboplatin	Pembrolizumab/ Pemetrexed/ Carboplatin or Cisplatin vs Placebo/Pemetrexed/ Carboplatin or cisplatin	N = 616 410 vs 206	48 (43-53) vs 19 (14-25) P < 0.001	8.8 (7.6 - 9.2)vs. 4.9 (4.7 -5.5) HR: 0.52 (0.43-0.64); p < 0.001	NR vs 11.3 HR: 0.49 (0.38-0.64); p < 0.001	No *EGFR*/ALK	Study KEYNOTE-189 (Gandhi L, et al, N Engl J Med 2018; 278: 2078-2091)

Regimen	Trial Design	Patient number N = Total	ORR (%); (95% CI)	mPFS (months); (95% CI)	mOS (months); (95% CI)	Histology/ Biomarker	Name of Trial (Reference)
Atezolizumab/ Bevacizumab/ Carboplatin/Paclitaxel	Atezolizumab/ Bevacizumab/ Carboplatin/ Paclitaxel (ABCP) vs Bevacizumab/ Carboplatin/ Paclitaxel (BCP) vs Atezolizumab/ Carboplatin/ Paclitaxel (ACP)	N = 1202 402 vs 400 vs 400	ABCP vs BCP: 64 (58-69) vs 48 (43-54)	ABCP vs BCP: 8.3 vs 6.8 HR: 0.62 (0.52 – 0.74) P < 0.001	ABCP vs BCP: 19.2 (17.0-23.8) vs 14.7 (13.3 - 6.9) HR: 0.78 (0.64-0.96) P = 0.02	Non-squamous	Study IMpower150 Socinski et al. N Engl J Med 2018 375:228-2301
Pembrolizumab	Pembrolizumab vs Chemotherapy	N= 305 154 vs 151	45 (37-53) vs 28 (21-36) p = 0.001	10.3 (6.7-NR) vs 6.0 (4.2 vs 6.2) HR: 0.50 (0.37-0.68); p < 0.001	30.0 (18.3, NR) vs 14.2 (9.8, 19.0) HR: 0.60 (0.41-0.89); p = 0.001	No *EGFR*/ALK With PD-L1 TPS ≥ 50%	Study KEYNOTE-024 (Reck M et al N Engl J Med 2016 375:1823-1833; USPI for KEYTRUDA®)
First Line – Maintenance							
Bevacizumab	Bevacizumab vs BSC	217 vs 134		4.4 vs 2.8 HR:0.64; p < 0.001	12.8 vs 11.4 HR: 0.75; p = 0.030	Non-squamous	ECOG Study 4599 (Lopez-Chavez, A. et al, Journal of Thoracic Oncology, 2012;7(11)1707-1712)

Regimen	Trial Design	Patient number N = Total	ORR (%); (95% CI)	mPFS (months); (95% CI)	mOS (months); (95% CI)	Histology/ Biomarker	Name of Trial (Reference)
Pemetrexed	Pemetrexed + BSC Vs Placebo + BSC	N = 539 359 vs 180	3 (1.3-5.3) vs. 0.6 (0.02-3.5) P = 0.18	4.1 (3.2-4.6) vs. 2.8 (2.6-3.1). HR = 0.62, (0.49-0.79); p < 0·0001	Final OS (2013): 13.9 vs. 11.0 HR: 0.78 (0.64 - 0.96)	Non-squamous	Study PARAMOUNT (Paz-Arez L et al Lancet Oncol 2012 13 (3):247-55 and Paz-Arez L et al J Clin Onco 2013 31 (23):2895-902)
Pembrolizumab	Carboplatin/ Paclitaxel → Pembrolizumab maintenance	25	48 (28-69)	10.3 months (95% CI, 6.1–14.6 months)		Mixed	KEYNOTE-021 (Gadgeel, S.M. et al, Lung Cancer 2018, 125: 273-281)
	Carboplatin/ Paclitaxel/ Bevacuzimab → Pembrolizumab maintenance	25	56 (35-76)	7.1 months (95% CI, 4.2–14.3)		Non-squamous	
Second Line							
Docetaxel	Docetaxel vs BSC	N = 104 55 vs 49	5.5 (1.1-15.1) vs NA	12.3 (9-18.3) weeks vs 7 (6.0-9.3) weeks	7.5 (5.5-12.8) weeks vs 4.6 (3.7-6.1) weeks HR: 0.56 (0.35, 0.88) p = 0.01	NSCLC	TAX317 (USPI for TAXOTERE®)
Pemetrexed	Pemetrexed vs Docetaxel	N = 571 283 vs 288	8.5 (5.2-11.7) vs 8.3 (5.1-11.5)	2.9 (2.4-3.1) vs 2.9 (2.7-3.4) HR: 0.97 (0.82-1.16)	8.3 (7.0-9.4) vs 7.9 (6.3-9.2) HR: 0.99 (0.82-1.20)	Non-squamous	Study JMEI (USPI for ALIMTA®)

Regimen	Trial Design	Patient number N = Total	ORR (%); (95% CI)	mPFS (months); (95% CI)	mOS (months); (95% CI)	Histology/ Biomarker	Name of Trial (Reference)
Ramucirumab/Docetaxel	Ramucirumab/ docetaxel vs Placebo/ docetaxel	N = 1253 628 vs. 625	23 (20-26) vs 14 (11-17); p < 0.001	4.5 (4.2-5.4) vs 3.0 (2.8-3.9) HR: 0.76 (0.68-0.86); p < 0.001	10.5 (9.5-11.2) vs 9.1 (8.4-10.0) HR: 0.86 (0.75-0.98); p = 0.024	NSCLC	REVEL (UPSI for CYRAMZA®)
Pembrolizumab	Pembrolizumab vs Docetaxel	N = 1034 346 vs 343	18 vs 9 P = 0.0002	4 vs 4 HR = 0.79 (0.66-0.94) p = 0.004	12.7 vs 8.5 HR: 0.61 (0.49-0.75) P < 0001	PD-L1	KEYNOTE-010 (Herbst, R.S et al. Lancet 2016, 3878:1540-1550)
Nivolumab	Nivolumab vs Docetaxel	N = 272 135 vs 137	20 (14-28) vs 9 (5-15) p = 0.0083	3.5 vs 2.8 HR: 0.62 (0.47-0.81); p = 0.0004	9.2 (7.3-13.3) vs 6.0 (5.1-7.3); p = 0.0002	Squamous	CHECKMATE-017 (UPSI for OPDIVO®)
Nivolumab	Nivolumab vs Docetaxel	N = 582 292 vs 290	19 (15-24) vs 12 (9-17) p = 0.02	2.3 (2.2 – 3.3) v 4.2 (3.5 – 4.9) HR: 0.92 (0.77 – 1.1) p = 0.39	12.2 (9.7 -15.0) vs 9.4 (8.1 – 10.7) HR: 0.73 (0.59 – 0.89) p = 0.002	Nonsquamous	CHECKMATE-057 (USPI for OPDIVO)
Atezolizumab	Atezolizumab Vs Docetaxel	N = 850 425 vs 425	14 (11, 17) vs 13 (10, 17)	2.8 (2.6 – 3.0) vs. 4.0 (3.3 – 4.2) HR: 0.95 (0.82-1.10)	13.8 (11.8 – 15.7) vs 9.6 (8.6-11.2) HR = 0.74 (0.63-0.87) p = 0.0004	Nonsquamous and Squamous	OAK Study Tecentriq USPI and Rittmeyer A et al. Lancet 2017, 289 (10066):255-265

Regimen	Trial Design	Patient number N = Total	ORR (%); (95% CI)	mPFS (months); (95% CI)	mOS (months); (95% CI)	Histology/ Biomarker	Name of Trial (Reference)
Non-small cell lung cancer (Phase 2, *RET* rearrangement/fusion required)							
Cabozantinib	Open -label, single arm	N = 26	28 (12-49)	5.5 (3.8-8.4)	9.9 (8.1-NR)	*RET*-fusion positive	(Drilon A et al. 2016, 17 (12):1653-1660)
Lenvatinib	Open -label, single arm	N = 25	16 (CI not reported)	7.3 (3.6-10.2)	NR (5.8-NR))	*RET*-fusion positive adenocarcinoma	(Velcheti T et al. 2016, 27 (6 suppl))
Vandetanib	Open -label, single arm	N= 19	53 (28-77)	4.7(2.8-8.5)	11.1 (9.4-NR)	*RET*-fusion positive	Study LURET (Yoh K et al. 2017, 5:42-50)
Vandetanib	Open -label, single arm	N- 18	18 (CI not reported)	4.5 (CI unknown)	11.6 (CI unknown)	*RET*-fusion positive	(Lee SH et al. 2017 28(2): 292-297)

CI: confidence interval; HR: hazard ratio; NR: not reached
Module 2.5 (NSCLC), Appendix 1

***RET*-mutant MTC** [Module 2.5 (MTC)]

Table 2.2 provides a tabulated summary of results for current treatment options for MTC and other thyroid cancers.

In patients with advanced MTC, chemotherapy has not demonstrated meaningful clinical benefit. Historically, doxorubicin, either alone or in combination with cisplatin was supported by literature studies (Shimaoka et al. 1985). Other published combination regimens have included 5 fluorouracil, dacarbazine, steptozocin, cyclophosphamide and vincristine (Nocera et al. 2000, Ball 2007). Yet recent American Thyroid Association (ATA) guidelines do not support the use of chemotherapy as first-line therapy in patients with persistent or recurrent MTC given the low response rates (Wells et al., 2015). Table 2.2 provides a tabulated summary of results for these current treatment options.

Vandetanib and cabozantinib are approved for patients with unresectable, locally advanced or metastatic MTC. However, it is important to note that these agents are promiscuous multikinase inhibitors that were not developed with the benefit of a biomarker, i.e. *RET* mutation status.

Although both cabozantinib and vandetanib improve PFS, managing their toxicities can be challenging. As a result, patient advocates commonly report that patients often forego these therapies in the setting of slowly progressive disease. The safety profiles of these therapies suggest high unmet need in first-line use.

For patients who cannot tolerate cabozantinib or vandetanib, or for those whose disease has progressed following treatment with these agents, there are no available therapies associated with clinical benefit, and these patients have a significant unmet medical need.

RET fusion-positive thyroid cancer

Patients with *RET* fusion-positive thyroid cancer have historically received standard of care for their respective, histology-based diagnosis: papillary, poorly differentiated, anaplastic, and Hurthle cell. Table 2.2 provides a tabulated summary of results for these current treatment options.

Patients with progressive, radioactive iodine-avid, advanced differentiated thyroid cancer (DTC) (excluding MTC, which does not take up iodine) are initially treated with radioactive iodine (RAI), although RAI is not curative, and the development of radioactive iodine-refractory disease is essentially universal. For patients with radioactive iodine-refractory DTC (irrespective of tumor genotype and excluding MTC), the approved anti-RET multikinase inhibitors (MKIs) sorafenib and lenvatinib demonstrated ORRs of 12.2% and 64.8% and median PFS of 10.8 and 18.3 months, respectively (DOR was not reported and median OS was not reached in either

study and was not significantly different compared to placebo) (Brose, Nutting et al. 2014; Schlumberger, Tahara et al. 2015). It is important to note that these agents are promiscuous multikinase inhibitors that were not developed with the benefit of a biomarker, i.e. *RET* fusion status. Most patients treated in each study had PTC; posthoc subgroup analyses demonstrated similar treatment benefit for the minority of patients with other thyroid cancer subtypes (i.e. PDTC, follicular thyroid cancer (FTC) and Hurthle cell variant; for sorafenib, the treatment effect for PDTC and FTC was lower).

Patients treated with these agents have reported significant toxicities requiring dose reductions (64.3% for sorafenib, 67.8% for lenvatinib), interruptions (66.2% for sorafenib, 82.4% lenvatinib) and treatment discontinuation (18.8% for sorafenib, 14.3% for lenvatinib).

We believe *RET* fusion-positive thyroid cancer defines a novel subpopulation that merits early identification and treatment with selpercatinib. For patients who cannot tolerate sorafenib or lenvatinib, or for those whose disease has progressed following treatment with these agents, there are no available therapies associated with clinical benefit, and these patients have a significant unmet medical need.

Table 2.2 Summary of Current Treatment Options for MTC and Other Thyroid Cancers

Regimen	Trial Design	Patient number N = Total	ORR (%); (95% CI)	mPFS (months); (95% CI)	mOS (months); (95% CI)	Histology/ Biomarker	Name of Trial (Reference)
Medullary Thyroid Cancer (irrespective of RET mutation)							
Vandetanib	Vandetanib vs Placebo	N = 331 231 vs 100	45 (NR) vs 13 (NR) p = < 0.001	30.5 vs 19.3 HR = 0.46 (0.31-0.69) p < 0.001	81.6 vs 80.4 HR = 0.99 (0.72-1.38) p = 0.975		ZETA (Wells et al. 2012 [PFS and ORR]; CAPRELSA USPI [OS] and SmPC [OS]).
Cabozantinib	Cabozantinib vs Placebo	N = ~~330~~ 219 vs 111	28 (NR) vs 0 (NR) p < 0.001	11.2 vs 4.0 HR = 0.28 (0.19, 0.40) p < 0.001	26.6 v 21.1 HR = 0.85 (0.64, 1.12) p = 0.2409		EXAM (Elisei et al. 2013, COMETRIQ USPI [OS] and SmPC [OS])
Thyroid Cancer*							
Doxorubicin	Doxorubicin vs Doxorubicin/ Cisplatin	N = 84 41 vs 43	17 vs 26; Not significant				(Shimaoka et al. Cancer; 1985, 56(9):2155-2160)
Lenvatinib	Lenvatinib vs placebo	N = 392 261 vs131	65 (59-71) vs 2 (0-4); p < 0.001	18.3 (15.1-NE) vs 3.6 (2.2-3.7) HR: 0.21 (0.16-0.28); p < 0.001	NE (22.1-NE) vs NE (20.3-NE) HR: 0.73 (0.50-1.07); p = 0.10		Study 1 (USPI for LENVIMA®)
Sorafenib	Sorafenib vs placebo	N = 417 207 vs 210	12 (7.6-16.8) vs 0.5 (0.01-2.7)	10.8 (9.1-12.9) vs 5.8 (5.3-7.8) HR: 0.59 (95% CI: 0.46-0.76); p < 0.001	42.8 (34.6-52.6) vs 39.4 (32.7-51.4) HR: 0.92 (0.71-1.21); p = 0.57		Differentiated Thyroid Carcinoma (USPI for NEXAVAR®)

CI: confidence interval; HR: hazard ratio; NE: not evaluable
* Medullary thyroid cancer is biologically distinct, non-radioiodine avid and not relevant to the enrolled population; no available systemic therapies for anaplastic thyroid cancer (ATC). Module 2.5 (MTC), Appendix 1

The FDA's Assessment:

FDA notes that Tables 2.1 and 2.2 above incorporate therapies approved for NSCLC, MTC, and non-medullary thyroid cancer. Table 2.1 also includes trials which included patients with *RET* fusion-positive NSCLC, but these agents are not approved for this indication. There are no therapies approved specifically for *RET*-altered cancers including *RET* fusion-positive NSCLC, *RET*-mutant MTC, and *RET* fusion-positive non-medullary thyroid cancers.

FDA also notes that the results reported from the Impower150 study, which formed the basis of approval of atezolizumab in combination with bevacizumab, carboplatin, and paclitaxel for the first line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations, are based on investigator-assessed responses. The atezolizumab product label provides the overall response rate as assessed by independent review, and includes a response rate of 55% in Arm B (atezolizumab, bevacizumab, carboplatin and paclitaxel; 95% CI 49, 60). The median DOR was 10.8 months (95% CI 8.4, 13.9).

Cabozantinib and vandetanib were approved in patients with MTC regardless of *RET* status; however, both products inhibit multiple kinases including RET. In the study which formed the basis of the approval of vandetanib, *RET* status was collected. 59.3% of patients in the vandetanib arm (56.5% overall) had tumors which demonstrated a *RET* mutation, 0.9% were negative for a *RET* mutation, and 39.8% of patients had unknown *RET* status. (Kim, 2011) Given the extremely small number of mutation-negative patients, it is unclear whether *RET* mutation positive and negative groups had a differential response to vandetanib. In the study used to support approval for cabozantinib in MTC, *RET* mutation testing was done retrospectively and should be interpreted cautiously. 46% of patients had a tumor which demonstrated a *RET* mutation, 40% of patients were *RET* negative, and 15% of patients had unknown *RET* status. The PFS HR for patients with *RET* mutations was 0.23 (95% CI 0.14, 0.38) and without *RET* mutations the PFS HR was 0.44 (95% CI 0.15, 1.3); for the unselected population, the HR was 0.30 (95% CI 0.16, 0.56). (Guisti, 2012)

As the Applicant notes, the studies which formed the basis of approval for sorafenib and lenvatinib in RAI-refractory DTC included multiple histologic subtypes (papillary, follicular) and were not performed in a biomarker selected population. Although it is likely that patients with *RET* fusion-positive thyroid cancer (most likely papillary thyroid cancer) were included in these studies based on the prevalence of this alteration, and both MKIs have anti-*RET* activity, *RET* status was not analyzed in either of these studies. It is therefore possible that patients with *RET* fusions experienced a relatively higher or lower response rate compared to the general population of RAI-refractory DTC.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:
To date, selpercatinib has not been granted market authorization.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

3.2 Summary of Presubmission/Submission Regulatory ActivityThe Applicant's Position:

In May 2017, the Sponsor initiated the clinical development program for selpercatinib under IND 133193 (submitted 02 March 2017). In September 2019, the pediatric study (LOXO-RET-18036) was initiated under IND 142299 (submitted on 13 December 2018). Table 3.1 summarizes key regulatory interactions for selpercatinib in the US in chronological order. [Module 2.5.1.3 (MTC); Module 2.5.1.3 (NSCLC)]

Table 3.1 Selpercatinib: Key Regulatory Interactions

31 March 2017 – IND 133193 submitted to the Division of Oncology Products 2 (DOP2) for the evaluation of NEW DRUG for the treatment of patients with solid tumors. • Included protocol LOXO-RET-17001 entitled "A Phase 1 Study of Oral LOXO-292 in Adult Patients with Advanced Solid Tumors, Including RET-Fusion Non-Small Cell Lung Cancer, Medullary Thyroid Cancer, and Other Tumors with Increased RET Activity." • Allowed to proceed on 31 March 2017
27 June 2018 – Type B Meeting (See Module 1.6.3 FDA Letter 27 June 2018 – Meeting Minutes) Purpose: To discuss LOXO-RET-17001 and the LOXO-292 development program Agreements/Recommendations included: • Selection of 160 mg BID as the recommended dose for further evaluation • Primary endpoint of ORR assessed by independent radiologic review was the appropriate endpoint for LOXO RET-17001 single arm phase 1/2 study • For the primary analysis for an NDA, patients who meet the Phase 2 (dose-expansion) eligibility but enroll in the Phase 1 (dose-escalation) portion of the study would be included. Regarding the patient populations to support an NDA, FDA stated the proposal was reasonable but said "whether the proposed sample size would support approval would depend on the response rates observed (and their associated 95% confidence intervals (CIs)) in the context of available therapy and the risk-benefit profile." FDA agreed the clinical pharmacology program for LOXO 292 was sufficient to support an NDA. FDA provided preliminary feedback on the drug product and substance specification.
30 August 2018 – FDA granted Breakthrough Therapy Designation to selpercatinib 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.

31 August 2018 – FDA granted Breakthrough Therapy Designation to selpercatinib 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.
11 October 2018 – FDA granted Breakthrough Therapy Designation to selpercatinib 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.
10 October 2018 – FDA granted Orphan Drug Designation to selpercatinib for the treatment of pancreatic cancer.
19 December 2018 - Type B Breakthrough Therapy-Initial Comprehensive Multidisciplinary Meeting (*RET*-mutant MTC, including CMC and nonclinical issues) (See Module 1.6.3 FDA Letter 19 Dec 2018 MTC_BTD Type B Meeting Minutes) Purpose: To discuss the overall development program for selpercatinib and plan future interactions with FDA Agreements: • Starting materials (CMC) • Inclusion of fertility assessment endpoints in the rat juvenile toxicity study; if results of the mating trial are positive, then an additional fertility study in females will be needed (PMR)* • A gating Single Ascending Dose study to be conducted prior to initiation of the thorough QT study • Renal and hepatic impairment studies will be submitted as PMRs • Proposed patient population and number of patients for the primary analysis set required for the NDA to ensure that the lower bound of the 95% confidence interval around ORR excludes 20% • Size of safety database of approximately 250 patients • Potential conversion strategies for accelerated approval to full approval and agreement that FDA will provide feedback on study design(s) provided by the Sponsor • *Subsequent to the meeting, the Sponsor decided to conduct a stand-alone fertility study
16 January 2019 - Type B Breakthrough Therapy-Initial Comprehensive Multidisciplinary Meeting (*RET*-fusion NSCLC) (See Module 1.6.3 FDA Letter 16 Jan 2019 NSCLC_BTD Type B Meeting Minutes) Purpose: To discuss the overall development program for selpercatinib and plan future interactions with FDA. Agreements: • Proposed patient population and number of patients for the primary analysis set required for NDA to ensure that the lower bound of the 95% confidence interval around ORR excludes 30% • (b) (4) • Filing of a single NDA with both the NSCLC and MTC indications
21 May 2019 – Type B Guidance Meeting Purpose: To gain FDA feedback on key design elements for the proposed Phase 3 medullary thyroid cancer study synopsis (See Module 1.6.3 FDA Letter 19 May 2019 MTC Ph3 protocol synopsis Meeting Minutes) Agreements:

• Agreement reached on endpoint design, choice of control and proposed timeline of study
08 August 2019 – Type B Pre-NDA Meeting – CMC Only (See Module 1.6.3 FDA Letter 08 August 2019 Finalized_Combined IND 133193 Meeting Minutes-CMC) Purpose: To gain FDA feedback on plans for the CMC sections of the planned NDA for selpercatinib Agreements: • Proposed acceptance criteria for certain specified impurities in LOXO-292 drug substance; • (b) (4) polymorph, comparative in vitro permeability data is not required; • PBPK modeling is supportive and will be included in the NDA though solubility and dissolution data may be sufficient; • Justification to be included in the NDA to exclude a specification in DS and DP for (b) (4) FDA agreed that the in vivo pharmacokinetic comparison of two formulations with a range of particle size is supportive in making the determination of the appropriate level of discrimination for the dissolution method; • Data would be collected with both the pH (b) (4) media dissolution method and the current QC method (0.1N HCl media), and justification for which method would be most appropriate as the long-term QC method should be provided in the NDA.
12 August 2019 – Type C Meeting Guidance (See Module 1.6.3 FDA Letter 13 August 2019 courtesy copy – IND 133193 Meeting Minutes Written Responses Only) Purpose: To discuss clinical content and format of the planned NDA for selpercatinib and to obtain feedback on the statistical analysis plans for the summaries of clinical safety and efficacy. Agreements: • FDA feedback received on clinical/statistical NDA content related to Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) section and clinical pharmacology • Nonclinical comment acknowledged regarding the stand-alone reproductive toxicology study will be ongoing at the time of NDA submission with the final study report to be filed during the NDA review cycle
30 October 2019 – FDA granted Orphan Drug Designation to selpercatinib for the treatment of *RET* fusion-positive non-small cell lung cancer.
21 November 2019 – FDA granted Orphan Drug Designation to selpercatinib for the treatment of *RET* fusion-positive or RET mutant thyroid cancers including poorly differentiated thyroid cancer, undifferentiated or anaplastic thyroid cancer, medullary thyroid cancer and locally advanced or metastatic follicular or papillary thyroid cancer
25 November 2019 – Type B Pre-NDA Meeting Clinical/Presentation of topline data Purpose: To provide an overview of the safety and efficacy analyses from the LOXO-RET-17001 study and to seek FDA feedback regarding the selpercatinib NDA

[Module 2.5.1.3 – Clinical Overview – MTC; Module 2.5.1.3 – Clinical Overview – NSCLC]

The FDA's Assessment:

FDA agrees with the summary of regulatory interactions as summarized by the Applicant.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

Three clinical investigators for study LIBRETTO-001 were selected for inspections: Manisha Shah (Site 105), Vivek Subbiah (Site 103), and Lori Wirth (Site 109). The facility responsible for central imaging review, (b) (4) was recently inspected in (b) (4) (findings "no action indicated") and not re-inspected for the current NDA. The on-site inspections of the three audited clinical investigator sites revealed no significant findings related to the data integrity or human subject protection in the study LOXO-RET-17001. There was no evidence of underreporting of adverse events. Based on the inspections, the data generated by the inspected clinical sites, submitted by the Applicant, appear to be acceptable in support of the NDA.

Details regarding inspections can be found in the dedicated review by the Office of Scientific Investigations.

4.2 Product Quality

The product quality review team completed an Integrated Quality Assessment. The following summary is excerpted with minor changes in format from the overview of that integrated review. Please see Integrated Quality Assessment for full details.

Product Overview

Selpercatinib capsules, available in 40 mg and 80 mg strengths, consist of (b) (4) drug substance and excipients in hard gelatin capsules. The 40 mg is a size 2 gray opaque capsule with black "Lilly", "3977" and "40 mg" script. The 80 mg product is a size 0 blue opaque capsule with black "Lilly", "2980" and "80 mg" script. Both capsules are produced (b) (4) with microcrystalline cellulose and colloidal silicon dioxide. Selpercatinib capsules are manufactured (b) (4)

Selpercatinib capsules are stored in HDPE bottles. The drug product is stored at controlled room temperature. Recommended dosage: 160 mg orally twice daily.

Two (b) (4) forms of selpercatinib (b) (4) were discovered. (b) (4)

(b) (4). Presence of (b) (4) tested in the clinical studies appears to have no significant effect on the in vivo performance.

Drug Substance

Selpercatinib drug substance is white to (b) (4) powder, it is slightly hygroscopic and exhibits polymorphism. The manufacturing process for selpercatinib drug substance (b) (4) The manufacturing process description is provided and is designed to (b) (4) The analytical characterization methods for the selpercatinib drug substance are complementary and support the proposed chemical structure. The applicants manufacturing process, in-process controls, control of critical steps and the manufacturing process development data ensure that impurities are maintained as the proposed control threshold. The batch analyses data for the commercial batches show that the levels of all the specified impurities were found to be ≤ (b) (4)%. The proposed selpercatinib specifications are adequate. The applicant provided a risk assessment of elemental impurities as per ICH Q3D of the application. (b) (4)

The CMC review team identified three impurities in the selpercatinib drug substance for qualification: (b) (4)
The proposed specifications for these impurities are no more than (NMT) (b) (4)%, (b) (4)%, and (b) (4)% for (b) (4) respectively.

The proposed specifications (b) (4) are justified by the available nonclinical or clinical data. See **Error! Reference source not found.** for the data supporting the justification.

Table 4.1: Impurity Specification Justification

	Proposed specification	Daily delivered Dose of Impurity at clinical recommended dose of 160 mg twice daily	Levels in Toxicology Batch (Minipig-13 week)	Delivered Dose of Impurity at HNSTD (Minipig 13-week)	Metabolite	Specification Justified by Nonclinical data?
(b) (4)						

*based on levels in the 4-week mini-pig study rather than the 13-week study

The applicant proposed the particle size distribution (PSD) acceptance criteria (NMT (b) (4) µm) based on in vivo performance, in vitro drug release and operational control of the manufacturing process. Selpercatinib drug substance will be packaged (b) (4) The applicant proposed a retest period of (b) (4) months based on the stability data when stored (b) (4) and based on the provided that this retest period is acceptable.

Drug Product

Retevmo is supplied as 40 mg or 80 mg capsules in HDPE bottles. The drug product is formulated as (b) (4) with common pharmaceutical excipients, microcrystalline cellulose, colloidal silicon dioxide encapsulated into gelatin capsules. The appearance of the 40 mg and 80 mg selpercatinib differ by the color, size, and imprint information. The 40 mg strength is gray opaque capsule imprinted with “Lilly”, “3977” and “40 mg” in black ink, size 2 while the 80 mg strength is blue opaque capsule imprinted with “Lilly”, “2980” and “80 mg” in black ink, size 0. Both selpercatinib capsules (b) (4) (b) (4) (b) (4) The 6-months stability studies at long-term (25 °C/60% RH) and intermediate (30 °C/75% RH) storage conditions support the proposed storage conditions of 20–25 °C with temperature excursion permitted between 15 °C and 30 °C. No significant chemical or physical changes at accelerated storage conditions are reported in the NDA. Based on the 9 months available data at long term, intermediate and accelerated storage conditions, 18 months expiration date may be granted at this time.

Manufacturing

(b) (4) The commercial batch formula reflects the proposed composition for the unit dose forms and is consistent with the batch record of the executed batches. Main unit operations include (b) (4). Considering the facility’s

acceptable compliance history and relevant manufacturing experience with similar, if not more complex, unit operations of oral solid dosage forms, the facility is recommended approval.

Biopharmaceutics

The dissolution method [900 ml of 0.1 N HCl using USP Apparatus 2 (paddles) at 75 rpm] and acceptance criterion [NLT (b) (4)% (Q) in 15 minutes] proposed by the Applicant for batch release and stability testing, are deemed acceptable, based on the totality of the information and data provided. The Applicant has included drug substance particle size acceptance criteria and control of polymorphic forms in the drug substance specification. Dissolution risk is further mitigated with the implementation of the approved dissolution specification for the proposed drug product. The proposed commercial selpercatinib 40 mg and 80 mg capsules have the same formulation and manufacturing site as for the capsule batches used in Phase 1/Phase 2 and Phase 3 efficacy and safety studies. Thus, bridging between the clinical formulation and commercial product is not needed.

Recommendations

Complete CMC information has been submitted to NDA 213246 and found to be adequate upon completion of the review. All the facilities are approvable based on acceptable compliance history, no pre-approval inspections (PAIs).

OPQ recommends approval of NDA 213246 for Retevmo (selpercatinib) Capsules 40 mg and 80 mg. OPQ grants an 18-month expiration period when stored at "Controlled room temperature: 20°C - 25°C (68°F – 77 ^{o}F); excursions permitted to 15-30 ^{o}C (59°F - 86°F) [See USP Controlled Room Temperature]".

In addition, OPQ grants a (b) (4) month re-test period for the drug substance when stored (b) (4)

4.3 Clinical Microbiology

As described in the Integrated Quality Review, the microbiology reviewer indicated that the assessment of microbiological controls was adequate.

4.4 Devices and Companion Diagnostic Issues

This application is seeking approval for selpercatinib for the treatment of *RET*-fusion positive NSCLC and thyroid cancer, and *RET*-mutant MTC without contemporaneous approval of a companion diagnostic. A variety of local tests were used in LIBRETTO-001.The Applicant is working with (b) (4) for the development of a companion diagnostic. The status of these programs is summarized below.

Per the pre-NDA meeting held on November 25, 2019, Loxo proposed (b) (4)

(b) (4)

(b) (4)

The tests used to enroll patients with RET fusions included NGS (tumor samples or blood/plasma samples), PCR, and FISH; patients with RET mutations were selected using NGS (tumor samples or blood/plasma samples) and PCR. Detailed descriptions of the tests used to select patients in each efficacy population are provided in section 8 and product labeling.

Given the efficacy of selpercatinib in patients with the RET fusion-positive and RET mutant tumors discussed in this Application, the overall rarity of these populations and the availability of non-companion diagnostic testing for RET fusions and mutations, the clinical review team determined that it is in the best interest of U.S. patients to approve selpercatinib before one or more companion diagnostic assays are ready for PMA submission. Since a PMA for an in vitro companion diagnostic device was not submitted for contemporaneous approval with this NDA, approved labeling will state that there is no FDA-approved for detection of RET fusions or mutations selecting patients for treatment with selpercatinib. The Applicant has agreed to a post-marketing commitment (PMC) to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect RET fusions and mutations for identifying patients who may benefit from selpercatinib.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

Rearranged during transfection (RET) is a receptor tyrosine kinase that plays a significant role in embryonic development of excretory and parasympathetic nervous systems. RET also helps to maintain adult tissues, such as male germ cell, neural, neuroendocrine, and hematopoietic tissues. RET binding to concomitant glial cell line-derived neurotrophic factor (GDNF) family ligands (GFLs) is facilitated by 1 of 4 members of the GDNF family receptor alpha (GFRα). Once bound to a GFL multi-subunit receptor complex, RET dimerizes and auto-phosphorylates tyrosine residues within its own intracellular domain, which leads to recruitment of signaling adaptors and activation of several cellular proliferation signal transduction pathways, such as mitogen activated protein kinase (MAPK), phosphoinositide-3 kinase (PI3K), Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT), and Protein Kinase A and C pathways. Genetic mutations, such as chromosomal rearrangements or point mutations, can lead to constitutive RET activation, and the development of human cancers, such as medullary thyroid cancer (MTC) (Yakushina, V et al. 2018; Thomas, CM et al. 2019).

Selpercatinib (LOXO-292) is a small molecule with an established pharmacologic class of kinase inhibitor. More specifically, it is an ATP competitive receptor tyrosine kinase (RTK) inhibitor of RET as well as several other kinases. In biochemical in vitro kinase profiling assays, selpercatinib inhibited wild type RET at an inhibitory concentration (IC_{50}) of 17.3 nM and several common RET mutations with IC_{50} values ranging from 28.7 to 67.6 nM. Selpercatinib also inhibited Aurora B (IC_{50} = 78.8 nM) as well as VEGFR1 and 3 and FGFR1, -2, and -3, with IC_{50} values of 11.9 to 65.4 nM. Based on a maximum concentration (C_{max}) of 2890 ng/mL (~5500 nM) and human protein binding of approximately 97%, the free concentration of selperctanib is ~165 nM. Therefore, these concentrations are clinically achievable in patients treated at the twice daily oral dose of 160 mg. Selpercatinib inhibited Aurora C, KDR (VEGFR2), AXL, and PLK4 at slightly higher concentrations. Inhibition of VEGF signaling is consistent with clinical findings of hypertension.

In a screening assay investigating inhibition of cellular proliferation in 87 cancer cell lines exposed to selpercatinib, 4 (LC-2, TPC1, TT, and MZ-CRC1) showed clear sensitivity, each of which harbored a RET fusion mutation. Using these cell lines in in vivo studies, investigators observed selpercatinib dose-dependent reduction in tumor growth in mice implanted with TT human thyroid medullary carcinoma and human LC-2/ad human lung adenocarcinoma. Mice did not show signs of weight loss or other overt signs of toxicity when exposed to up to 30 mg/kg selpercatinib, but lost 14% of their body weight by Day 14 at the 100 mg/kg dose level.

To assess the safety of selpercatinib, Loxo conducted GLP-compliant toxicology studies of up to 13-weeks in Sprague Dawley rats and Gottingen mini pigs. There were no unique human metabolites present at meaningful levels, and all metabolites were present in human plasma at levels ≤ 3%; with these levels the toxicological coverage of all metabolites is sufficient. Skeletal findings were present in both species used for toxicological assessment. In female minipigs there were findings of minimal to marked increases in physeal thickness at the 15 mg/kg high dose level (0.3 times the clinical AUC of 51600 ng*hr/mL at the 160 mg twice daily dose). Similarly, rats had signs of physeal hypertrophy in 4-week studies at exposures 3 times the human exposure. In rats there were also findings of tooth dysplasia, malocclusion and tooth discoloration. Bone and teeth findings may be relevant to a pediatric population and are included in Section 8.4 of the label.

Due to sex-specific differences in exposure, in the 13-week toxicology study male rats received selpercatinb at doses of 2, 7.5, or 20 mg/kg while females received 7.5, 25, or 75 mg/kg daily via oral gavage, followed by a 4-week recovery. Selpercatinib-exposed rats experienced hair thinning, and skin scabs. In both the general toxicology study and the embryo-fetal development study, female rats at the high dose had increased weight gain, suggesting some potential hormonal or thyroid-related effects of selpercatinib. Reticulocyte counts were decreased in males and there were dose-dependent increases in liver enzymes. Pathology findings in the rat toxicology study included mild decreases in hematopoiesis within the bone marrow, lung inflammation, and testicular atrophy. At the end of the dosing period exposures at the high dose level were 1.5 and 2.8 times the human exposure of 51600 ng*hr/mL at the 160 mg twice daily dose in male and female rats, respectively. Additional findings observed in rats at the high dose levels (3-5 times the human exposure at the 160 mg twice daily dose) during the 4-week studies included signs of multiorgan mineralization that correlated with increased serum phosphorous levels, consistent with frequent findings in drugs that inhibit the FGFR family, as well as moderate degeneration/necrosis of pancreatic acinar cells in high-dose males, and weight loss correlating with reduced food consumption, malocclusion, and missing teeth.

In a 13-week study in minipigs, male and female animals received selpercatinib at doses of 2, 5, or 15 mg/kg/day for 13 weeks via oral gavage. Seven pigs died or had to be euthanized due to high toxicity in the 15 mg/kg group. Animals in this high-dose cohort showed signs of minimal to marked stomach atrophy, skin inflammation, and brain infiltrates. GI toxicity and rash were both common findings in clinical trials. In the 4-week studies in minipigs, animals also had increases in ALP and phosphorous. Liver enzyme increases are a common clinical event. Though hERG potassium current assays demonstrated low potential for LOXO-292 to cause QTc prolongation, with IC_{50}s of 1.1 or 2.79 µM, respectively, female mini pigs in the 4-week study that received 5 or 12 mg/kg selpercatinib for 28 days had statistically significant QT prolongation compared to controls. While this increase was not significant when corrected for heartrate (i.e. QTc interval), the trend towards an increase was still present at the 12 mg/kg

high dose (approximately 0.6 times the clinical exposure at the 160 mg twice daily dose). The label includes a warning for QTc prolongation.

To assess the potential effects of selpercatinib on fertility, Loxo included histopathological assessments of reproductive organs in general toxicology studies as well as dedicated fertility studies in both male and females rats. Both rats and minipigs had findings of testicular degeneration with reduced testicular weight as well as reductions in sperm in the testis and epididymis at exposures lower than the clinical exposure at the 160 mg twice daily dose. Similarly, in a dedicated fertility study, male rats treated with selpercatinib for 28 days prior to cohabitation with untreated females through 2 weeks post-mating at doses up to 30 mg/kg/day showed dose-dependent increases in testicular germ cell depletion and spermatid retention at doses ≥3 mg/kg (~0.2 times the clinical exposure by AUC) accompanied by altered sperm morphology at 30 mg/kg (~twice the clinical exposure by AUC). Despite these changes, there were no effects on clear effects on mating or fertility in this study.

In female minipigs, animals at the 15 mg/kg high dose level had decreased or absent corpora lutea and decreases in the number of size of follicles and stromal proliferation along with increases in corpora luteal cysts at doses ≥2 mg/kg (~0.07 times the human exposure at the 160 mg twice daily dose). Rats showed few ovarian findings in the general toxicology studies, though there were increases in cornification and in vaginal mucification suggestive of estrous cycle effects. Consistent with these findings, there were decreases in the number of estrous cycles at a dose of 75 mg/kg (approximately equal to the human exposure at the 160 mg twice daily clinical dose) in a dedicated fertility study in female rats treated with selpercatinib for 15 days before mating to Gestational Day 7. While selpercatinib did not have clear effects on mating performance or ability to become pregnant at any dose level, half of the females at the 75 mg/kg dose level had 100% nonviable embryos. At the same dose level, in females with viable embryos there was still 69% post-implantation loss. Based on these findings, the potential for at least transient effects on female and, to a smaller extent, male fertility exists in humans.

To assess the potential developmental and reproductive toxicity of selpercatinib, Loxo conducted embryo-fetal development studies of oral selpercatinib in Sprague-Dawley rats (Gestation Day 7-17). At doses greater than or equal to 100 mg/kg (approximately 3.6 times the clinical selpercatinib AUC exposure of 51600 ng*hr/mL at the 160 mg dose twice daily) pregnant rats experienced 100% post-implantation loss. At a dose of 50 mg/kg (approximately equal to the human exposure), 6 of 8 females experienced 100% early resorptions. Two other females at this dose had early resorptions and only 3 viable fetuses across 2 litters. These fetuses had lower body weight than fetuses born to control dams. Two fetuses from 1 litter had a short tail; one fetus from the other litter had a small snout and fetal edema. Because of high fetal toxicity at doses resulting exposures similar to the human exposure at the 160 mg twice daily clinical dose, studies in a second species were not warranted. Based on data from the

embryo-fetal development studies a warning for embryo-fetal toxicity is included in the label for RETEVMO. No studies were conducted or necessary to investigate the presence of selpercatinib in milk. As many drugs are secreted in breastmilk, the label includes a warning not to breastfeed during treatment or for 1 week after the final dose.

In the standard genotoxicity battery, selpercatinib was negative in both the Ames and the in vitro micronucleus assay regardless of metabolic activation. In the in vivo micronucleus assay in rats, selpercatinib did cause increases in micronuclei at high dose levels; the lowest dose that did not result in micronuclei was 150 mg/kg (~7 times the human Cmax at the 160 mg twice daily dose). These findings may be related to the inhibition of Aurora kinase B and, at higher concentrations, observed in in vitro screening assays. Given the negative in vitro findings and the occurrence of micronuclei only at high exposure multiples compared to the human exposure, the recommendations for contraception followed the guidelines for non-genotoxic drugs or drugs that are aneugenic but only at high concentration margins discussed in the FDA guidance, Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations.

Dedicated carcinogenicity studies were not conducted with selpercatinib, as they are not needed to support the use of a drug intended to treat patients with advanced cancer; however, as the MTC indication includes patients who can have a prolonged life expectancy, FDA has requested carcinogenicity studies for selpercatinib as postmarketing requirements (PMRs). From a pharmacology/toxicology perspective, there are no outstanding issues that would prevent the approval of selpercatinib in patients with *RET* mutant MTC, *RET* fusion-positive thyroid cancer or *RET* fusion-positive NSCLC.

5.2 Referenced NDAs, BLAs, DMFs

The Applicant's Position:
Not applicable

The FDA's Assessment:
Not applicable

5.3 Pharmacology

Primary pharmacology—Completed by FDA

Dr. Brian Cholewa reviewed many of the primary pharmacology studies for LOXO-292 under the original IND submission. His review of the primary pharmacology reviewed under IND 133193 is reproduced with minor editorial changes in this document.

Reviewed under IND by Dr. Brian Cholewa:
The Applicant determined the IC_{50}s of LOXO-292 against wild-type and mutant RET at ATP concentrations of 1mM and/or K_m (concentration specific to each kinase; Table 5.1:) using CisBio's HTRF Kinase-TK assay technology (Study # LOXO-292-PHARM-003). LOXO-292 inhibited both wild-type and mutant RET at nanomolar concentrations. Wild type RET was the most sensitive to LOXO-292 with an IC_{50} value of 0.4 nM when incubated with ATP concentrations at K_m. LOXO-292 also inhibited Aurora B, FGFR1, FGFR2, FGFR3, FLT1 (VEGFR1), and FLT4 (VEGFR3) at low nanomolar ranges that were similar to RET mutants.

Table 5.1: Enzyme activity of LOXO-292

Enzyme	ATP Concentration	IC50 (nM)		
		AVE	STDEV	n
wt RET	K_M	0.4	0.1	24
wt RET	1 mM	17.3	6.7	48
V804M RET	1 mM	36.7	17.9	49
V804L RET	1 mM	30.5	4.2	30
G810R RET	1 mM	680.4	273.7	23
M918T RET	1 mM	28.7	5.5	30
A883F RET	1 mM	67.6	32.2	21
S891A RET	1 mM	32.9	10.3	21
Aurora A	No ATP	782.2	112.3	29
Aurora B	No ATP	78.8	13.7	30
FGFR1	K_M	65.4	9.8	14
FGFR2	K_M	26.7	4.4	14
FGFR3	K_M	53.8	14.2	14
FLT1	1 mM	27.7	11.7	35
FLT4	1 mM	11.9	4.3	22

(Applicant Table excerpted from Study # LOXO-292-PHARM-003)

Reviewed under NDA by Dr. Amy Skinner:
In another assay, investigators employed the KinEASE-TK Assay kit to quantify the enzyme activity of wild type RET and several mutant isoforms (A764T, L790F, V804M, 898-901, and M918T) following incubation with titrated concentrations of selpercatinib (Study LOXO-292-PHARM-021). This assay uses fluorescent energy transfer detection to determine kinase activity following incubation of the kinase with a biotinylated target substrate, followed by the addition of a Eu (donor)-labelled anti-phosphotyrosine antibody and a streptavidin-labelled XL665 acceptor molecule. In the presence of 1 mM ATP, selpercatinib inhibited wild type and mutant RET isoforms in concentration-dependent fashion. Each reaction had 8 replicates.

Table 5.2: Selpercatinib-Mediated Inhibition of Wild Type and Mutant RET Isoforms Determined by a KinEASE-TK Assay

RET isoform	Selpercatinib Mean IC_{50} (nM)
Wild type	2.79
RET (A764T)	1.81
RET (790F)	0.92
RET (V804M)	6.40
RET (M918T)	1.50
RET Delta(898-901)	0.97

An in vitro RBC HotSpot kinase assay (Study LOXO-292-PHARM-022) assessed LOXO-292 activity on non-RET kinases Aurora C, AXL, KDR/VEGFR2, PLK4, and TIE2/TEK. When ATP was equal to K_M, selpercatinib inhibited these non-RET kinases with IC_{50}s, ranging from 28 nM to 4260 nM. The IC_{50}s of VEGFR2 and PLK4 are within a range that is clinically achievable, although follow-up assays in cells lines showed VEGFR2 inhibition at slightly higher than clinical concentrations based on cell line data (LOXO-PHRM-010, below).

Table 5.3: LOXO-292 Activity on Non-RET Kinases

Kinase	ATP (µM)	IC_{50} (M)
Aurora C	15	2.9×10^{-7}
AXL	100	2.37×10^{-7}
KDR/VEGFR2	20	2.83×10^{-8}
PLK4/SAK	10	6.81×10^{-8}
TIE2/TEK	30	4.26×10^{-6}

Investigators conducted a subsequent analysis of selpercatinib-mediated inhibition of TIE2 via a KINOME*scan*™ (Study # LOXO-292-PHARM-026). This assay quantified competitive inhibition between a DNA-tagged kinase (TIE2) and an immobilized ligand with quantitative PCR. Upon addition of serial titrations, selpercatinib bound TIE2 with a mean K_D of 93 nM (not shown).

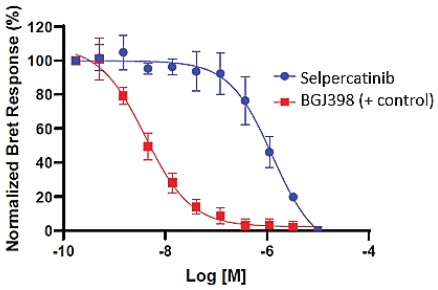
A minor metabolite of selpercatinib, M4, formed by N-dealkylation, inhibited wild-type RET with and IC_{50} of 70 nM in the presence of 1 mM ATP as determined via CisBio's HTRF Kinase-TK assay technology (Study # LOXO-292-PHARM-029). M4 also inhibited mutant RET, albeit with lower activity, in an in vitro assay employing KIF5B-RET fusion protein-expressing HEK-293 cells (IC_{50} of 1667 nM).

The Applicant conducted additional studies investigating the activity of selpercatinib in cellular assays. Measured by ELISA, selpercatinib inhibited VEGFR3 kinase activity at an IC_{50} concentration of 33 nM in murine embryonal fibroblasts (MEFs) expressing a high level of full-

length human VEGFR3 incubated with serial dilutions of selpercatinib for 90 minutes (LOXO-292-PHARM-009).

Investigators incubated three human embryonic kidney (HEK)-293 cell lines expressing doxycycline-inducible wild type FGFR1, FGFR2, or VEGFR2 with serial dilutions of selpercatinib for 1 hour then stimulated cells with 100 ng/mL human acidic FGF (FGF-1) or 56 ng/mL human VEGF for 5 minutes (LOXO-292-PHARM-010) before lysing cells and quantifying selperctainib-mediated inhibition of phosphorylation of the selected receptors via ELISA assay (antibodies against protein for capture, anti-phosphotyrosine for detection). Selpercatinib inhibited phosphorylation in FGFR1 and -2 targets with IC_{50}s of 248 or 242 nM, respectively, and of VEGFR2 with an IC_{50} of 683 nM. In the nanoBRET target engagement assay, a tracer molecule bound to a Nano-luciferase fused-target kinase becomes displaced by competitors, leading to loss of a bioluminescence energy transfer (BRET) signal; selpercatinib showed concentration-dependent inhibition of tracer binding to FGFR1 in FGFR1-Nanoluc-expressing HEK-293T cells following a 1-hour exposure to serial dilutions of selpercatinib, but at a concentration 5-fold higher than the previous experiment (IC_{50} = 1286 nM, Study # LOXO-292-PHARM-025), and significantly higher than a comparator FGFR inhibitor.

Figure 5.1: FGFR1 Resistance to Selpercatinib Inhibition via In Vitro Target Engagement (NanoBRET) Assay



(Applicant figure excerpted from Study #LOXO-292-PHARM-025)

The Oncopanel Multiplexed Cytotoxicity Assay characterized the cellular responses of 87 cancer cell lines to serial dilutions of selpercatinib (LOXO-292-PHARM-016). The 4 cancer cell lines harboring RET fusion mutations (LC-2, TPC1, TT, and MZ-CRC1) exhibited the greatest sensitivity to selpercatinib, with EC_{50}s < 10 nM. Of the 87 cell lines employed in the Oncopanel, the Applicant did not specify if any harbored VEGFR or FGFR mutations.

Table 5.4: Summary of Oncopanel Cytotoxicity Panel Results Following 72-Hour Selpercatinib Exposure

Cell line (Cancer Type)	Cell Count GI_{50} (nM)*	G1/S Cell Cycle Block (nM)**

LC-2 (RET+ Lung Adenocarcinoma)	5.12	12.0
TPC1 (RET+ Papillary Thyroid Carcinoma)	4.13	8.04
TT (RET+ Medullary Thyroid Carcinoma)	1.41	7.41
MZ-CRC1 (RET+ Medullary Thyroid Carcinoma)	2.9	13.5

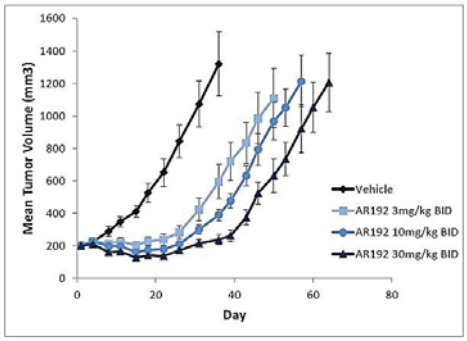
*GI_{50} is concentration needed to inhibit observed growth by 50%
**G1/S Block assessed via phospho-histone H3 labeling

Reviewed under IND by Dr. Brian Cholewa:

Anti-tumor activity of LOXO-292 in mouse tumor models

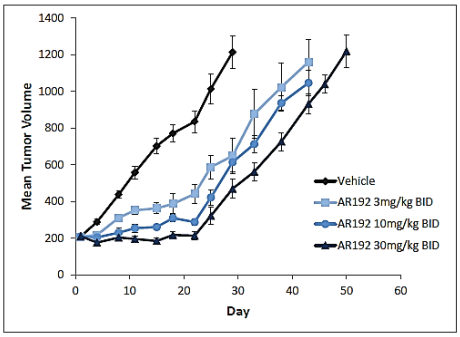
Anti-tumor activity of LOXO-292 (AR192) was tested in non-GLP xenograft and allograft mouse tumor models. At doses of 3, 10, and 30 mg/kg twice daily, LOXO-292 demonstrated modest dose-dependent in vivo tumor growth inhibition in both TT human thyroid medullary carcinoma (Study # LOXO-292-PHARM-004**)** and human LC-2/ad human lung adenocarcinoma (Study # LOXO-292-005A1**)** cells.

Figure 5.2: Anti-tumor activity of LOXO-292 in TT thyroid carcinoma tumor xenografts



(Applicant Figure excerpted from Study# LOXO-292-PHARM-004)

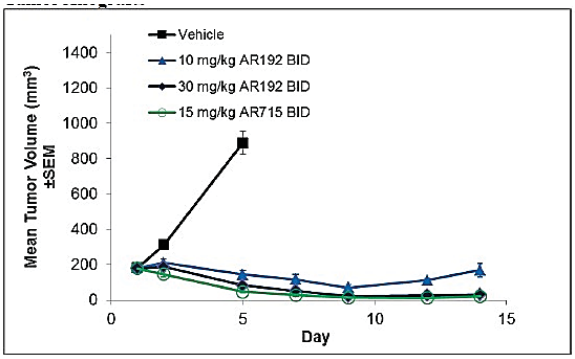
Figure 5.3: Anti-tumor activity of LOXO-292 in LC-2/ad human lung adenocarcinoma tumor xenografts



(Applicant Figure excerpted from Study # LOXO-292-005A1)

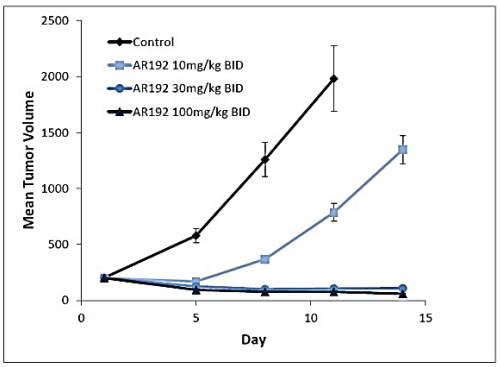
In two mouse fibroblast tumor models, NIH-3T3 cells were stably transfected with the KIF5B-RET fusion (Study # LOXO-292-PHARM-006) or with KIF5B RET V804M (Study # LOXO-292-PHARM-007) and allografted into nu/nu NCr mice. LOXO-292 was administered at doses of 10 and 30 mg/kg twice daily in both studies and at 100 mg/kg twice daily in the mutant RET model. LOXO-292 resulted in tumor growth inhibition and regression at 10 and 30 mg/kg in the wild-type RET model and at 30 and 100 mg/kg in mutant RET model. Doses up to 30 mg/kg were tolerable throughout the studies but treatment groups generally had some weight loss when compared to controls. The 100 mg/kg dose was not well-tolerated and animals lost 14% of body weight by Day 14 (data not shown).

Figure 5.4: Anti-tumor activity of LOXO-292 in NIH 3T3 KIF5B RET tumor allografts



(Applicant Figure excerpted from Study # LOXO-292-PHARM-006)

Figure 5.5: Tumor activity of LOXO-292 in NIH 3T3 KIF5B RET V804M mouse fibroblast tumors



(Applicant Figure excerpted from Study # LOXO-292-PHARM-007)

Inhibition of phosphor-RET in in vitro and mouse fibroblast tumor models

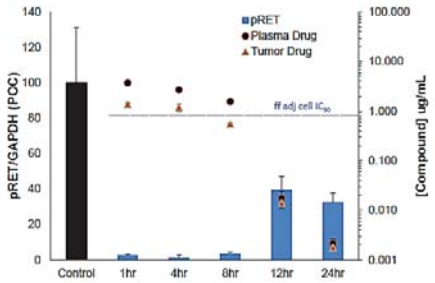
The Applicant investigated the effects of LOXO-292 on RET activation in both cell based and in vivo by examining levels of RET phosphorylation. For wild-type RET, ligand binding leads to RET dimerization and autophosphorylation. LOXO-292 inhibited RET phosphorylation in cell lines expressing fusions with wild-type and V804 mutant RET with IC_{50} values in the low nanomolar range. LOXO-292 also inhibited autophosphorylation of RET in cells expressing full length RET with the M918T point mutation (Study # LOXO-292-012). In addition investigators demonstrated inhibition of phospho-RET in vivo using the KIFB-wild-type or mutant- RET fusion mouse fibroblast tumor models (Study # LOXO-292-PHARM-008) by measuring inhibition of phospho-RET and drug concentration in both tumor tissue and plasma following a single oral dose of LOXO-292. These studies showed an inverse correlation between drug concentration and phospho-RET inhibition, with phospho-RET being almost completely abrogated up to 8 hours. At 30 mg/kg, LOXO-292 was more efficient at inhibiting RET at 2 hours post-dose than 60 mg/kg of cabozantinib, an approved multi-kinase inhibitor that targets RET.

Table 5.5: Inhibition of phospho-RET by LOXO-292 in RET cell assays

Cell Assay:	LOXO-292	
	IC_{50} ± SD (nM)	N
KIF5B-RET	4 ± 2	55
KIF5B-RET V804L	11 ± 2	2
KIF5B-RET V804M	32 ± 28	2
RET M918T	8 ± 1	2

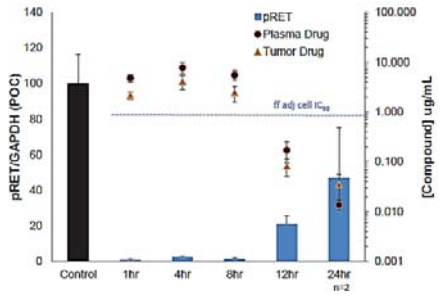
(Applicant table excerpted from Study# LOXO-292-012)

Figure 5.6: Inhibition of phospho-RET in NIH-3T3 KIF5B-RET tumors from mice receiving 10 mg/kg LOXO-292



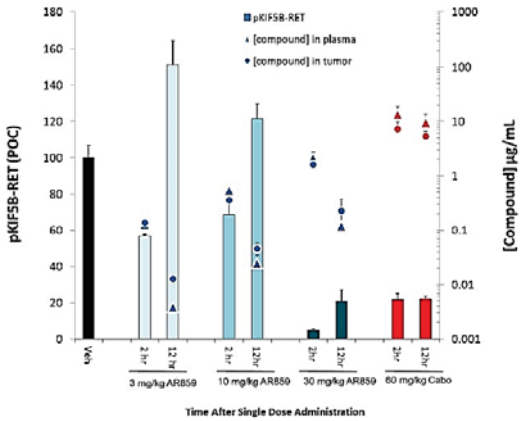
(Applicant figure excerpted from Study #LOXO-292-PHARM-008)

Figure 5.7: Inhibition of phospho-RET in NIH-3T3 KIF5B-RET tumors in mice receiving 30 mg/kg LOXO-292



(Applicant figure excerpted from Study #LOXO-292-PHARM-008)

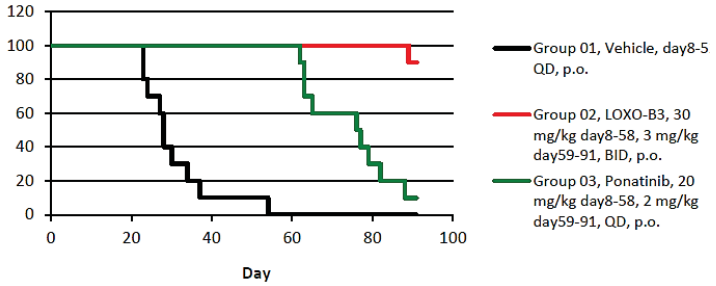
Figure 5.8: Inhibition of phospho-RET in NIH-3T3 KIF5B-RET tumors from mice receiving a single oral dose LOXO-292 or cabozantinib



(Applicant figure excerpted from Study #LOXO-292-PHARM-008)

Reviewed under NDA by Dr. Amy Skinner:
Investigators explored the in vivo activity, including the potential for brain penetration, of selpercatinib using a patient-derived human RET fusion colorectal cancer model (PDX CR2518) intracranially implanted in nude mice. Tumor-bearing mice received oral administration (p.o.) of 30 mg/kg LOXO-292 twice per day on Days 8-58, then 3 mg/kg on Days 59-91; or 20 mg/kg of ponatinib (a multi-kinase inhibitor that includes RET as a target approved for use in leukemia) p.o., once per day on Days 8-58, then 2 mg/kg on Days 59-91. LOXO-292-treated mice demonstrated a 90% survival rate (Study # LOXO-292-PHARM-013). Selpercatinib-treated mice maintained steady body weight (not shown).

Figure 5.9: Increased Survival Rate in Intracranial Tumor Xenograft Following Selpercatinib Treatment



(Applicant figure excerpted from Study #LOXO-292-PHARM-013)
LOXO-B3 in legend is LOXO-292

Secondary Pharmacology

The Applicants Position:

Selpercatinib is a highly potent and selective inhibitor of RET, with minimal inhibition of other kinase and non-kinase targets. Selpercatinib was at least 250-fold more selective for RET over 98% of 329 non-RET kinases and maintained significant selectivity for RET against non-kinase targets. Selpercatinib had no significant anti-proliferative effects in human cancer cell lines that do not express constitutively activated RET. Selpercatinib at a concentration of 1 µM, significantly inhibited only two targets 5-HT transporter and $a_{2c}(h)$ in a binding screening assay against 54 targets that included transmembrane and soluble receptors, ion channels, and monoamine transporters. [Module 2.4.2.2]

The FDA's Assessment:

Selpercatinib is an inhibitor of RET as well as VEGFR1 and 3. The drug also inhibits FGFR1, 2, and 3 as well as Aurora kinase B. Investigators employed a comprehensive screening Biopharma Radioligand Array that included binding, enzyme and uptake, and cellular and nuclear receptor function assays (Study # LOXO-292-PHARM-002). Results >50% represent significant effects in these assays. At a concentration of 1.0 µM, selpercatinib demonstrated weak binding activity (52%) toward human cellular receptor α_{2C}, but stronger activity (70%) toward human 5-HT transporter. Selpercatinib did not inhibit assayed enzymes or uptake, or exhibit activity in the cellular and nuclear receptor functional assay, suggesting little potential for off-target effects.

Selpercatinib bound hormone- (adrenergic β and testosterone) and hormone receptor ligands (thyroid receptor α and β coactivators) at nanomolar concentrations (IC_{50} = 0.24 – 2.77 nM) in a radioligand binding assay (Study # LOXO-292-PHARM-018). Selpercatinib did not bind human cell binding receptors α1A, β1, β2, or estrogen ERα in a subsequent in vitro binding assay (Study

LOXO-292-PHARM-019).

Safety Pharmacology

The Applicant's Position:
There were no effects observed in respiratory or neurobehavioral safety pharmacology evaluations conducted in rats.[Modules 2.6.2.4.2.2, 2.6.2.4.2.3]. In ion channel-blocking assays [Module 2.6.2.4.1.1], selpercatinib was found to only block hERG and had minimal to no effects on other cardiac channels. Selpercatinib had an IC_{50} value of 1.1 µM in the GLP hERG assay [Module 2.6.2.4.1.4]. No abnormal ECGs and hemodynamic data occurred at single oral doses in minipigs. At this dose, the C_{max} was approximately 0.3 times the human C_{max} at the clinical dose of 160 mg BID (to be marketed dose). In the 91-day repeated-dose study, female minipigs given 5 mg/kg/day, had slight QTc prolongation which was not considered adverse. This dose corresponded to a mean C_{max} approximately 0.2 times the human maximum concentration at to be marketed. Dose limiting toxicities in minipigs prevented any opportunity to study cardiovascular effects of exposures that exceeded the hERG IC_{50} or those measured in patients at the to be marketed dose. [Module 2.6.2.4.2.1]

The FDA's Assessment:
Dr. Brian Cholewa reviewed the hERG study under the original IND submission.

LOXO-292 inhibited the hERG potassium current with IC_{50} of 1.1 µM in the GLP in vitro hERG assay studies, respectively, suggesting low potential for QTc prolongation. In the 28-day minipig study, statistically significant QT prolongation was observed in females administered 5 and 12 mg/kg LOXO-292 when compared to controls though when corrected for heartrate, QTc intervals were no longer statistically significant and were more similar to baseline and controls; however, the trend towards increased QTc remained at 12 mg/kg (approximately 0.6 times the clinical exposure at the 160 mg twice daily dose).

Table 5.6: QTc in the Mini-pig 4-week study

Group	Dose Level (mg/kg/day)		Predose Phase Day 6	Predose Phase Day 13	Dosing Phase Day 3 (2 hours postdose)	Dosing Phase Day 23 (2 hours postdose)
1	0	Mean	351	348	355	346
		SD	14.5	16.5	18.3	14.2
		N	6	6	6	6
2	2	Mean	353	355	358	344
		SD	7.8	15.9	11.9	9.0
		N	6	6	6	6
3	5	Mean	360	358	362	356
		SD	10.8	12.3	15.7	15.7
		N	6	6	6	6
4	12	Mean	356	362	371	364
		SD	14.9	12.5	21.2	19.3
		N	5	6	6	6
		P(Overall)	-	-	0.3919	0.1129
		Statistics	X	X	A	A

A = ANOVA and Dunnett's.
X = Not analyzed.

(Applicant Table Excerpted from Study #8350673)

5.4 ADME/PK

The Applicant's Position:

Overall, the pharmacokinetic (PK) data for selpercatinib have the appropriate characteristics to enable its pharmacological and toxicological evaluation. Selpercatinib was absorbed and orally bioavailable in all species tested.[Module 2.6.4.3.3.1] Exposure of selpercatinib was generally greater in males than females across all studies. In the toxicology species (rat and minipig, exposure (C_{max} and AUC_{0-24}), increased with the increase in dose level. [Modules 2.6.4.3.4.1, 2.6.4.3.4.2]. Selpercatinib distributes into tissues of all species [Module 2.6.4.4.1] with evidence of some limited penetration into the CNS in rodents [Modules 2.6.4.4.2, 2.6.4.4.3.1]. Humans and rats had a similar extent of plasma protein binding whereas minipigs showed a lower bound fraction [Module 2.6.4.4.4]. CYPP450-mediated oxidation was the major route of metabolism in all species examined. [Module 2.6.4.5.3]. Analysis of plasma from the toxicity species and from human cancer patients, showed that unchanged selpercatinib was the major component in plasma. Metabolites are less potent than selpercatinib and are present in low amounts, and therefore are unlikely to contribute to the pharmacological action of selpercatinib [Module 2.6.4.5.7]. None of the metabolites of selpercatinib accounted for more than 10% of total drug-related material in plasma of humans and therefore, were not quantified in the toxicology studies and no further studies on these metabolites were performed. [Module 2.6.4.5.8]. Renal excretion appears to be a minor pathway of elimination of selpercatinib [Module 2.6.4.6].

The FDA's Assessment:

Type of Study	Major Findings
Protein Binding	
Study # LOXO-292-DMPK-012: Assessment of Reversible Protein Binding of Array-192 in Mouse, Rat, Minipig, Dog and Human Plasma by Equilibrium Dialysis	The mean plasma protein binding for 1 µM selpercatinib was 88-98% in all 5 species examined, as determined by equilibrium dialysis.

Species	% Protein Bound
CD-1 mouse	98.4
Sprague Dawley rat	97.2
Gottingen mini-pig	88.3
Beagle dog	89.9
Human	97.3

Absorption	
LOXO-292-DMPK-009: Pharmacokinetics of LOXO-292 Following Single PO or IV Dose Administration to Sprague Dawley Rats	Rats received a single PO dose of selpercatinib

Dose		10 mg/kg	30 mg/kg	100 mg/kg	300 mg/kg	600 mg/kg
# of animals#		(n = 3)	(n = 3)	(n = 3)	(n = 3)	(n = 3)
C_{max} (µg/mL)	M	1.44	4.69	8.84	31.4	36.9
	F	ND	3.15	12.8	18.7	27.3
AUC_{0-t} (µg*h/mL)	M	25.5	89.6	271	1710	2180
	F	ND	26.8	173	568	917
%F*	M	62.5	73.2	66.3	NA	NA
	F	ND	64.0	124	NA	NA
Dose Proportionality**						
Dose Fold	M		-	3.3x	10x	20x
	F		-			
C_{max}	M		--	2.6	9.2	10.8
	F		-	4.1	5.9	8.7
AUC_{0-t}	M		-	3.8	24.1	30.7
	F		-	6.5	21.2	34.2

M = Male; F = Female; (#) 3 animals per sex
*Bioavailability (dose normalized to AUC_{0-t} PO divided by mean dose normalized AUC_{0-t} IV x100), IV data was accrued in a different study
**30 mg/kg dose is baseline
NA = not applicable; ND = no data (females not treated at that dose)

LOXO-292-DMPK-004: Pharmacokinetics of LOXO-292 Free Base and LOXO-292 Phosphate Salt Following Single PO or IV Dose Administration to Gottingen Mini-Pigs and Yorkshire Pig	Gottingen mini-pigs and a Yorkshire pig received a single PO dose of selpercatinib; another minipig received a single IV dose (1 mg/kg) of selpercatinib in order to calculate oral bioavailability.

Dose	10 mg/kg	30 mg/kg	60 mg/kg	100** mg/kg
	(n = 4)	(n = 4)	(n = 2)	(n = 4)
C_{max} (µg/mL)	0.506	0.933	1.43	4.18
AUC_{0-t} (µg*h/mL)	9.42	28.8	28.4	101
%F*	29.9	30.5	15.0	-

*Bioavailability (dose normalized to AUC_{0-t} PO divided by mean dose normalized AUC_{0-t} IV x100
**Yorkshire pig, all other groups were mini-pigs

Distribution

Study # LOXO-292-DMPK-013: In Vitro Partitioning of ARRY-192 into Mouse, Rat, Dog and Human Blood and Plasma

Investigators prepared aliquots of blood and plasma isolated from CD-1 mice, Sprague Dawley rats, beagle dog, or human, then spiked specimens with 1.0 µM selpercatinib, incubated for 30 minutes, and quantified blood-to-plasma partitioning via LC-MS/MS.

Species	Blood : Plasma Ratio
Mouse	0.65
Rat	0.62
Dog	0.99
Human	0.70

Study # LOXO-292-DMPK-029: Quantitative Whole-Body Autoradiography in Male Long Evans Rats After a Single Oral Administration of [^{14}C]LOXO-292

Tissues from male rats that received 10 mg/kg [^{14}C]-labeled selpercatinib showed the highest levels in uveal tract (24 hours post-dose), eyes (24 hr), Harderian gland (2 hr), meninges (72 hr), and pigmented (melanin-containing) skin (8 hr). Selpercatinib was undetectable in most tissues by 72 hours post-dose. Selpercatinib remained in non-pigmented skin longer than 672 hours.

Metabolism

Study # LOXO-292-DMPK-030: Exposure Margin Determination for LOXO-292 and Identified Metabolites in Matrix-Normalized Rat, Minipig, and Human Plasma Samples and Cross-Subject Exposure Comparison in Plasma from Individual Human Subjects

There were no significant unique human metabolites of selpercatinib. Selpercatinib most frequently underwent oxidative metabolism at the N-6 nitrogen of the diazabicycloheptanyl moiety and the isobutanol side chain, to LOXO-292 N_6-oxide (M2). Though some studies suggested M2 levels in human plasma of 17-21% (see table below; included for general in vivo comparisons between species) or more of parent selpercatinib in human plasma, a follow-up quantitative study of radiolabeled selpercatinib only in humans showed levels of ~3% for M2 with similar levels for M4 and M3 and trace levels of other metabolites. Given the low levels of all metabolites in humans and the presence of M2, M4, and M3 metabolites in animal serum, the metabolites, despite

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Study # LOXO-292-DMPK-040: Studies of the N-Oxide Metabolite of Loxo-292

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potentially higher levels in humans, have an adequate safety assessment.

Normalized male plasma metabolites (from non-definitive study LOXO-292-DMPK-030)

Component	Human (% of total)	Rat (% of total)	Minipig (% of total)
LOXO-292	70.6	97.8	92.6
M2	20.4	0.53	1.18
M5	4.49	0.661	0.960
M4	3.45	0.801	5.25
M7	0.791	ND	ND
M3	0.163	0.179	0.0508
M6	0.0351	ND	ND
Total	100	100	100

ND = Not detected. Female data is comparable

Investigators examined plasma protein binding of major selpercatinib metabolite, M2 (N-oxide-LOXO-292, A0008751). Rapid equilibrium dialysis revealed that N-oxide-LOXO-292 plasma protein binding was comparable at concentrations of 300 or 3000 ng/mL in rat, minipig, or human plasma. M2 exhibited stability, with little to no formation of LOXO-292, when incubated with whole blood, liver microsomes, or hepatocytes from all examined species. M2 was stable following incubation in buffers ranging from pH 2.0 to 9.0.

Plasma Protein Binding (% bound average)

M2 ng/mL	Human	Mini Pig	Rat
30	81.8%	60.5%	85.0%
300	77.4%	59.9%	78.3%

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Excretion

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There was no dedicated excretion study submitted under the NDA or IND; however, an assessment of excretion was included in Study LOXO-292-DMPK-004 (reviewed above in Absorption) in minipigs. After a single 1 mg/kg IV dose of selpercatinib, there was renal excretion of ~3%.

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5.5 Toxicology

5.5.1 General Toxicology

The Applicant's Position:

Rats (Sprague-Dawley) and minipig (Göttingen) were chosen as relevant rodent and non-rodent species for toxicology program based on pharmacokinetic and metabolic considerations. Target organs of toxicity common to the rat and minipig were hematopoietic system, lymphoid

system, tongue, pancreas, skeletal system (epiphyseal growth plate of femur/sternum) and male reproductive system (testes and epididymis). In general, the toxicities induced in rats and minipig reversed or were partially reversible; the exception was the testis. In the minipig, all regions of the gastrointestinal tract were targets and gastrointestinal lesions caused moribundity. The ovary was a target in the minipig at higher doses and with prolonged dosing. Prolonged oral dosing in both species induced changes in the reproductive system that included: vagina (rat), testis and epididymis (rat; minipig). Targets specific to the rat included: liver (clinical pathology changes only), incisor tooth, Brunner's gland, and lungs. In addition, multi-tissue mineralization associated with hyperphosphatemia was noted only in rats. Minipigs were exquisitely sensitive to selpercatinib and was the most sensitive species. Major toxicological findings that occurred in the minipig were at doses that induced moribundity/lethality with exposures below therapeutic exposures in human. [Modules 2.6.6.1.1, 2.6.6.1.2]

The toxicology findings were compared to adverse events (AEs) observed in adult patients treated with selpercatinib. Certain AEs in patients had comparable findings with animals in the non-clinical toxicity studies. Similar findings included: changes in hematopoietic, lymphoid, and GIT systems, liver and altered inorganic phosphorus levels (hyperphosphatemia). Some of the changes identified in the toxicology studies were predictive for AEs in humans. [Module 2.6.6.9]

The FDA's Assessment:

Study title/ number:
A 13-Week Daily Oral Gavage Toxicity and Toxicokinetic Study of LOXO-292 in Rats with a 4-Week Recovery Phase/ Study # LOXO-292-TOX-011

- Effects on incisor teeth, including malocclusion and discoloring/demineralization, were apparent at toward the end of dosing phase
- Increased weight gain/food consumption in HD females
- The lung and male and female reproductive organs were targets as well as decreased bone marrow cellularity at the high dose in each sex

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: Males = 2, 7.5, 20 mg/kg/day
Females = 7.5, 25, 75 mg/kg/day

Route of administration:	oral gavage
Formulation/Vehicle:	(b) (4)
Species/Strain:	Sprague-Dawley rats
Number/Sex/Group:	15/sex/group
Age:	10-11 weeks old
Satellite groups/ unique design:	6/sex/group for toxicokinetic analysis
Deviation from study protocol affecting interpretation of results:	None that affected interpretation of results

Observations and Results: changes from control

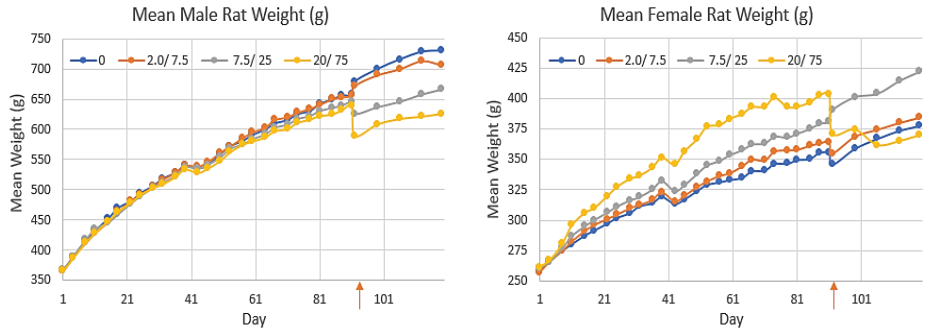
Parameters	Major findings
Mortality	There were no drug-related deaths
Clinical Signs	One male and 4 females in the highest treatment group (20 or 75 mg/kg, respectively) had malocclusion that progressed to such severity the animals had to be fed powdered food. During recovery, 2 females lost teeth and 3 females had malocclusion, all in the high-dose group.

	Male				Female			
Sign	0	2 mg/kg	7.5 mg/kg	20 mg/kg	0	7.5 mg/kg	25 mg/kg	75 mg/kg
malocclusion				1, 1R				4, 4R
discolored hair		2, 1R		1	2, 1R	1, 1R	1R	
scab	2, 1R	6	2, 2R	4	1R	2	3	2
thinning hair	3, 1R	8, 1R	2, 4R	8, 2R	1, 1R	1	5, 4R	5, 1R

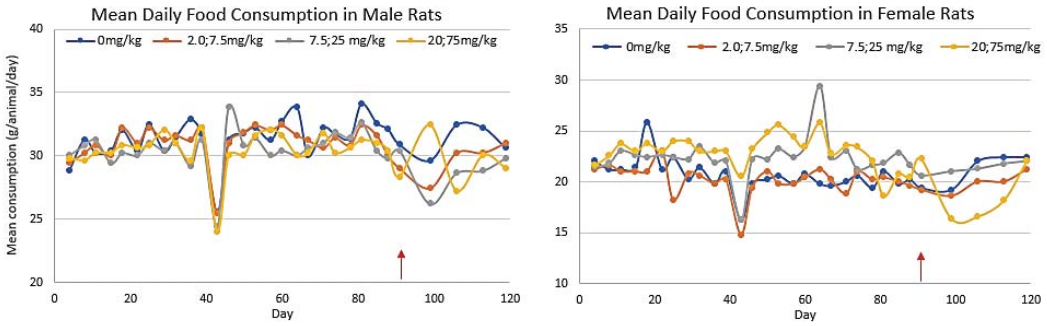
R denotes clinical sign was observed during recovery phase, all other observations occurred during dosing phase

Body Weights	Male animals gained weight at the same rate throughout treatment. Females in the high-dose group gained weight faster than other groups, with greatest increase over control group observed on Day 67 (+15%). Toward the end of treatment phase, rats in the high-dose group ate less food as teeth showed signs of toxicity (demineralization/ malocclusion) but had increased food consumption when powdered food was introduced.

Mean Body Weights (13-Week Study; Rats)



Arrows indicate end of dosing phase, beginning of recovery phase



Arrows indicate end of dosing phase, beginning of recovery phase

Ophthalmoscopy	No significant findings.
Hematology	Loxo-292 reduced reticulocyte counts in dose-dependent fashion in males. Reticulocyte reduction is likely secondary to mild myelosuppression (supported by mild decrease in bone marrow cellularity in histopathology study, but without concurrent decrease in other hematopoietic cell types). Animals recovered to values comparable to vehicle-treated control group by Day 120 (sacrifice at end of recovery phase).

Hematology: % Change from Vehicle-Treated Control Group

		Male			Female		
Test	Day	2.0 mg/kg	7.5 mg/kg	20 mg/kg	7.5 mg/kg	25 mg/kg	75 mg/kg
	42	-8%	-13%	-24%	-5%	2%	-3%
	92	-12%	-25%	-32%	7%	6%	-8%
Reticulocytes	120	-13%	-5%	-1%	-15%	-33%	2%

Day 42 = dosing phase, Day 92 = end of dosing phase, Day 120 = end of recovery phase/sacrifice. (-) denotes no change from vehicle-treated control

Clinical Chemistry	There were some minor dose-dependent liver enzymes increases during dosing phase. Bilirubin level were also modestly elevated and remained elevated during recovery phase in males.

Clinical Chemistry: % Change from Vehicle-Treated Control Group

		Male			Female		
Test	Day	2.0 mg/kg	7.5 mg/kg	20 mg/kg	7.5 mg/kg	25 mg/kg	75 mg/kg
ALT	42	5%	8%	129%	–	-2%	49%
	120R	13%	1%	-17%	107%	97%	- 20%
ALK	42	3%	20%	27%	-1%	16%	68%
	120R	–	3%	-10%	7%	-5%	8%
AST	42	9%	12%	40%	-12%	-4%	12%
	120R	12%	8%	12%	97%	85%	-14%
Bilirubin	42	50%	33%	31%	-11%	7%	–
	120R	–	50%	100%	-20%	20%	7%
CK	42	117%	58%	24%	4%	16%	115%
	120R	50%	42%	12%	-12%	23%	21%

Day 42 = dosing phase; Day 120 = recovery phase. (-) denotes no change from vehicle-treated control

Urinalysis	No significant findings
Gross Pathology	Males in the 20 mg/kg/day had testis degeneration/ atrophy
Organ Weights	Changes in organ weight occurred in the male reproductive tract.

%Change in Organ Weight Following 13-Week Selpercatinib Exposure in Rats

	Male					
	2.0 mg/kg		7.5 mg/kg		20 mg/kg	
Organ/Tissue	T	R	T	R	T	R
Epididymis	-6%	0%	0%	-6%	-7%	-31%
Testis	-8%	-7%	-7%	-6%	-28%	-37%

T = terminal phase; R = recovery phase

Histopathology Adequate battery: Yes	

Rat Histopathology Following 13-Week Exposure to Selpercatinib

			Male				Female			
Organ	Finding	Severity	0	2.0	7.5	20	0	7.5	25	75
Epididymis	Cell debris, luminal (diffuse)	Min			1R	5 4R				
		Mild				1R				
	Infiltrate mononuclear cell (multifocal)	Min	4 3R	5 2R	2 3R	3 3R				
		Min				1				

			Male				Female			
Organ	Finding	Severity	0	2.0	7.5	20	0	7.5	25	75
	Reduced sperm, luminal (diffuse)					1R				
		Mild				2 3R				
		Marked				1R				
Lung	Hemorrhage (focal)	Min		1	1R	1R			1	
	Infiltrate, macrophages alveolus	Min	3	3 1R	3 3R	8 3R	2 3R	1 2R	5 1R	8 4R
	Inflammation mixed cell	Min	1R	1	1R	1R		1	1	
Bone Marrow	Cellularity, decreased (diffuse)	Min				4				6
Vagina	Cornification, epithelial cell; diffuse	Mild								1
	Mucification, increased, epithelium, diffuse	Min							1	
		Mild								1
		Mod								5
Testis	Degeneration Atrophy, tubular (uni-/bilateral)	Min	1R	1	2 1R	8				
		Mild				2 1R				
		Mod				4R				
	Stasis, sperm	Min			1R	1				

R = Recovery phase; all other data are dosing phase

Toxicokinetics	• TK parameters generally increased proportionally with dose in males, but not females. • There was accumulation in females at all dose levels and in males at the low and high doses

Mean TK Parameters in Rats Exposed to Selpercatinib for 13 Weeks

Interval (Day)	Dose Group	Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)
1	2	2	M	529	4.00	4470	NC
		7.5	F	926	0.500	1740	1.32
	3	7.5	M	1990	2.00	18800	4.14
		25	F	7360	1.00	29600	2.93
	4	20	M	5740	2.00	56500	4.48
		75	F	12400	0.500	59100	2.91
91	2	2	M	508	4.00	6030	NC
		7.5	F	1570	0.500	3040	1.24
	3	7.5	M	1490	4.00	18500	NC
		25	F	10700	2.00	50400	2.25
	4	20	M	6780	2.00	80400	NC
		75	F	15700	1.00	149000	3.92

NC Not calculated due to an inability to characterize the elimination phase per SOP criteria.

Study title/ number: A 13-Week Daily Oral Gavage Toxicity and Toxicokinetic Study of LOXO-292 in Gottingen Minipigs with a 4-Week Recovery Phase/ # LOXO-292-TOX-012

- Seven animals were euthanized early due to moribund condition brought on by inflammation, necrosis, atrophy, and/or ulcer of the stomach: 3 males (5 mg/kg, Day 27) and 4 females (15 mg/kg, Day 26)
- Major target organs included the stomach, lung, skin, and male and female reproductive organs

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

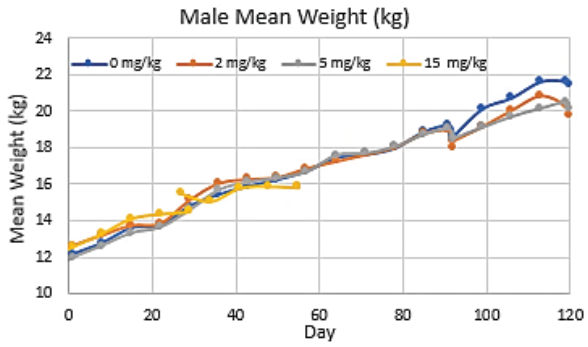
Dose and frequency of dosing: 2, 5, 15 mg/kg/day
Route of administration: oral gavage
Formulation/Vehicle: (b) (4)

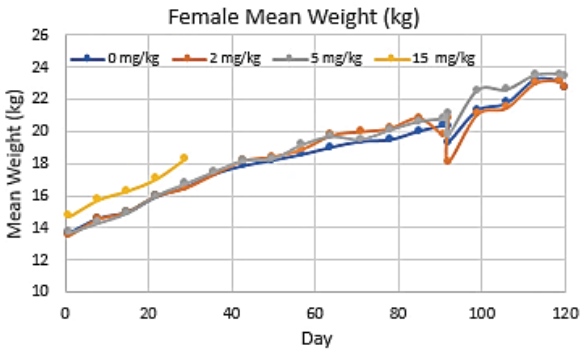
Species/Strain: Porcine Gottingen Minipigs®
Number/Sex/Group: 6/sex/group
Age: 5-7 months
Satellite groups/ unique design: None

Deviation from study protocol affecting interpretation of results: None that affect interpretation of results

Observations and Results: changes from control

Parameters	Major findings
Mortality	Several drug-related deaths occurred in the high-dose group: 3 males (5 mg/kg, Day 27) and 4 females (15 mg/kg, Day 26) were euthanized in moribund condition. The animals exhibited lameness, tremors, ataxia, and appeared to be in intractable pain caused by stomach inflammation/erosion.
Clinical Signs	One female pig in the 5 mg/kg group had a scab on its hind foot during dosing and recovery phases.
Body Weights	





Ophthalmoscopy	No significant drug-related findings
ECG	No significant drug-related findings
Hematology	Female mini pigs exposed to 2 or 5 mg/kg selpercatinib for 13 weeks had a 73% or 81% reduction in neutrophils, respectively, than non-treated females during the recovery phase (Day 120). All other hematology and coagulation parameters were not significant.
Clinical Chemistry	Female pigs that received 5 mg/kg selpercatinib experienced a 49% increase in blood urea nitrogen (BUN) during treatment (Day 92) and 64% increase during recovery (Day 120), compared to controls.
Gross Pathology	No significant drug-related findings
Organ Weights	Increased ovary weight in selpercatinib-exposed pigs correlated with corpora luteal cysts. Females in the 2 mg/kg or 5 mg/kg Recovery groups had 144% or 71% increased ovary weight compared to control. Males treated with ≥2 mg/kg selpercatinib had decreased testis weight, which correlated with moderate/ marked testicular tubular degeneration/ atrophy. Males in the 2, 5, or 15 mg/kg Recovery group experienced 29%, 35%, or 52% decrease in testis weight compared to control, respectively.

Histopathology Adequate battery: Yes	See Table 5.7: for summary of major findings • Major target organs included the stomach, skin, ovary, testis/epididymis, and bone
Toxicokinetics	

Interval (Day)	Dose Group	Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24} (h*ng/mL)
1	2	2	M	166	4.00	2780
			F	202	8.00	3620
			MF	184	6.00	3200
	3	5	M	493	4.00	7740
			F	413	8.00	7810
			MF	453	8.00	7780
	4	15	M	1220	4.00	19000
			F	1080	16.0	17000
			MF	1150	4.00	18100
91	2	2	M	255	6.00	4710
			F	183	8.00	3690
			MF	222	8.00	4250
	3	5	M	712	4.00	13200
			F	565	4.00	11900
			MF	639	4.00	12600

Table 5.7: 13-Week Minipig Histopathology

			Male				Female			
Organ	Finding	Severity	0	2	5	15	0	2	5	15
STOMACH	Atrophy, epithelium	Min				2				
		Mod				2				3
		Marked				1				1
	Degeneration/necrosis, mucosa, non-glandular	Mild				3				2
		Mod								1
		Marked								1
	Erosion/ulcer	Mild								1
		Mod								3
	Inflammation, neutrophils	Min				1				1
		Mild				1				1
		Mod				1				2
OVARY	Corpora lutea, decreased	Marked								2
	Cyst, corpus luteum							2	3	2
LUNG	Congestion	Mod				1				
	Fibrosis, pleural/subpleural and interstitial	Marked				1				
	Foreign material					1				
	Hemorrhage	Mild				1				1
	Hemorrhage	Mod					1			

			Male				Female			
Organ	Finding	Severity	0	2	5	15	0	2	5	15
	Inflammation, mixed cell	Min					1			
	Inflammation, mixed cell	Marked				1				
SKIN/ SUBCUTIS	Degeneration/necrosis, epidermis	Mod			1	1				
	Erosion/ulcer	Mild			1	1				
	Exudate				1	1				
	Inflammation, mixed cell	Mod			1	1				
EPIDIDYMIS	Cyst				1					
	Debris, cellular, lumen	Min		1	2	4				
		Mild		3	4					
BRAIN	Infiltrate, mononuclear cell	Min	1	3	2	1		2		3
BONE, FEMUR	Increased thickness, physis	Min				3				
		Mild								1
		Mod								1
		Marked								2
JOINT, TARSUS	Edema	Mild				1				
LYMPH NODE	Congestion/hemorrhage	Mod				1				
	Infiltrate, neutrophils	Mild				1				
	Pigment	Mild				1				
Testis	Degeneration/ Tubular atrophy	Min	4	1						
		Mild		1						
		Mod		2	1					
		Marked			3					

General toxicology; additional studies

Dr. Brian Cholewa reviewed the 28-day repeat-dose toxicology studies in rats and minipigs under the original IND submission (IND 133193). The summaries of these studies are based on and adapted from his review.

In the GLP-compliant 28-day toxicology study in rats, males and females received selpercatinib at doses up to 75/45 mg/kg and 150/120 mg/kg, respectively. Doses were reduced after Day 8 or 18 after the sacrifice of 2/15 males and 1/15 females due to poor general health. At the end of the dosing phase of the study, selpercatinib exposures in high dose males and females were approximately 3 and 5 times the human exposure at the 160 mg twice daily clinical dose. The cause of death in high dose animals was not determined but animals exhibited minimally decreased bone marrow cellularity, with accompanying decreases in reticulocyte counts and weight loss attributed in part decreased food consumption associated with malocclusion and

missing teeth. Males in the high dose group had moderate degeneration of pancreatic acinar cells. At the high dose levels in each sex there were signs of multiorgan mineralization that correlated with increased serum phosphorous levels, consistent with frequent findings with drugs that inhibit FGFR. Other high dose findings included moderate to marked hypertrophy/hyperplasia in the chondrocyte zone of the femur physis in both sexes, and moderate degeneration/necrosis of pancreatic acinar cells in high-dose males.

In the 28-day minipig study, findings were generally consistent with the findings in the 13-week study, particularly atrophy in the stomach, though skin findings were less prominent and the lung was not a major target organ. See the safety pharmacology section for a discussion of the QT assessment included in this study. Two animals in the mid-dose (5 mg/kg) group had >50-fold elevations in SDH levels compared to predose levels. One of these animals showed signs of minimal liver congestion and hepatocyte degeneration in a few lobules of 1 liver section, while the other had unremarkable microscopic observations. There were minor increases in ALP, phosphorous, BUN, and cholesterol levels in selpercatinib-treated minipigs, but the findings were not considered adverse.

5.5.2 Genetic Toxicology

The Applicant's Position:
Selpercatinib was not mutagenic or clastogenic in vitro. Selpercatinib was positive at doses of ≥ 300 mg/kg (exposures at this dose were 11–12-fold above the peak human exposures at the marketed dose) in the in vivo micronucleus assay in rat. Importantly, despite the presence of minimal bone marrow effects at 150 mg/kg, there was no statistically significant increase in the incidence of MnPCEs relative to controls. Exposures at this dose were 7-fold above the peak human exposures at the marketed dose. [Module 2.6.6.4.4.3]

The FDA's Assessment:

FDA agrees with the Applicant's assessment. The C_{max} at the 150 mg/kg dose that did not result in in vivo increases in micronuclei was 21000 ng/mL. This concentration was approximately 7 times the human Cmax of 2980 ng/mL at the 160 mg twice daily dose.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)
Study title/ number: LOXO-292-TOX-006: Bacterial Reverse Mutation Assay
Key Study Findings:

- Selpercatinib was not mutagenic in strains tested, in the presence or absence of S9
- Standard positive controls confirmed the sensitivity and validity of the assay

GLP compliance: Yes

Test system: *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* strain WP2 *uvr*A +/- S9 metabolic activation; up to 5000 µg per plate
Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: LOXO-292-007: *In Vitro* Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL)

Key Study Findings:

- Selpercatinib did not induce significant or dose-dependent structural or numerical chromosomal aberrations in the presence or absence of S9
- Standard positive and negative controls confirmed the validity and sensitivity of the assay

GLP compliance: Yes
Test system: Human peripheral blood lymphocytes (PHBL); up to 500 µg/mL in preliminary toxicity assay, and up to 50 µg/mL for chromosome aberrations/ 4 hours +/- S9 and 20 hours - S9
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: LOXO-292-021: *In Vivo* Mammalian Erythrocyte Micronucleus Assay in Rats

Key Study Findings:

- Selpercatinib at 150 mg/kg led to decreased hematopoietic cells and increased mitoses; ≥300 mg/kg led to necrosis and multilobulated cells
- A statistically significant increase in micronuclei occurred 48 hours after exposure to 300 or 500 mg/kg (mean = 0.54% or 0.59%, respectively)

GLP compliance: Yes
Test system: Male Sprague-Dawley rats received up to 500 mg/kg selpercatinib; bone marrow harvested 24 or 48 hours post-dose
Study is valid: Yes

Other Genetic Toxicity Studies

None

5.5.3 Carcinogenicity

The Applicant's Position:

An evaluation on the carcinogenic potential of selpercatinib has not been conducted, consistent

with principles in ICH S9 guidance. However, because MTC has a high prevalence of *RET* mutations but is often a slow growing tumor, as agreed with the FDA at the Type B Initial Comprehensive Multidisciplinary Breakthrough Therapy Meeting on December 19, 2018, carcinogenicity studies will be conducted as a post-marketing commitment.[Module 2.6.6.5]

The FDA's Assessment:
FDA agrees that the carcinogenicity studies to support the MTC indication can be conducted as a post-marketing requirement. Consistent with the principles of the ICH S9 guidance, carcinogenicity are not necessary to support the use of selpercatinib in patients with advanced NSCLC.

5.5.4 Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

The Applicant's Position:
Development of selpercatinib followed the guidance ICH S9, and thus a study of fertility and early embryonic development was not warranted to support this initial NDA. However, because MTC has a high prevalence of *RET* mutations but is often a slow growing tumor, as agreed with the FDA at the Type B Initial Comprehensive Multidisciplinary Breakthrough Therapy Meeting on December 19, 2018, a GLP fertility and early embryonic development study in female rats and a GLP fertility and general reproduction study in male rats will be conducted as post-marketing commitments and are in progress. [Module 2.6.6.6]

The FDA's Assessment:
Consistent with the principles described in the ICH S9 Questions and Answers document, FDA agrees that while drugs intended for the treatment of patients with often slow growing tumors such as MTC can be developed following the principles of ICH S9, additional studies, such as a full battery of reproductive toxicology studies and carcinogenicity studies may be warranted to support further development in these patient populations. With these factors in mind, FDA requested that the Applicant submit fertility and early development studies with the original NDA submission for selpercatinib for the treatment of patients with MTC, but agreed that the Applicant could submit these studies late without triggering a major amendment. The Applicant submitted study reports on February 28, 2020, consistent with agreements made during preNDA meetings.

A Fertility and General Reproduction Study of LOXO-292 Administered by Oral (Gavage) in Male Rats

Key Study Findings

- Males exposed to 30 mg/kg selpercatinib had a 20% reduction in testes weight compared to control, likely due to germ cell depletion; abnormal sperm morphology was also apparent at the 30 mg/kg dose
- There were no effects on mating behavior or on fertility upon exposure to untreated females

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	3, 10, 30 mg/kg; once daily dosing from Day 1 (DS 1) to DS 49
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4)
Species/Strain:	Sprague Dawley rat
Number/Sex/Group:	22 males/group in main study
Satellite groups:	toxicokinetic (TK) analysis: 3 non-treated and 6 treated males/group
Study design:	Males received 49 total doses of selpercatinib: 28 days in individual housing, 7 days in cohabitation 1:1 with an untreated female, then continuing through until the day before euthanasia
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	There were 2 deaths: 1 animal in the 10 mg/kg group was found dead on DS 26, 1 animal in the 30 mg/kg group was euthanized on DS43 due to extreme body weight loss. While the Applicant does not consider either death to be drug-related, the overall mean weight loss across individual animals in the 30 mg/kg group would support that weight

	loss leading to euthanasia of the animal in that group was likely drug-related.
Clinical Signs	Clinical signs observed in male rats exposed to selpercatinib Fertility parameters of females mated to selpercatinib-exposed males

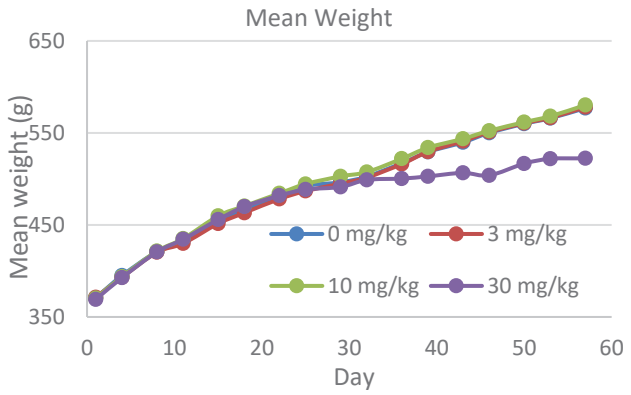
Clinical signs observed in male rats exposed to selpercatinib

Sex	Dose (mg/kg/day)			
Clinical sign	**0**	**3**	**10**	**30**
	# of animals affected			
dehydration	0	0	0	9
hunched posture	0	0	0	10
ungroomed fur	0	0	1	8
abnormal breathing	2	1	1	5
thin	0	0	0	5
teeth: broken	0	0	0	17
teeth: malocclusion	0	1	0	3

Fertility parameters of females mated to selpercatinib-exposed males

Sex	Female			
Dose (mg/kg/day)	**0**	**3**	**10**	**30**
Mating index (%)	100	100	100	100
Fertility index (%)	86	96	100	100
Pregnancy index (%)	86	96	100	88

Body Weights



Necropsy findings

Males were euthanized at the end of study, on DS 57 through 60

Organ Weights

Decreased testicular weight was likely caused by germ cell depletion in the animals that received 30 mg/kg selpercatinib

% Differences in Absolute Organ Weight in Controls vs. Treated

		Dose (mg/kg)		
Organ		**3**	**10**	**30**
Epididymis	left	6.7	-1.7	-8.4
	right	-9.7	-14.65	-21.56
Seminal Vesicle		0.43	-5.0	**-20.7***
Testis	left	**8.3***	2.1	**-16.2***
	right	3.5	-1.4	**-20.7***

*p ≤ 0.05

Histopathology

Germ cell depletion in selpercatinib-treated animals exhibited a dose-response relationship, with subtle to severe microscopic changes observed in animals from the 3- or 30 mg/kg group, respectively

Summary of histopathology changes

Dose (mg/kg/day)		**0**	**3**	**10**	**30**
Testes		**# of animals with finding**			
Germ cell depletion	total	0	2	9	22
	min	0	2	9	11
	mild	0	0	0	8
	marked	0	0	0	3
Spermatid retention	total	0	3	3	16
	min	0	3	3	9
	mild	0	0	0	7
Epididymis					
Cellular debris; lumen	total	5	1	1	9
	min	5	1	1	6
	mild	0	0	0	2
	marked	0	0	0	1

min < mild < mod(erate) < marked

Reproductive changes

Selpercatinib-related sperm abnormalities correlated with histologic findings of cellular debris in the epididymal lumen in the 30 mg/kg group

Summary of Sperm Parameters

Dose (mg/kg/day)	**0**	**3**	**10**	**30**
Sperm morphology	**# abnormal/200 cells counted**			
Abnormal (%)	4.5	4.1	5.0	9.5
Detached head (%)	2.5	2.4	2.9	5.1
No head (%)	1.8	1.5	1.8	3.8
Broken flagellum (%)	0.2	0.2	**0.5***	**0.8***

Sperm Motility	# abnormal/200 cells counted			
Motility (%)	80	79	78	69

*p ≤ 0.05

Summary of Female Reproductive Performance

Dose (mg/kg/day)	0	3	10	30
Pregnancy (%)	86.4	95.5	100	100
Live Embryos (%)	100	100	100	100
Mating Index [f] (%)	100	100	100	100
Fertility Index [f] (%)	86.4	95.5	100	100
Pregnancy Index [f] (%)	86.4	95.5	100	100
Ovarian/ Uterine Examination				
# Corpora Lutea (mean)	17.1	17.8	16.5	16.6
# Implantations (mean)	16.0	16.7	15.2	15.4
Pre-implantation loss (%)	6.0	5.4	8.7	7.1
# Live Embryos (mean)	14.8	16.3	14.2	14.3
# Dead Embryos (mean)	1.2	0.4	1.0	1.1
Post-implantation loss (%)	7.2	2.5	6.4	7.4

Toxicokinetics

- Exposures (C_{max} and AUC) were close to dose-proportional on DS1 and DS49

TK parameters of male rats exposed to selpercatinib

	Males		
Dose (mg/kg/day)	**3**	**10**	**30**
	Day (DS) 1		
C_{max} (ng/mL)	703	2560	8070
AUC_{0-24} (ng·h/mL)	8180	34000	91600
	Day (DS) 49		
C_{max} (ng/mL)	846	2970	8070
AUC_{0-24} (ng·h/mL)	12100	45700	117000

A Fertility and Early Embryonic Development Study of LOXO-292 Administered by Oral (Gavage) in Female Rats

Key Study Findings

- Females in the 75 mg/kg group demonstrated elevated body weight gain, experienced fewer estrous cycles per 14-day period, and yielded more nonviable litters than the control group.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 7.5, 25, and 75 mg/kg; once daily dosing starting 15 days prior to cohabitation, 14 days of cohabitation, and continuing until Gestation Day (GD) 7 in females

Route of administration: Oral gavage

Formulation/Vehicle: (b) (4)

Species/Strain: Sprague Dawley rat

Number/Sex/Group: 22 females per group in main study

Satellite groups: 3/group in control group; 6/group in treatment groups for toxicokinetic evaluation

Study design: Females treated with selpercatinib were cohabitated 1:1 with non-treated males until evidence of mating was present (GD 0). Female necropsies occurred on GD13

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	No drug-related deaths
Clinical Signs	

Dose (mg/kg)	0	7.5	25	75
Observation	% of animals with observed clinical sign			
	Premating			
Abnormal breathing sounds				5
Thin fur/ Fur loss			9	
Skin, Scab			9	5
	Gestation			
Thin fur/ Fur loss		10	10	5
Skin, Scab	5		10	5

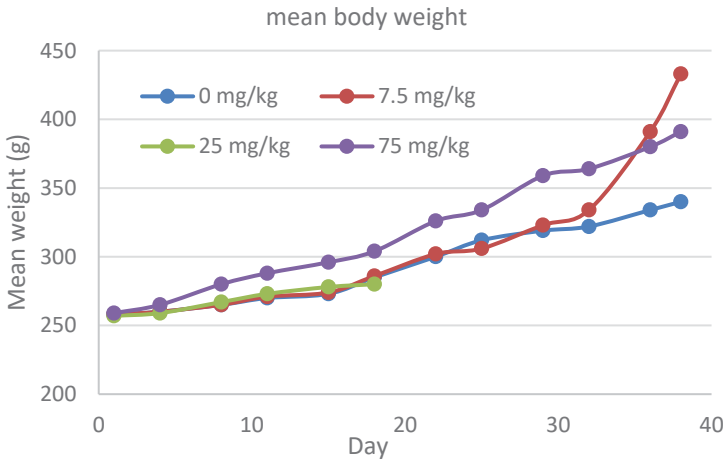
Reproductive Performance

Dose (mg/kg/day)	0	7.5	25	75
# of estrous cycles prior to pairing (D-13 → D0)	2.4	2.2	2.3	1.8**
Pre-coital Interval (Mean Days)	2.1	3.0	2.4	4.2**
Mating index (%)	95.5	100.0	100.0	100.0
Pregnancy index (%)	86.4	100.0	95.2	90.9

**p ≤ 0.01

Body Weights

- Females in the 75 mg/kg group gained significantly more weight during the premating interval, compared to controls (DS 1 to 15 = +137%). Other groups were unremarkable during premating.
- Dams in the 75 mg/kg group failed to gain weight comparably to other cohorts, likely due to significant post-implant embryo loss (see Reproductive changes, below).



Necropsy findings

Reproductive changes

Percent Differences in Mean Values vs. Concurrent Controls

Dose (mg/kg)	0	7.5	25	75
Number gravid	19	22	20	20
Females with live embryos (#)	19	22	20	8**
Litters with nonviable embryos (#)	0	0	0	10**
Pre-implantation loss (Mean %)	12	9	6	9
Total # embryos (Mean #)	14	16	16	17**
# of Live embryos (Mean #)	13	15	15	6*
# Dead embryos (Mean #)	1	1	1	11**
Post-implant embryo loss (Mean %)	12	4	7	69**

*p ≤ 0.05; **p ≤ 0.01

Toxicokinetics	• Rats in the 7.5 mg/kg group had decreased C_{max} of nearly 50% from DS 1 to GD 7 • C_{max} increased nearly proportional to dose from 7.5 to 75 mg/kg on GD 7

	Females		
Dose (mg/kg/day)	**7.5**	**25**	**75**
C_{max} (ng/mL) DS 1	2080	4040	9240
C_{max} (ng/mL) GD 7	1220	4060	12700
AUC_{0-24} (ng·h/mL) DS 1	4890	15600	NA*
AUC_{0-24} (ng·h/mL) GD 7	3470	16300	NA*

*Not applicable: the extrapolation value >25%

5.5.5 Carcinogenicity

The Applicant's Position:
An evaluation on the carcinogenic potential of selpercatinib has not been conducted, consistent with principles in ICH S9 guidance. However, because MTC has a high prevalence of *RET* mutations but is often a slow growing tumor, as agreed with the FDA at the Type B Initial Comprehensive Multidisciplinary Breakthrough Therapy Meeting on December 19, 2018, carcinogenicity studies will be conducted as a post-marketing commitment.[Module 2.6.6.5]

The FDA's Assessment:
FDA agrees that the carcinogenicity studies to support the MTC indication can be conducted as a post-marketing requirement. Consistent with the principles of the ICH S9 guidance, carcinogenicity are not necessary to support the use of selpercatinib in patients with advanced NSCLC.

5.5.6 Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

The Applicant's Position:
Development of selpercatinib followed the guidance ICH S9, and thus a study of fertility and early embryonic development was not warranted to support this initial NDA. However, because MTC has a high prevalence of *RET* mutations but is often a slow growing tumor, as agreed with the FDA at the Type B Initial Comprehensive Multidisciplinary Breakthrough Therapy Meeting on December 19, 2018, a GLP fertility and early embryonic development study in female rats and a GLP fertility and general reproduction study in male rats will be conducted as post-marketing commitments and are in progress. [Module 2.6.6.6]

The FDA's Assessment:
Consistent with the principles described in the ICH S9 Questions and Answers document, FDA agrees that while drugs intended for the treatment of patients with often slow growing tumors such as MTC can be developed following the principles of ICH S9, additional studies, such as a full battery of reproductive toxicology studies and carcinogenicity studies may be warranted to support further development in these patient populations. With these factors in mind, FDA requested that the Applicant submit fertility and early development studies with the original NDA submission for selpercatinib for the treatment of patients with MTC, but agreed that the Applicant could submit these studies late without triggering a major amendment. The Applicant submitted study reports on February 28, 2020, consistent with agreements made during preNDA meetings.

A Fertility and General Reproduction Study of LOXO-292 Administered by Oral (Gavage) in Male Rats

Key Study Findings

- Males exposed to 30 mg/kg selpercatinib had a 20% reduction in testes weight compared to control, likely due to germ cell depletion; abnormal sperm morphology was also apparent at the 30 mg/kg dose
- There were no effects on mating behavior or on fertility upon exposure to untreated females

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	3, 10, 30 mg/kg; once daily dosing from Day 1 (DS 1) to DS 49
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4)
Species/Strain:	Sprague Dawley rat
Number/Sex/Group:	22 males/group in main study
Satellite groups:	toxicokinetic (TK) analysis: 3 non-treated and 6 treated males/group
Study design:	Males received 49 total doses of selpercatinib: 28 days in individual housing, 7 days in cohabitation 1:1 with an untreated female,

	then continuing through until the day before euthanasia
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

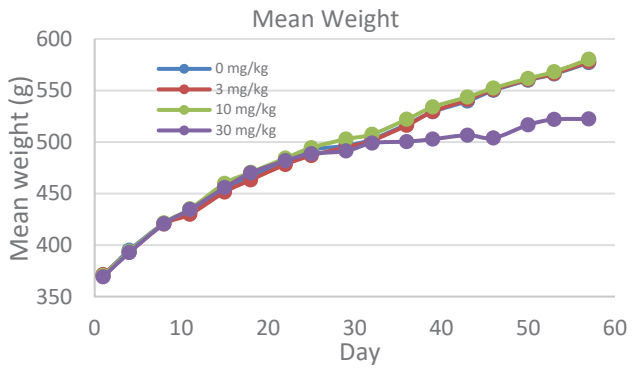
Parameters	Major findings
Mortality	There were 2 deaths: 1 animal in the 10 mg/kg group was found dead on DS 26, 1 animal in the 30 mg/kg group was euthanized on DS43 due to extreme body weight loss. While the Applicant does not consider either death to be drug-related, the overall mean weight loss across individual animals in the 30 mg/kg group would support that weight loss leading to euthanasia of the animal in that group was likely drug-related.
Clinical Signs	Clinical signs observed in male rats exposed to selpercatinib

Sex	Dose (mg/kg/day)			
Clinical sign	**0**	**3**	**10**	**30**
	# of animals affected			
dehydration	0	0	0	9
hunched posture	0	0	0	10
ungroomed fur	0	0	1	8
abnormal breathing	2	1	1	5
thin	0	0	0	5
teeth: broken	0	0	0	17
teeth: malocclusion	0	1	0	3

Fertility parameters of females mated to selpercatinib-exposed males

Sex	Female			
Dose (mg/kg/day)	**0**	**3**	**10**	**30**
Mating index (%)	100	100	100	100
Fertility index (%)	86	96	100	100
Pregnancy index (%)	86	96	100	88

Body Weights	



Necropsy findings

Males were euthanized at the end of study, on DS 57 through 60

Organ Weights

Decreased testicular weight was likely caused by germ cell depletion in the animals that received 30 mg/kg selpercatinib

% Differences in Absolute Organ Weight in Controls vs. Treated

		Dose (mg/kg)		
Organ		**3**	**10**	**30**
Epididymis	left	6.7	-1.7	-8.4
	right	-9.7	-14.65	-21.56
Seminal Vesicle		0.43	-5.0	**-20.7***
Testis	left	**8.3***	2.1	**-16.2***
	right	3.5	-1.4	**-20.7***

*p ≤ 0.05

Histopathology

Germ cell depletion in selpercatinib-treated animals exhibited a dose-response relationship, with subtle to severe microscopic changes observed in animals from the 3- or 30 mg/kg group, respectively

Summary of histopathology changes

Dose (mg/kg/day)		**0**	**3**	**10**	**30**
Testes		**# of animals with finding**			
Germ cell depletion	total	0	2	9	22
	min	0	2	9	11
	mild	0	0	0	8
	marked	0	0	0	3
Spermatid retention	total	0	3	3	16
	min	0	3	3	9
	mild	0	0	0	7
Epididymis					
Cellular debris; lumen	total	5	1	1	9
	min	5	1	1	6
	mild	0	0	0	2
	marked	0	0	0	1

min < mild < mod(erate) < marked

Reproductive changes
Selpercatinib-related sperm abnormalities correlated with histologic findings of cellular debris in the epididymal lumen in the 30 mg/kg group

Summary of Sperm Parameters

Dose (mg/kg/day)	**0**	**3**	**10**	**30**
Sperm morphology	**# abnormal/200 cells counted**			
Abnormal (%)	4.5	4.1	5.0	9.5
Detached head (%)	2.5	2.4	2.9	5.1
No head (%)	1.8	1.5	1.8	3.8
Broken flagellum (%)	0.2	0.2	**0.5***	**0.8***
Sperm Motility	**# abnormal/200 cells counted**			
Motility (%)	80	79	78	69

*p ≤ 0.05

Summary of Female Reproductive Performance

Dose (mg/kg/day)	**0**	**3**	**10**	**30**
Pregnancy (%)	86.4	95.5	100	100
Live Embryos (%)	100	100	100	100
Mating Index [f] (%)	100	100	100	100
Fertility Index [f] (%)	86.4	95.5	100	100
Pregnancy Index [f] (%)	86.4	95.5	100	100
Ovarian/ Uterine Examination				
# Corpora Lutea (mean)	17.1	17.8	16.5	16.6
# Implantations (mean)	16.0	16.7	15.2	15.4
Pre-implantation loss (%)	6.0	5.4	8.7	7.1
# Live Embryos (mean)	14.8	16.3	14.2	14.3
# Dead Embryos (mean)	1.2	0.4	1.0	1.1
Post-implantation loss (%)	7.2	2.5	6.4	7.4

Toxicokinetics

- Exposures (C_{max} and AUC) were close to dose-proportional on DS1 and DS49

TK parameters of male rats exposed to selpercatinib

	Males		
Dose (mg/kg/day)	**3**	**10**	**30**
	Day (DS) 1		
C_{max} (ng/mL)	703	2560	8070
AUC_{0-24} (ng·h/mL)	8180	34000	91600
	Day (DS) 49		
C_{max} (ng/mL)	846	2970	8070
AUC_{0-24} (ng·h/mL)	12100	45700	117000

A Fertility and Early Embryonic Development Study of LOXO-292 Administered by Oral (Gavage) in Female Rats

Key Study Findings

- Females in the 75 mg/kg group demonstrated elevated body weight gain, experienced fewer estrous cycles per 14-day period, and yielded more nonviable litters than the control group.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	7.5, 25, and 75 mg/kg; once daily dosing starting 15 days prior to cohabitation, 14 days of cohabitation, and continuing until Gestation Day (GD) 7 in females
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4)
Species/Strain:	Sprague Dawley rat
Number/Sex/Group:	22 females per group in main study
Satellite groups:	3/group in control group; 6/group in treatment groups for toxicokinetic evaluation
Study design:	Females treated with selpercatinib were cohabitated 1:1 with non-treated males until evidence of mating was present (GD 0). Female necropsies occurred on GD13
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No drug-related deaths
Clinical Signs	

Dose (mg/kg)	0	7.5	25	75
Observation	% of animals with observed clinical sign			
	Premating			

Abnormal breathing sounds				5
Thin fur/ Fur loss			9	
Skin, Scab			9	5
	Gestation			
Thin fur/ Fur loss		10	10	5
Skin, Scab	5		10	5

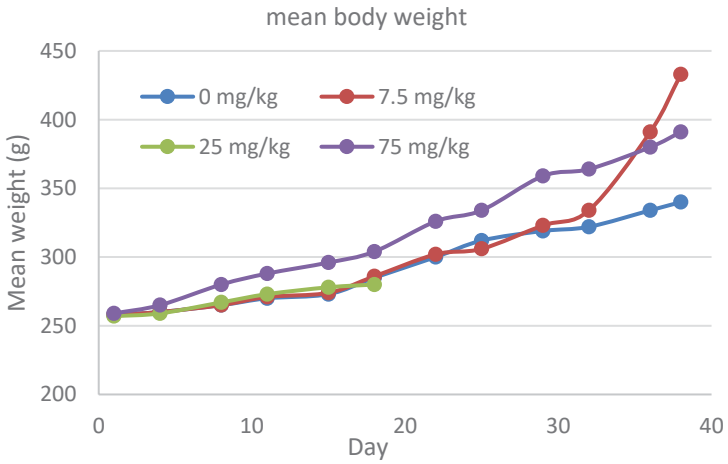
Reproductive Performance

Dose (mg/kg/day)	0	7.5	25	75
# of estrous cycles prior to pairing (D-13 → D0)	2.4	2.2	2.3	1.8**
Pre-coital Interval (Mean Days)	2.1	3.0	2.4	4.2**
Mating index (%)	95.5	100.0	100.0	100.0
Pregnancy index (%)	86.4	100.0	95.2	90.9

**p ≤ 0.01

Body Weights

- Females in the 75 mg/kg group gained significantly more weight during the premating interval, compared to controls (DS 1 to 15 = +137%). Other groups were unremarkable during premating.
- Dams in the 75 mg/kg group failed to gain weight comparably to other cohorts, likely due to significant post-implant embryo loss (see Reproductive changes, below).



Necropsy findings

Reproductive changes

Percent Differences in Mean Values vs. Concurrent Controls

Dose (mg/kg)	0	7.5	25	75
Number gravid	19	22	20	20
Females with live embryos (#)	19	22	20	8**
Litters with nonviable embryos (#)	0	0	0	10**

Pre-implantation loss (Mean %)	12	9	6	9
Total # embryos (Mean #)	14	16	16	17**
# of Live embryos (Mean #)	13	15	15	6*
# Dead embryos (Mean #)	1	1	1	11**
Post-implant embryo loss (Mean %)	12	4	7	69**

*p ≤ 0.05; **p ≤ 0.01

Toxicokinetics

- Rats in the 7.5 mg/kg group had decreased C_{max} of nearly 50% from DS 1 to GD 7
- C_{max} increased nearly proportional to dose from 7.5 to 75 mg/kg on GD 7

	Females		
Dose (mg/kg/day)	**7.5**	**25**	**75**
C_{max} (ng/mL) DS 1	2080	4040	9240
C_{max} (ng/mL) GD 7	1220	4060	12700
AUC_{0-24} (ng·h/mL) DS 1	4890	15600	NA*
AUC_{0-24} (ng·h/mL) GD 7	3470	16300	NA*

*Not applicable: the extrapolation value >25%

Embryo-Fetal Development

The Applicant's Position:
Selpercatinib caused maternal toxicity in rats at 200 mg/kg/day (exposures 5-fold above the peak human exposures at the marketed dose). The NOAEL for maternal toxicity was 100 mg/kg/day. At 50 mg/kg/day (exposure 1.5-fold above the peak human exposures at the marketed dose), 6 of 8 females had resorbed litters (100% early resorptions); the remaining 2 females had primarily early resorptions and only 3 viable fetuses across the 2 litters. Based on these results, selpercatinib is a selective developmental toxicant and embryolethal. No additional embryofetal studies are warranted. [Module 2.6.6.6]

The FDA's Assessment:

Study title / number: LOXO-292-TOX-009: An Oral (Gavage) Dose Range-Finding Study of the Effects of LOXO-292 on Embryo/Fetal Development in Rats

Key Study Findings

- 100% early resorptions in 100 and 200 mg/kg groups; 6 of 8 dams in the 50 mg/kg group had 100% resorbed litters
- The 3 viable fetuses produced from a dam exposed to 50 mg/kg selpercatinib displayed morphological malformations, including short tails, neck edema, and short snout as well

as decreased fetal weight

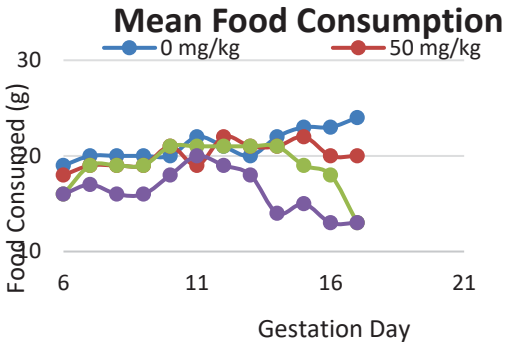
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

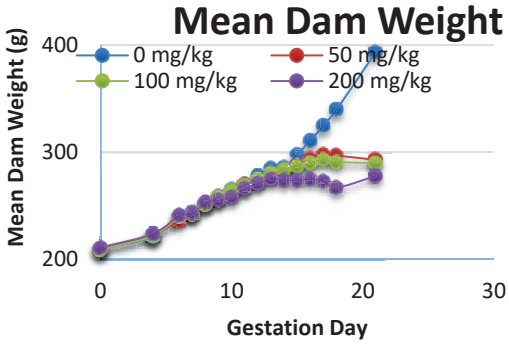
Methods

Dose and frequency of dosing:	0, 50, 100, or 200 mg/kg per day
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4)
Species/Strain:	Sprague Dawley [Crl:CD(SD)] rats
Number/Sex/Group:	8 females per group
Satellite groups:	TK groups of 4 vehicle- and 8 test article-treated dams
Study design:	Treatment period = gestation days (GD) 6-17; post-treatment period = GD 18-21
Deviation from study protocol affecting interpretation of results:	None that affected study interpretation

Observations and Results

Parameters	Major findings
Mortality	There were no deaths
Clinical Signs	Dams in the 200 mg/kg group experienced hair loss (n = 5), dried red material on forelimbs (n = 6), dried red material in the uro-genital area (n = 4), and red material around the mouth (n = 5). All other groups did not exhibit clinical signs of toxicity.
Body Weights and Feed Consumption	There was significantly lower mean body weight gain, compared to controls, in all groups exposed to selpercatinib. Lower weight correlated with lower gravid uterine weight in selpercatinib-exposed dams; the weight gain did not appear to be due to maternal toxicity.





Gravid Uterine Weights

Dose	0 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg
mean gravid uterine weight (g)	98.5	4.2**	0.8**	0.9**

** = Significantly different from control group at p = 0.01

Necropsy Findings: Maternal, Gross

Unremarkable

Necropsy Findings: Cesarean Section Data

Cesarean Section Data (EFD Study; Rats)

mg/kg/day	0	50	100	200
Pregnancy index (%)	100%	100%	100%	100%
# Females w/ viable fetuses for GD20 exam	8	2	0	0
Number pregnant	8	8	8	8
Number not pregnant	0	0	0	0
Gravid uterine weight (g)	98.5	4.2**	0.8**	0.9**
Mean corpora lutea	13.4	12.6	17.6**	13.8
Mean implantation sites	13.0	11.8	12.5	12.4
Mean % pre-implantation loss	3%	7%	29%	10%
Mean % post-implantation loss	8%	97%	100%	100%
Mean litter size	12	0.4	0	0
Mean early resorptions	1	11.4	12.5	12.4
Mean late resorptions	0	0	0	0
**** p < 0.01**				
Fetal weight changes relative to controls				
Male (g)	6.3	5.5 (n = 2)	no viable fetuses	
Female (g)	6.0	4.9 (n = 1)	no viable fetuses	

Toxicokinetic Parameters in Dams

Dose mg/kg/day	50	100	200
Gestational Day 6			
T_{max} (hr)	2	4	2
C_{max} (ng/mL)	9260	15700	18400
AUC(0-24) (ng*hr/mL)	46100	152000	280000
Gestational Day 17			
T_{max} (hr)	2	2	4
C_{max} (ng/mL)	9580	14600	23100
AUC(0-24) (ng*hr/mL)	75800	185000	241000

AR = Accumulation Ratio; NC = not calculable due to limited data in terminal elimination phase

Table 5.8: Fetal Malformations and Variations (EFD Study; Rats)

Dose mg/kg/day	0	50	100	200
Number of Fetuses/(Litters Evaluated)	96/(8)	3/(2)		
Gross malformations: # of fetuses affected, (% of fetuses); number of litters affected				
Localized fetal edema of neck and thorax		1 (50%)		
small snout		1 (50%)		
Short tail		2 (100%)		

Prenatal and Postnatal Development

The Applicant's Position:
Prenatal and postnatal development studies have not been conducted, consistent with principles in ICH S9 guidance, and clear findings in the female fertility and embryo-fetal development studies at clinically relevant doses.

The FDA's Assessment:
While pre- and postnatal development (PPND) studies might be warranted for the MTC indication due to natural history of the disease, the EFD studies showed severe embryolethality and teratogencity at doses resulting in exposures less than or equal to the human exposure at the 160 mg twice daily dose. Given the severity of the findings at the human equivalent exposure level, an additional PPND is unlikely to provide information that would significantly affect the human risk assessment and such a study is not warranted either to support approval in either of the proposed indications or as a postmarketing requirement.

Study # LOXO-292-TOX-017: A Single-Dose Oral (Gavage) Pharmacokinetic Study of LOXO-292 in Juvenile Sprague Dawley Rats

In this non-GLP study, male and female Sprague Dawley rats received a single oral dose of selpercatinib via oral gavage on postnatal Day (PND) 7. Rat pups in groups receiving 5, 25, or 75 mg/kg (n = 12, 12, or 13/sex, respectively) of selpercatinib exhibited no mean difference in body weight across groups and no clinical signs of toxicity; therefore, the Applicant added another dose group of 150 mg/kg. At 150 mg/kg, (n = 14/sex) 2 males and 2 females died within 24 hours post-dose but the cause of death could not be determined, as the bodies were missing or in poor condition due to cannibalization and/or autolysis.

At all dose levels, C_{max} was at 4 hours post-dose in juvenile rat pups. Males and females exhibited comparable exposure in terms of C_{max} and AUC_{0-t}. Exposure increased in a mostly dose-proportional manner. There was <2-fold difference in exposure between male and female juveniles. Treatment of PND 7 juvenile rats with selpercatinib at doses up to 75 mg/kg did not result in overt toxicity.

Table 5.9: Toxicokinetic Parameters in Juvenile Rats Exposed to Selpercatinib

Sex:	Males				Females			
LOXO-292 Dose (mg/kg):	5	25	75	150	5	25	75	150
Parameter (Units)	PND 7							
AUC(0-t) (ng•h/mL)	8830	56,300	162,000	281,000	8330	58,000	148,000	256,000
AUC(0-t)/D	1770	2250	2160	1870	1670	2320	1970	1710
Cmax (ng/mL)	544	3090	10,900	15,000	486	3220	9730	16,400
Cmax/D	109	124	145	99.8	97.2	129	130	110
Tmax (h)	4	4	4	4	4	4	4	4
Tlast (h)	24	24	24	24	24	24	24	24

(*Excerpted from Applicant's submission*)

5.5.7 Other Toxicology Studies

The Applicant's Position:
Selpercatinib did not demonstrate phototoxic potential in the in vitro neutral red uptake assay in BALB/c 3T3 mouse fibroblasts. [Module 2.6.6.8.7]

The FDA's Assessment:
In a GLP-compliant experiment (Study # LOXO-292-004), investigators assessed the viability of BALB/c 3T3 murine fibroblasts by quantifying selpercatinib concentration-dependent reduction in neutral red dye uptake in live cells in the presence or absence of ultraviolet radiation (5 J/cm^2 UVA or 21-22 mJ/cm^2 UVB). The photoirritancy factor (PIF, the IC_{50} in the absence of UVR divided by IC_{50} in the presence of UVR) of 1 indicated that selpercatinib was not phototoxic. A PIF of 1 was assigned because selpercatinib was not cytotoxic in this assay and a formal PIF could not be calculated.

X X

Primary Reviewer Supervisor

6 Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:
Selpercatinib is a small molecule inhibitor of wild-type and mutant RET, VEGFR1, and VEGFR3. The Applicant is seeking approval of selpercatinib for the treatment of:

- Adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC)
- Adult and pediatric patients 12 years of age and older with *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy
- Adult and pediatric patients 12 years of age and older with advanced *RET* fusion-positive thyroid cancer who require systemic therapy and (b) (4) (if radioactive iodine is appropriate)

The Applicant's proposed selpercatinib dosing regimen for all indications is 160 mg orally twice daily with or without food. The clinical pharmacology review focused on dose selection, genomics, organ dysfunction, drug-drug interactions (including acid-reducing agents), and QT/QTc prolongation.

Recommendations: The Office of Clinical Pharmacology has reviewed the information submitted in NDA 213246. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below in **Table 6.1**. Post-marketing requirements are detailed in **Table 6.2**.

Table 6.1: Key FDA Clinical Pharmacology Review Issues

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness comes from the first-in-human, Phase 1/2, dose escalation and expansion Study LOXO-RET-17001 (LIBRETTO-001). The Applicant's proposed dosing regimen is supported by the ORR observed in patients with *RET* fusion-positive NSCLC and thyroid cancers and *RET*-mutant MTC treated with selpercatinib.
General dosing instructions	The Applicant's proposed selpercatinib dosing regimen (160 mg orally twice daily with or without food) is acceptable for approval for patients with body weight ≥50 kg. For patients with body weight <50 kg, the recommended dose of selpercatinib is 120 mg twice daily. • Selpercatinib 160 mg twice daily demonstrated clinically meaningful ORR and DOR in patients enrolled in LIBRETTO-001. • Body weight affects selpercatinib PK with higher exposure (C_{max} and AUC) in patients with lower body weight. Selpercatinib exhibits concentration-dependent QTc prolongation. Based on exposure-matching and avoidance of

Review Issue	Recommendations and Comments
	excess QTc-prolongation risk, the recommended dose of selpercatinib in lower body weight patients (<50 kg) is 120 mg twice daily. • Administration with or without food is acceptable, unless administered with a proton pump inhibitor (PPI). Refer to drug-drug interactions below.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Body Weight: Reduce the dose to 120 mg twice daily in patients with body weight <50 kg. Renal Impairment: No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr 30 to <90 mL/min). The effect of severe renal impairment (CLcr <30 mL/min) on selpercatinib PK has not been adequately studied. Hepatic Impairment: Reduce the dose to 80 mg twice daily in patients with severe hepatic impairment (total bilirubin greater than 3 to 10 times ULN and any AST). No dose adjustment is recommended for patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) or moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST) hepatic impairment. Genomics: Confirmed responses were observed in patients with advanced MTC across different RET mutations. Outstanding Issues: Dedicated renal and hepatic impairment studies will be submitted as PMRs.
Drug-drug interactions	Acid-Reducing Agents: Selpercatinib demonstrates pH-dependent solubility. Avoid concomitant use of PPIs, histamine-2 (H2) receptor antagonists, and locally-acting antacids. If concomitant use cannot be avoided: • Take selpercatinib with food when coadministered with a PPI. • Take selpercatinib 2 hours before or 10 hours after administration of an H2 receptor antagonist. • Take selpercatinib 2 hours before or 2 hours after administration of a locally-acting antacid. CYP3A Inhibitors and Inducers: Selpercatinib is primarily metabolized by CYP3A4. • Strong and moderate CYP3A inhibitors: Avoid coadministration with strong and moderate CYP3A inhibitors. If coadministration cannot be avoided, reduce the dose of selpercatinib. • Strong and moderate CYP3A inducers: Avoid coadministration with strong and moderate CYP3A inducers. Effects of Selpercatinib on Other Drugs: Selpercatinib is a moderate CYP2C8 inhibitor and a weak CYP3A inhibitor. Avoid coadministration with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to serious adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling. Outstanding Issues: Selpercatinib inhibits P-gp *in vitro* and has the potential to cause drug interactions with P-gp substrates in the gastrointestinal tract. A clinical drug interaction study with a P-gp substrate will be conducted as a PMR.

Review Issue	Recommendations and Comments
Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement to the FDA revisions to the label.

Table 6.2: Clinical Pharmacology Post-Marketing Requirements and Commitments

PMR or PMC	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
PMR	Determination of an appropriate safe selpercatinib dose for use in patients with renal impairment.	There is evidence of renal elimination of selpercatinib. Renal impairment may increase selpercatinib systemic exposures and require dose adjustment.	Conduct a clinical trial to evaluate the pharmacokinetics and safety of selpercatinib in patients with normal renal function and patients with renal impairment.
PMR	Determination of an appropriate safe selpercatinib dose for use in patients with hepatic impairment.	Selpercatinib is primarily metabolized by CYP3A4. Hepatic impairment may increase selpercatinib systemic exposures and require dose adjustment.	Conduct a clinical trial to evaluate the pharmacokinetics and safety of selpercatinib in patients with normal hepatic function and patients with hepatic impairment.
PMR	Determination of appropriate management strategies for potential drug interactions with P-gp substrates.	Selpercatinib inhibits P-gp. Coadministration with P-gp substrates may alter the pharmacokinetics of P-gp substrates via inhibition of P-gp in the gastrointestinal tract.	Conduct a clinical trial to evaluate the effect of selpercatinib on the pharmacokinetics of a P-gp substrate.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Data:

The pharmacokinetics of selpercatinib were studied in healthy subjects and in patients with advanced solid tumors, including *RET* fusion-positive solid tumors, *RET*-mutant MTC, and other tumors with *RET* alterations. Doses of selpercatinib capsules up to 240 mg BID show approximately linear to slightly supra-proportional pharmacokinetics in cancer patients, but there is evidence of sub-proportional exposure with single doses of 320 mg or higher in healthy subjects. [Module 2.7.2.1] Based on population pharmacokinetic analysis of patient data, the pharmacokinetics of selpercatinib was affected by the administered dose and body weight. The clearance of selpercatinib decreased with increasing dose levels. [Module 2.7.2.2.11.2]

In patients who received selpercatinib capsules at 160 mg twice daily, peak plasma levels (C_{max}) of selpercatinib were achieved at approximately 2 hours after oral administration. Systemic exposure (AUC_{0-12h}) increases approximately 3-fold with repeated dosing. Selpercatinib steady-state geometric mean (GM) ([coefficient of variation (CV%)] for C_{max} was 2980 ng/mL (53%) and for AUC_{0-24h} was 51600 ng*h/mL (58%). [Module 2.7.2.4.2, Table 17]

Absorption:
The geometric mean absolute oral bioavailability of a 160-mg dose of selpercatinib given as two 80-mg capsules ((b) (4) capsule formulation) was 73.2% (range: 60% to 82%). [Module 2.7.1.2.3.2]
There was an increase of approximately 9% in selpercatinib AUC and an approximately 14% decrease in the C_{max} when administered with a high-fat meal compared to fasting conditions. There was a decrease of approximately 69% in selpercatinib AUC, compared to when selpercatinib was administered in the absence of omeprazole in the fasted condition, which is consistent with the pH-dependent solubility of selpercatinib. [Module 2.7.1.2.1.3] Increasing gastric pH by ranitidine under fasted conditions had no effect on the overall exposure (AUC) to selpercatinib.[Module 2.7.1.2.2.3]

Distribution:
Selpercatinib is 97% bound to human plasma proteins in vitro. [Module 2.7.2.3.2]. The blood-to-plasma concentration ratio is 0.7. [Module 2.7.2.3.3] The GM (%CV) volume of distribution (Vz) is 127 L (57%) following intravenous administration of a single [^{14}C] radiolabeled micro-dose (~10 µg) in healthy volunteers. [Module 2.7.1.2.3.2, Table 30]

Elimination:
The GM (CV%) apparent clearance (CL/F) is 6.8 L/h (20%) and the mean (standard deviation) terminal half-life is 37 hours following oral administration of a single [^{14}C] radiolabeled 160 mg dose in healthy subjects. [Module 2.7.1.2.3.2, Table 30]

Metabolism:
CYP3A4 is the only CYP450 enzyme that contributes to the metabolism of selpercatinib. [Module 2.7.2.3.5] Oxidative metabolism represented the major biotransformation pathways (oxidation, N-dealkylation, O-demethylation). [Module 2.7.1.2.3.2, Figure 15]

Following oral administration of a single [^{14}C] radiolabeled 160 mg dose of selpercatinib to healthy subjects, unchanged selpercatinib constituted 86% of the circulating radioactive drug components in plasma. All remaining plasma metabolites were present at trace to minor levels (<4%). [Module 2.7.1.2.3.2, Table 30]

Excretion:
Following oral administration of a single [^{14}C] radiolabeled 160 mg dose of selpercatinib to

healthy subjects, 69% (14% unchanged) of the administered radioactivity was recovered in feces and 24% (12% unchanged) was recovered in urine. [Module 2.7.1.2.3.2, CSR LOXO-RET-18016]

The Applicant's Position:

Overall the clinical pharmacology profile of selpercatinib is considered supportive of the planned marketed dose of 160 mg BID in adults.

The FDA's Assessment:
The FDA generally agrees with the Applicant's assessment of Pharmacology and Clinical Pharmacokinetics.

6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

Data:
The proposed dosing regimen of selpercatinib is 160 mg orally twice daily with or without food.

Dose Selection Rationale and Dose- and Exposure-Response Relationships:
Selpercatinib dosing regimen of 160 mg BID was selected as the recommended Phase 2 dose (RP2D) based on Phase 1 results from study LOXO-RET-17001 (LIBRETTO-001). A modeling study of the population PK, tumor size, and exposure-response modeling study showed that the rate of reduction in tumor size was impacted by exposure to selpercatinib via a saturable relationship. The AUC_{0-24} at steady state that gave rise to 50% of the maximum tumor decay rate constant was associated with a selpercatinib dose of approximately 30 mg twice daily (BID). The results supported the selection of 160 mg BID for further study, as it was a dose approximately five-fold greater than the dose associated with a 50% maximal tumor reduction rate. [Module 2.7.2.2.11.1; Module 2.7.2.4.5]

Updated modeling and simulation analysis utilizing Phase 2 results from study LOXO-RET-17001 showed that decreases in tumor size were associated with increases in survival probability for patients with both *RET*-fusion NSCLC and *RET*-mutant MTC tumors. Modeling showed that an increase in selpercatinib does not increase the likelihood of adverse events of interest including ALT or AST AEs, hypersensitivity AEs, or hypertension AEs. Simulations were performed using the updated model parameters for 160 mg BID and dose reductions of 80 mg BID, and 40 mg BID selpercatinib. The tumor shrinkage simulations show similar profiles for all three dose levels over 15 months [Module 2.7.2.2.11.2]

The Applicant's Position:
These results support the recommended dosage of 160 mg BID as the to-be marketed dose and support that the recommended dose reductions for AEs will maintain sufficient selpercatinib levels to provide continued overall clinical benefit. [Module 2.7.2.4.5]

The FDA's Assessment:
FDA generally agrees with the Applicant's assessment of the 160 mg BID dosage regimen. In addition to the above analyses, FDA assessed selpercatinib exposure across the body weight range relevant to adults and adolescents (≥12 years) given that selpercatinib causes concentration-dependent QTc-prolongation. Based on exposure-matching and avoidance of excess QTc-prolongation risk, the recommended selpercatinib dosage is 120 mg BID in patients with body weight <50 kg. Additional detail is described in **Section 6.3.2.2**.

6.2.2.2 Therapeutic Individualization

Data:
Effect of Strong P-glycoprotein (P-gp) Inhibitors: Coadministration of a single 160 mg dose of selpercatinib capsules with a P-gp inhibitor (rifampin) increased the AUC_{0-24} of selpercatinib by 6% and the C_{max} by 19% as compared to selpercatinib administered alone. [Module 2.7.2.2.4]

Effect of Strong CYP3A Inhibitors: Coadministration of a single 160 mg dose of selpercatinib capsules with a strong CYP3A inhibitor (itraconazole) increased the AUC_{0-INF} of selpercatinib by 2.3-fold and the C_{max} by 1.3-fold as compared to selpercatinib administered alone [Module 2.7.2.2.4]

Effect of Strong CYP3A Inducers: Coadministration of a single 160 mg dose of selpercatinib capsules with a strong CYP3A inducer (rifampin) decreased the AUC_{0-INF} of selpercatinib by 87% and the C_{max} by 70% as compared to selpercatinib administered alone[Module 2.7.2.2.4]

Effect of Proton-Pump Inhibitors: Coadministration of a single 160 mg dose of selpercatinib capsules under fasted conditions with multiple daily doses of a PPI (omeprazole) decreased the AUC_{0-INF} of selpercatinib by 69% and the C_{max} by 88% as compared to selpercatinib administered alone. [Module 2.7.1.2.1] When administered with a high fat meal, and omeprazole, the AUC_{0-INF} of selpercatinib was increased by 2% and the C_{max} reduced by 49% as compared to selpercatinib administered alone under fasted conditions. [Module 2.7.1.2.1] When administered with a low-fat meal, and omeprazole, the AUC_{0-INF} of selpercatinib was unchanged and the C_{max} reduced by 22% as compared to selpercatinib administered alone under fasted conditions. [Module 2.7.1.2.2]

Effect of H2 Antagonists: Coadministration of a single 160 mg dose of selpercatinib capsules under fasted conditions with multiple daily doses of an H2 antagonist (ranitidine) given 10 hours prior to and 2 hours after the selpercatinib dose decreased the AUC_{0-INF} of selpercatinib by 7% and the C_{max} by 18% as compared to selpercatinib administered alone [Module 2.7.1.2.2]

The Applicant's Position:

No dose adjustment is recommended for coadministration of P-gp inhibitors with selpercatinib.

Avoid coadministration of strong CYP3A4 inhibitors with selpercatinib. If coadministration of a strong CYP3A4 inhibitor cannot be avoided, reduce the selpercatinib dose (b) (4) After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume selpercatinib at the dose taken prior to initiating the CYP3A4 inhibitor.

Avoid coadministration of strong CYP3A4 inducers with selpercatinib. (b) (4)

The absorption of selpercatinib may be decreased by agents that raise gastric pH (e.g. proton pump inhibitors (PPIs), H2 blockers, antacids). If PPIs are required, take selpercatinib with food. If H2 blockers or antacids are required, take selpercatinib 2 hours before the H2 blocker or antacid.

The FDA's Assessment:
FDA agrees with the Applicant's recommendations for coadministration with P-gp inhibitors and acid-reducing agents. FDA recommends selpercatinib dose reduction for coadministration with strong and moderate CYP3A inhibitors and avoidance of both strong and moderate CYP3A inducers. (b) (4) Additional detail is described in **Section 6.3.2.4**.

6.2.2.3 Outstanding Issues

The Applicant's Position:
No outstanding issues. As agreed with FDA, the Hepatic and Renal Impairment studies are currently ongoing and will be completed as a PMR.

The FDA's Assessment:
Data from the dedicated hepatic impairment study were submitted during the review cycle and are described below in **Section 6.3.2.3**. The final study report for the hepatic impairment study will be submitted as a PMR.

The final study report and datasets for the dedicated renal impairment study will be submitted as a PMR.

A clinical drug interaction study to evaluate the effects of selpercatinib on the pharmacokinetics of a P-gp substrate will be conducted as a PMR.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Data:

Pharmacology	
Mechanism of Action	Selpercatinib is a small molecule inhibitor of the RET receptor tyrosine kinase. Chromosomal rearrangements involving in-frame fusions of *RET* with various partners can result in constitutively activated chimeric RET fusion proteins that can act as oncogenic drivers by promoting cell proliferation and survival in tumor cell lines. Point mutations in *RET* can also result in constitutively activated RET proteins that can promote cell growth and survival in tumor cell lines. [Modules 2.7.3.2 (NSCLC); 2.7.3.2 (MTC); 2.7.4.2] In enzyme assays, selpercatinib inhibited wild-type RET and the mutant isoforms RET-V804L, RET-V804M, RET-A883F, RET-S904F and RET-M918T with IC_{50} values of 0.20 nM to 2.21 nM. Two other kinases (FLT1 and FLT 4) were inhibited in this range. [Modules 2.6.2.2.1.1; 2.6.2.3.1.1] In in vitro and in vivo tumor models, selpercatinib demonstrated anti-tumor activity in cells harboring constitutive activation of RET protein resulting from gene fusions and mutations, including CCDC6-RET, KIF5B-RET, RET-V804M, and RET-M918T. Selpercatinib had minimal activity in cell lines without activating *RET* fusions or mutations. In addition, selpercatinib exhibits intracranial anti-tumor activity of patient-derived *RET* fusion xenograft tumors implanted directly into the brain of mice. [Module 2.6.2.2.2]
Active Moieties	Selpercatinib
QT Prolongation	Concentration-QTc analysis of the healthy volunteer study (placebo and positive-controlled) showed that selpercatinib at the studied doses (320 mg and 640 mg single dose) caused prolongation of QTc less than that observed with moxifloxacin, and no other clinically relevant effects on studied ECG parameters. A concentration-QTc analysis showed that a QTcF effect above 10 ms and 20 ms can be excluded up to selpercatinib plasma concentration of approximately 2470 ng/mL and 4770 ng/mL, respectively. Therapeutic concentrations of selpercatinib (geometric mean C_{max} ~of 2980 ng/mL) can cause a small increase in the corrected QT (QTc) interval (< 20 ms). Supra-therapeutic concentrations, as could be obtained if selpercatinib were co-administered with a strong inhibitor of CYP3A4 could lead to an increase in QTc > 20 ms. [Module 2.7.2.2.8; CSR LOXO-RET-18032]
General Information	
Bioanalysis	Selpercatinib was measured using validated LC-MS/MS assay methods over the range of 1 to 1000 ng/mL. Accuracy (%RE) and precision (%CV) of the quality controls (QCs) for the runs used in measuring selpercatinib plasma concentrations were ≤15%, which are acceptable based on the current Bioanalytical Method Validation Draft FDA Guidance for Industry. [Module 2.7.1.1.2 - Tables 16 & 18]
Healthy vs. Patients	The geometric means of oral clearance (CL/F) in healthy subjects (160 mg single dose, N=6, ADME study) and patients (160 mg BID, N = 512, PopPK analysis) were 6.8 L/h and 5.9 L/h, respectively. [Module 2.7.2.2.11.2; Module 2.7.1.2.3 - Table 30]
Drug Exposure at Steady State	The geometric mean (%CV) steady-state AUC_{0-24h} was 51600 ng·h/mL (58%) following selpercatinib 160 mg BID dosage regimen. [Module 2.7.2.4.2 - Table 17]
Range of Effective	160 mg BID (recommended to be marketed dose) to 40 mg BID (lowest

Dose or Exposure	recommended dose reduction) [Module 2.7.2.4.5]
Maximally Tolerated Dose or Exposure	A maximum tolerated dose (MTD) was not established in Phase 1/2 study LOXO-RET-17001. The highest assessed dosage in study LOXO-RET-17001 was 240 BID (n = 6). 9 of the 531 patients (1.7%) received doses higher than the 160 mg BID recommended dose. [Module 2.7.4.4.3 - Table 9]
Dose Proportionality	Selpercatinib doses of 20 mg QD up to 240 mg BID show approximately linear to slightly supra-proportional pharmacokinetics in cancer patients. Sub-proportional exposure with single doses of 320 mg to 720 mg in healthy subjects. [Modules 2.7.2.4.2; 2.7.1.2.4]
Accumulation	The geometric mean (%CV) accumulation ratio following selpercatinib 160 mg BID was 3.4 (68%). [Module 2.7.2.4.2 - Table 17]
Variability	The inter-subject variability (CV%) at steady-state $AUC_{0\text{-}24h}$ was 58% and C_{max} was 53% in patients given 160 mg BID of selpercatinib. [Module 2.7.2.4.2 – Table 17]
Absorption	
Bioavailability	The mean absolute bioavailability of selpercatinib capsules was 73% (range: 60% to 82%). [Module 2.7.1.2.3.2]
Tmax	Following selpercatinib 160 mg BID, the median T_{max} is 2 hours (range: 0 - 8 hours). [Module 2.7.2.4.2 - Table 17]
Food effect	After oral administration of a single dose of selpercatinib 160 mg capsule to healthy subjects taken with a high-fat meal, there was an increase of approximately 9% in AUC and an approximately 14% decrease in the C_{max} compared to the C_{max} and AUC in the fasted state. [Module 2.7.1.2.1]
Distribution	
Volume of Distribution	The mean (CV%) volume of distribution (Vz/F) of selpercatinib is 323 L (45%) following oral administration of a single [14C] radiolabeled 160 mg dose in healthy subjects. [CSR LOXO-RET-18016, Table 14.2.2.1-1]
Plasma Protein Binding	Selpercatinib is 97% bound to human plasma proteins in vitro. The blood-to-plasma concentration ratio is 0.7. [Modules 2.7.2.3.2; 2.7.2.3.3]
As Substrate of Transporters	Selpercatinib is a substrate for P-gp and BCRP. In transfected BCRP and P-gp cell lines, the efflux ratios were 24 and 8 to 26, respectively. Selpercatinib is not a substrate for the transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K. [Module 2.7.2.3.6]
Elimination	
Terminal Elimination Half-Life (SD)	Following oral administration of 160 mg BID dose of selpercatinib in patients, the geometric mean (CV%) of the apparent clearance (CLss/F) of selpercatinib is 6.2 L/h (58%) and the mean (standard deviation) terminal half-life is 37 hours (18%) following oral administration of a single [^{14}C] radiolabeled 160 mg dose in healthy subjects. [Module 2.7.2.4.2; Table 17;Module 2.7.1.2.3; Table 30]
Metabolism	
Fraction Metabolized, %dose	The fraction of the dose metabolized is approximately 74%, based on the mean percentage of the dose recovered as metabolites in the excreta. [Module 2.7.1.2.3.2]
Primary Metabolic Pathway(s)	CYP3A4 is mainly responsible for the metabolism of selpercatinib based on experiments with cloned expressed human cytochrome P450 enzymes and CYP3A4-inactived human liver microsomes. [Module 2.7.2.3.5] Oxidative metabolism represented the major biotransformation pathways (oxidation, N-dealkylation, O-demethylation) of selpercatinib. Plasma metabolites

	were present at trace to minor levels (<4%). [Module 2.7.1.2.3.2, Figure 15]
Excretion	
Primary Excretion Pathways, % dose (SD)	Following administration of a single dose of 160 mg of [^{14}C]-selpercatinib, a mean of 69% of the administered radioactivity was recovered in feces and 24% was recovered in urine through the last collection interval (432 hours). The overall mean recovery of radioactivity in urine and feces was 93.5%, with most of the recovery in the first 144 hours postdose (85%). Unchanged selpercatinib accounted for 26% of the dose in total excreta (12% in urine; 14% in feces). Desmethyl-selpercatinib was the most abundant metabolite identified in feces (29%). [Module 2.7.1.2.3.2; CSR LOXO-RET-18016]
Interaction liability (Drug as Victim)	
Inhibition/Induction of Metabolism	Coadministration of a single 160 mg dose of selpercatinib capsules with a strong CYP3A inhibitor (itraconazole) increased the $AUC_{0\text{-}INF}$ of selpercatinib by 2.3-fold and the C_{max} by 1.3-fold as compared to selpercatinib administered alone [Module 2.7.2.2.4] Coadministration of a single 160 mg dose of selpercatinib capsules with a strong CYP3A inducer (rifampin) decreased the $AUC_{0\text{-}INF}$ of selpercatinib by 87% and the Cmax by 70% as compared to selpercatinib administered alone. [Module 2.7.2.2.4]
Inhibition/Induction of Transport Systems	Coadministration of a single 160 mg dose of selpercatinib capsules with a P-gp inhibitor (rifampin) increased the $AUC_{0\text{-}24}$ of selpercatinib by 6% and the Cmax by 19% as compared to selpercatinib administered alone. [Module 2.7.2.2.4] Selpercatinib is not a substrate for the transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K. [Module 2.7.2.3.6]
Effects on Absorption	Selpercatinib has low solubility at higher pH and moderate to high solubility in very acidic media (pH-dependent solubility). [Module 2.7.1.1.1.3.2] Coadministration of a single 160 mg dose of selpercatinib capsules under fasted conditions with multiple daily doses of a PPI (omeprazole) decreased the $AUC_{0\text{-}INF}$ of selpercatinib by 69% and the C_{max} by 88% as compared to selpercatinib administered alone. When administered with a high fat meal, and omeprazole, the $AUC_{0\text{-}INF}$ of selpercatinib was increased by 2% and the C_{max} reduced by 49% as compared to selpercatinib administered alone under fasted conditions. When administered with a low-fat meal, and omeprazole, the $AUC_{0\text{-}INF}$ of selpercatinib was unchanged and the C_{max} reduced by 22% as compared to selpercatinib administered alone under fasted conditions. [Modules 2.7.1.2.1; 2.7.1.2.2; 2.7.2.2.1; 2.7.2.2.2] Coadministration of a single 160 mg dose of selpercatinib capsules under fasted conditions with multiple daily doses of an H2 antagonist (ranitidine) given 10 hours prior to and 2 hours after the selpercatinib dose decreased the $AUC_{0\text{-}INF}$ of selpercatinib by 7% and the C_{max} by 18% as compared to selpercatinib administered alone [Module 2.7.1.2.2]
Interaction liability (Drug as perpetrator)	
Inhibition/Induction of Metabolism	Selpercatinib is a weak inhibitor of CYP2C8 and a weak time-dependent inhibitor of CYP3A4; it is not an inhibitor of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP3A4

	at clinically relevant concentrations. Selpercatinib is a weak concentration-dependent inducer of CYP1A2, CYP2B6, and CYP3A4. [Module 2.7.2.3.9] Coadministration of selpercatinib 160 mg twice daily with a sensitive CYP3A4 substrate (midazolam) increased the $AUC_{0\text{-}INF}$ of midazolam by 1.5-fold and the C_{max} by 1.4-fold as compared to midazolam administered alone. The AUC0-INF of 1-hydroxymidazolam, the main metabolite of midazolam, was increased by 27% and Cmax by 6% as compared to when midazolam was administered alone. [Module 2.7.2.2.5]
Inhibition/Induction of Transporter Systems	Selpercatinib inhibits the transporter MATE1 with an IC_{50} of 0.666 µM and weakly inhibits BCRP and P-gp. Selpercatinib is not an inhibitor of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BSEP, MATE1 and MATE2-K at clinically relevant concentrations. [Module 2.7.2.3.8] Administration of 160 mg BID selpercatinib for 10 days to healthy volunteers resulted in mild changes in serum creatinine without any evidence of renal injury. [Modules 2.7.2.2.5 and 2.7.2.2.6]

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of General Pharmacology and Pharmacokinetic Characteristics with the following exceptions:

- Selpercatinib is a moderate inhibitor of CYP2C8 *in vivo* based on results of a clinical drug interaction study with repaglinide.
- Selpercatinib increases serum creatinine in both healthy volunteers (mean increase 0.14 mg/dL) and patients (mean increase 0.15 mg/dL). There is insufficient evidence to support the Applicant's claim that administration of selpercatinib does not cause renal injury.

6.3.2 Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:
The majority of studies in the clinical pharmacology program were conducted in healthy volunteers. The primary evidence of effectiveness comes from the LOXO-RET-17001 study in cancer patients and is discussed in Section 8.

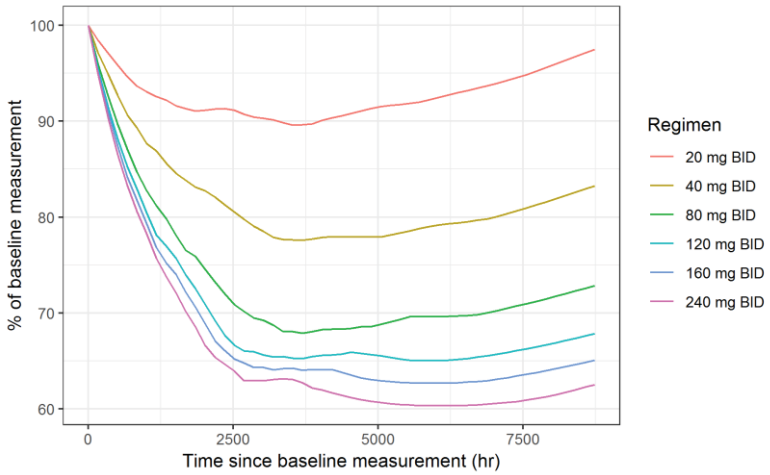
The FDA's Assessment:
FDA generally agrees with the Applicant's assessment. See the FDA's assessment in **Sections 6.3.2.2** and **8.1** for additional details.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

A modeling study of the population PK, tumor size, and exposure-response modeling was conducted using patient data (N = 85–99) from LOXO-RET 17001 (cutoff 19 July 2018) to support the selection of 160 mg BID as the recommended dose for RP2D. The modeling study showed that the rate of reduction in tumor size was impacted by exposure to selpercatinib via a saturable relationship. The AUC_{0-24} at steady state that gave rise to 50% of the maximum tumor decay rate constant was associated with a selpercatinib dose of approximately 30 mg twice daily (BID). A dose of 160 mg BID selpercatinib appeared to provide maximal benefit in terms of tumor shrinkage across all tumor types and cohorts. [Module 2.7.2.2.11.1]

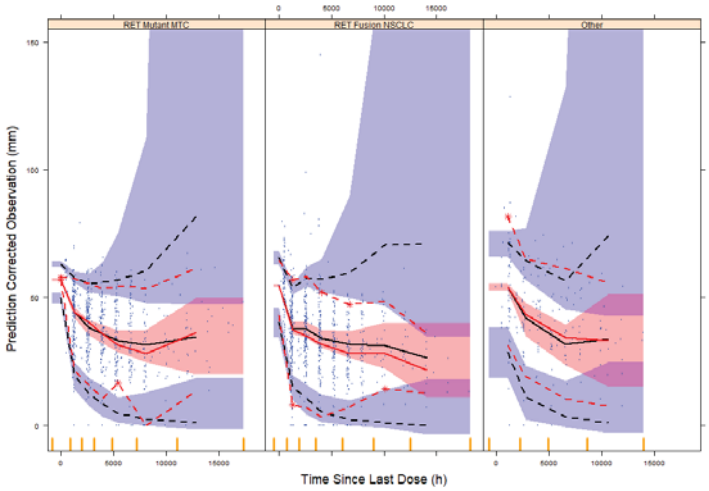
Figure 6.1: Median Simulated Percent Change From Baseline Tumor Size Following Treatment with Selpercatinib at Doses Ranging from 20 mg BID to 240 mg BID, Data Cutoff: 19 July 2018



BID = twice daily
Source: LOXO-292-DMPK-031, Figure 18

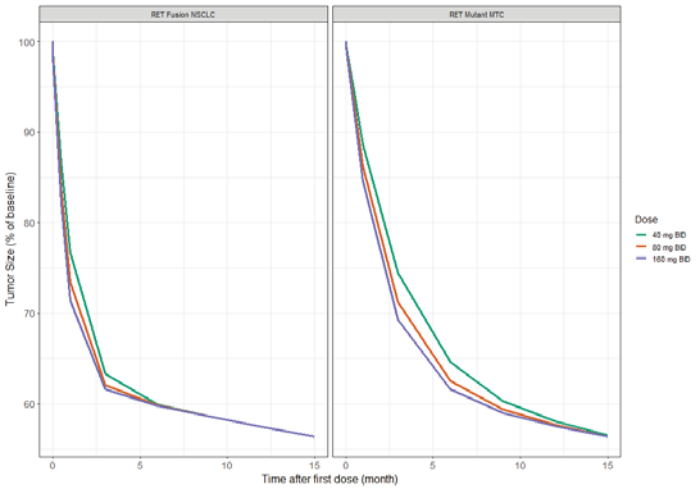
An updated modeling and simulation study (N = 476–512; cutoff 17 June 2019) confirmed that increases in selpercatinib exposure are associated with the rate of decrease in tumor size for both *RET*-fusion NSCLC and *RET*-mutant MTC tumors. The steady-state selpercatinib exposure required to elicit 50% maximal increase in tumor decay rate was 6526 ng*h/mL and was independent of tumor type. Tumor shrinkage was a predictor of both OS and PFS for both tumor groups. Parametric survival models showed that both OS and PFS increase as tumor shrinkage increases. Simulations of the PK, tumor size and progression-free survival for both *RET*-fusion NSCLC and *RET*-mutant MTC were performed using the typical model parameters for the recommended dose reductions for AEs (40 mg BID, 80 mg BID) and 160 mg BID selpercatinib over 15 months. The tumor shrinkage results show similar profiles for all three dose levels over 15 months. At the dose levels tested, an increase in selpercatinib does not increase the likelihood of increase in ALT or AST AEs, hypersensitivity AEs, or hypertension AEs. [Module 2.7.2.2.11.2]

Figure 6.2: Prediction-Corrected VPC of the Final Population Tumor Size Model (tcovfd1) for Selpercatinib Stratified by Tumor Group



Abbreviations: h = hour; VPC = visual predictive check.
Note: The blue circles represent prediction-corrected observed data, the red solid line represents the median of the prediction-corrected observed data, and the red dashed lines represent the 5th and 95th percentiles of the prediction-corrected observed data. The red stars represent observed values that lie outside of the 90% prediction interval. The black solid line represents the median of the prediction-corrected simulation data, and the black dashed lines represent the 5th and 95th percentiles of the prediction-corrected simulation data. The blue shaded areas represent the 90% prediction interval for the 5th and 95th percentiles of the predicted data, and the red shaded areas represent the 90% prediction interval for the median of the predicted data. The yellow vertical ticks on x-axis represent the edges of the bins used to group the data for calculation of the quartiles.
Source: LOXO-292-DMPK-050, Figure 24.

Figure 6.3: Simulated Tumor Shrinkage Profiles for a Typical Patient with Either a *RET*-Fusion NSCLC Tumor or *RET*-Mutant MTC Tumor Receiving 40 mg BID, 80 mg BID or 160 mg BID Selpercatinib



Abbreviations: BID = twice daily; MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer.
Source: LOXO-292-DMPK-050, Figure 33

The Applicant's Position:
Together with the clinical effectiveness and safety results, the modeling results support the recommended dosage of 160 mg BID as the to-be marketed dose and support that the recommended dose reductions for AEs will maintain sufficient selpercatinib levels to provide continued overall clinical benefit.

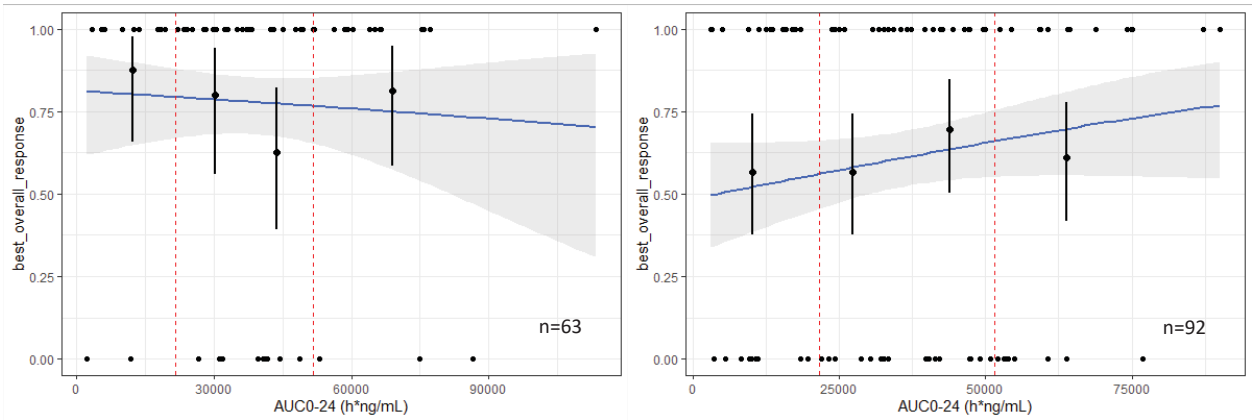
The FDA's Assessment:
FDA agrees with the Applicant's assessment of the effects of selpercatinib on tumor shrinkage and exposure-response analysis for selected safety events (increase in ALT or AST, hypersensitivity, and hypertension) as described above. In addition, FDA evaluated the effects of selpercatinib on the QT interval and conducted an additional exposure-response analysis for ORR vs selpercatinib exposure.

In a thorough QT study in healthy volunteers, selpercatinib was associated with concentration-dependent QTc prolongation. The mean increase in the QTc interval at the geometric mean C_{max} observed after administration of the Applicant's proposed dosing regimen (160 mg BID) is 10.6 msec (90% CI: 9.1, 12.1 msec). A mean change in QTc of >20 msec can be excluded at selpercatinib concentrations <4,770 ng/mL. Refer to the Interdisciplinary Review Team for Cardiac Safety Studies QT Consultation Review for additional detail.

The Applicant's exposure-response analysis for ORR utilized selpercatinib exposure parameters from the time of most recent response (for responders) or the last treatment period (for non-responders) for each individual patient. FDA review of dosing records identified some patients with temporary dose adjustments (i.e., 1-2 doses) at the time of response or end of treatment. Therefore, to better reflect the selpercatinib steady-state exposure, the reviewer modified the exposure-response analysis to utilize average exposure over the last 10 doses at the relevant time for each individual patient. Refer to the Exposure-Response Analysis Appendix (**Section 19.4.4**) for additional details.

Based on FDA's revised E-R analysis for ORR, prior radiotherapy was identified as a significant predictor for best overall response. Patients without prior radiotherapy had higher ORR than patients with prior radiotherapy. Selpercatinib exposure ($AUC_{0\text{-}24h}$, C_{max}, and C_{min}) was not a significant predictor for response. For patients with prior radiotherapy, there was a trend towards higher ORR with higher selpercatinib $AUC_{0\text{-}24h}$, but the relationship was not significant (**Figure 6.4**).

Figure 6.4: ORR vs Selpercatinib $AUC_{0\text{-}24h}$ in Patients Without Prior Radiotherapy (Left) and Patients With Prior Radiotherapy (Right)

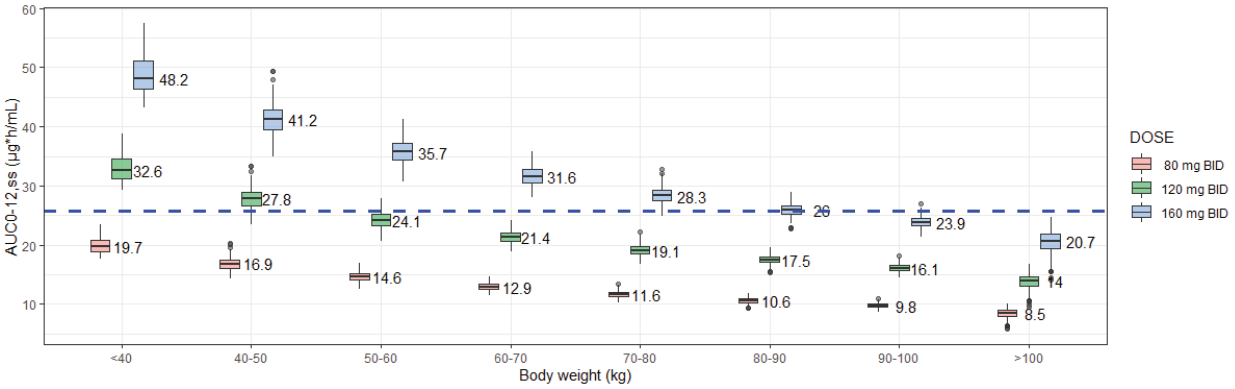


Notes: Red dotted lines represent the observed geometric mean selpercatinib steady-state $AUC_{0\text{-}24h}$ in patients treated with 80 mg BID (21,645 h*ng/mL) and 160 mg BID (51,372 h*ng/mL).
Source: FDA Analysis

(b) (4)

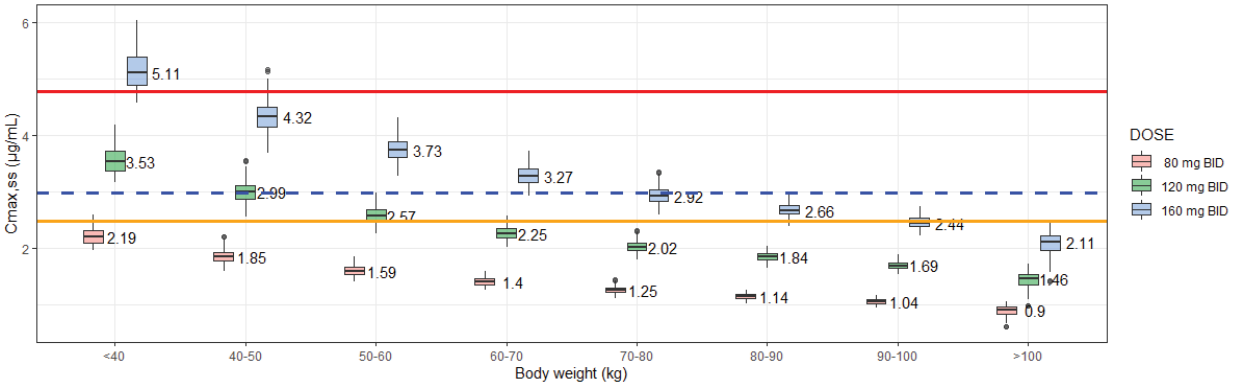
Based on population PK analysis, body weight affects selpercatinib exposure with higher exposure at lower body weight. Using the final population PK model, selpercatinib steady-state exposure was simulated after administration of 80 mg BID, 120 mg BID, and 160 mg BID across the relevant body weight range in adults and adolescents [**Figure 6.5** ($AUC_{0\text{-}12h}$) and **Figure** 6.6 (C_{max})].

Figure 6.5: Simulated Selpercatinib Steady-State $AUC_{0\text{-}12h}$ vs Body Weight in Adults and Adolescents



Notes: Blue dashed line represents the observed geometric mean selpercatinib steady-state $AUC_{0\text{-}12h}$ in patients treated with 160 mg BID (25.7 h*µg/mL).
Source: FDA Analysis

Figure 6.6: Simulated Selpercatinib Steady-State C_{max} vs Body Weight in Adults and Adolescents



Notes: Red and orange lines represent the selpercatinib concentrations predicted to result in ≥20 msec (4.77 µg/mL) and ≥10 msec (2.47 µg/mL) QT prolongation, respectively. Blue dashed line represents the observed geometric mean selpercatinib steady-state C_{max} in patients treated with 160 mg BID (2.98 µg/mL).
Source: FDA Analysis

As shown in **Figure** 6.6, in patients with a body weight <50 kg, treatment with 160 mg BID is predicted to result in selpercatinib steady-state C_{max} exceeding the 20 msec QTc prolongation threshold concentration in some patients. Reducing the dose to 120 mg BID in patients with body weight <50 kg results in similar selpercatinib steady-state $AUC_{0\text{-}12h}$ and C_{max} relative to the geometric mean observed steady-state exposure in LIBRETTO-001. In addition, by reducing the dose to 120 mg BID in patients with body weight <50 kg the predicted steady-state C_{max} remains below the concentration predicted to result in ≥20 msec QTc prolongation for all patients. Therefore, based on exposure-matching and avoidance of excess QT-prolongation risk, the recommended dosage of selpercatinib is 120 mg BID in patients with body weight <50 kg and 160 mg BID in patients with body weight ≥50 kg.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:

Hepatic Impairment: Selpercatinib is primarily eliminated by the liver [Modules 2.7.1.2.3; 2.7.2.2.3]. The pharmacokinetics of selpercatinib in patients with hepatic impairment have not been evaluated.

Renal Impairment: There is evidence of renal contribution to the elimination of selpercatinib [Modules 2.7.1.2.3; 2.7.2.2.3]The pharmacokinetics of selpercatinib in patients with renal impairment have not been evaluated.

The Applicant's Position:

A recommended dose has not yet been determined for patients with hepatic or renal impairment.

The FDA's Assessment:
Yes. Alternative dosing regimens are necessary for patients with low body weight (<50 kg) or severe hepatic impairment (total bilirubin greater than 3 to 10 times ULN and any AST). Dose adjustment is not necessary for the following other intrinsic factors: mild or moderate renal impairment (CrCL ≥30 to <90 mL/min by Cockcroft-Gault), mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) or moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST) hepatic impairment, age (15 to 90 years), or sex. In the labeling, the FDA stated that the effect of severe renal impairment (CrCL <30 mL/min) on selpercatinib PK has not been adequately studied. Confirmed responses were observed in patients with advanced MTC across different RET mutations.

Body Weight: Reduce the dose of selpercatinib to 120 mg BID in patients with body weight <50 kg as described above in **Section 6.3.2.2**.

Hepatic Impairment:
During the review cycle, the Applicant submitted data from a dedicated hepatic impairment study (LOXO-RET-18022). Study LOXO-RET-18022 is an open-label, single-dose study of the PK of selpercatinib in subjects with normal hepatic function (n=12) and mild, moderate, and severe hepatic impairment (n=8 each) classified by Child-Pugh. Subjects received a single dose of 160 mg selpercatinib while fasted. Blood samples were collected for determination of selpercatinib concentration and PK parameters were calculated using non-compartmental analysis. The geometric least squares mean for each parameter was calculated using ANCOVA with group, sex, age, and BMI as covariates. Results of this analysis for total and unbound selpercatinib are shown in **Table 6.3**.

Table 6.3: Total and Unbound Selpercatinib PK in Subjects with Normal Hepatic Function and Subjects with Mild, Moderate, or Severe Hepatic Impairment by Child-Pugh Classification

Parameter		**Child-Pugh**	**Normal**	**Mild**	**Moderate**	**Severe**
			N=12	N=8	N=8	N=8
C_{max} (ng/mL)	**Total**	Geo LSM	911	1,070	723	1,030
		Ratio of GLSM (90% CI)	*Ref*	117.7 (55.3, 250.7)	79.7 (37.7, 168.2)	113.5 (54.2, 237.8)
	Unbound	Geo LSM	35.1	43.8	31.8	78.4
		Ratio of GLSM (90% CI)	*Ref*	125.0 (60.5, 258.2)	90.6 (44.2, 185.7)	223.5 (109.9, 454.4)

$AUC_{0\text{-}INF}$ (h*ng/mL)	**Total**	Geo LSM	17,900	19,300	15,200	29,500
		Ratio of GLSM (90% CI)	*Ref*	107.8 (70.3, 165.3)	84.7 (55.5, 129.3)	165.2 (108.7, 250.9)
	Unbound	Geo LSM	689	789	664	2,240
		Ratio of GLSM (90% CI)	*Ref*	114.5 (76.4, 171.6)	96.3 (64.6, 143.7)	325.2 (218.9, 483.1)

Source: Applicant's Response to IR dated 10 Apr 2020, Tables 14.2.1-2.1 and 14.2.1-2.2

All subjects were reclassified based on NCI-ODWG criteria using screening laboratory values for bilirubin and AST and the analyses as described above were repeated. Results of this analysis are shown in **Table 6.4**.

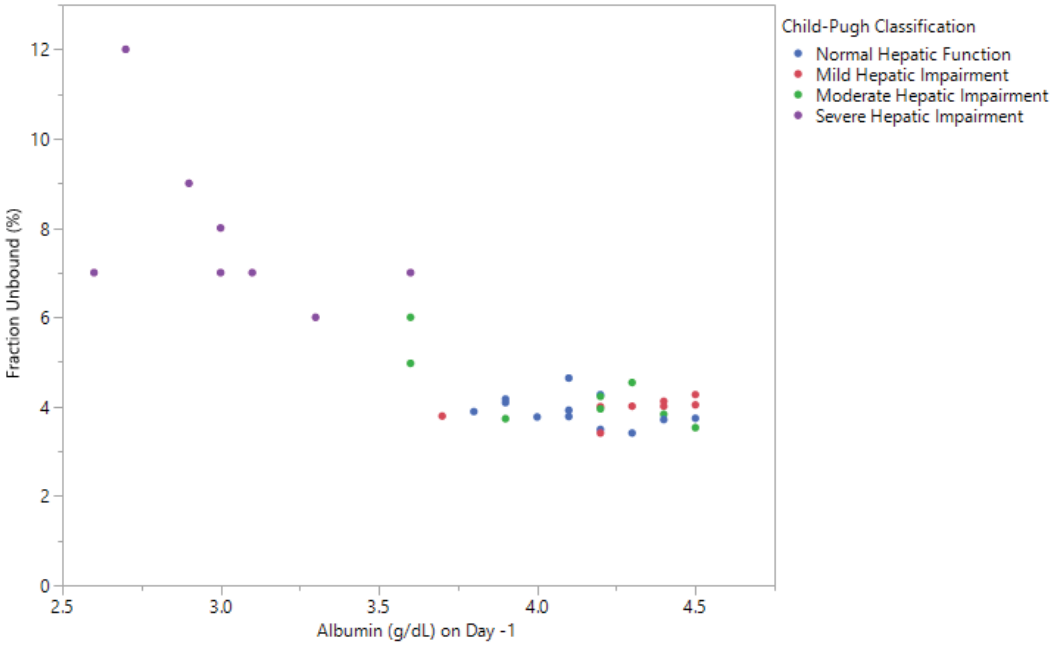
Table 6.4: Total and Unbound Selpercatinib PK in Subjects with Normal Hepatic Function and Subjects with Mild, Moderate, or Severe Hepatic Impairment by NCI-ODWG Classification

Parameter		**NCI-ODWG**	**Normal**	**Mild**	**Moderate**	**Severe**
			N=22	N=4	N=5	N=5
C_{max} (ng/mL)	**Total**	Geo LSM	890	1,100	885	1,020
		Ratio of GLSM (90% CI)	*Ref*	123.1 (44.9, 337.2)	99.5 (41.4, 239.1)	115.2 (48.3, 274.8)
	Unbound	Geo LSM	35.0	44.6	51.6	87.7
		Ratio of GLSM (90% CI)	*Ref*	127.3 (48.0, 337.7)	147.4 (63.1, 344.7)	250.5 (107.9, 581.5)
$AUC_{0\text{-}INF}$ (h*ng/mL)	**Total**	Geo LSM	17,300	18,500	22,900	30,700
		Ratio of GLSM (90% CI)	*Ref*	107.0 (59.4, 192.6)	132.2 (79.2, 220.5)	177.4 (106.8, 294.7)
	Unbound	Geo LSM	681	753	1,330	2,630
		Ratio of GLSM (90% CI)	*Ref*	110.6 (62.0, 197.3)	195.9 (118.3, 324.3)	385.8 (234.1, 636.0)

Source: Applicant's Response to IR dated 10 Apr 2020, Tables 14.2.1-2.1 and 14.2.1-2.2

Using either Child-Pugh or NCI-ODWG classification, the selpercatinib total AUC was increased by 65 – 77% in subjects with severe hepatic impairment. There was no significant change in selpercatinib total AUC for subjects with mild or moderate hepatic impairment and no significant change in selpercatinib total C_{max} for any degree of hepatic impairment.

Figure 6.7: Selpercatinib Fraction Unbound vs Albumin



Source: FDA Analysis

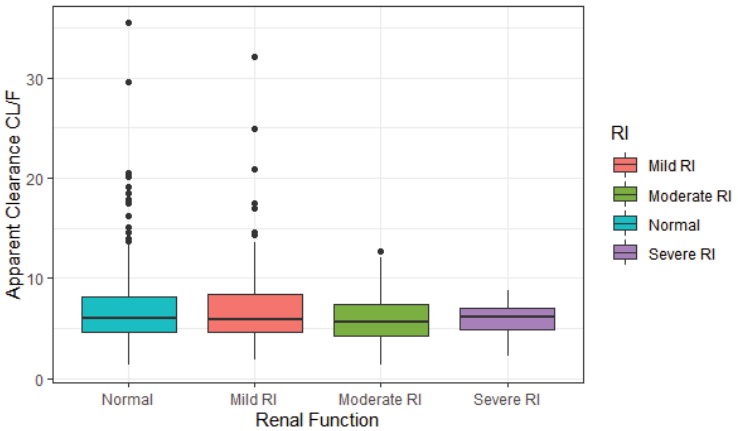
As shown in **Figure 6.7**, subjects with low albumin had an increased selpercatinib fraction unbound. This relationship resulted in a greater increase in unbound selpercatinib exposure relative to the increase in total selpercatinib exposure, particularly in subjects with severe hepatic impairment. Using either Child-Pugh or NCI-ODWG classification, selpercatinib unbound AUC was increased by 224 – 286% and unbound C_{max} was increased by 124 – 151% in subjects with severe hepatic impairment. Selpercatinib unbound C_{max} was not significantly changed in subjects with mild or moderate hepatic impairment.

While no exposure-response relationships were identified for selpercatinib AUC vs common adverse events in study LIBRETTO-001, hepatic transaminase elevations were common adverse events and the most frequent cause of selpercatinib dose interruptions and reductions. In addition, the increased unbound C_{max} observed in subjects with severe hepatic impairment increases the risk of QT prolongation. Given the potential for adverse events (hepatotoxicity and QT prolongation) and the observed increase in AUC and unbound C_{max}, the dose of selpercatinib should be reduced to 80 mg BID in patients with severe hepatic impairment.

Renal Impairment:
Patients with mild (CrCL ≥60 - <90 mL/min by Cockcroft-Gault, n=175), moderate (CrCL ≥30 - <60 mL/min, n=74), and severe (CrCL ≥15 - <30 mL/min, n=4) renal impairment were enrolled in LIBRETTO-001 and included in the population PK model. As shown in **Figure 6.8**, mild and moderate renal impairment did not significantly change the apparent clearance of selpercatinib

relative to patients with normal renal function (CrCL ≥90 mL/min, n=259). No dose adjustment is recommended for patients with mild or moderate renal impairment. There was not enough data available from patients with severe renal impairment to adequately assess the effect of severe renal impairment on the PK of selpercatinib. The Applicant has completed a dedicated renal impairment study (LOXO-RET-18023) and will submit the results as a PMR.

Figure 6.8: Effect of Renal Impairment on Selpercatinib Apparent Clearance



Source: FDA Analysis

Other Factors: The effect of age (15 to 90 years) and sex on selpercatinib PK was evaluated in the population PK analysis. No clinically significant differences were identified based on these factors. See the Population PK Analysis Appendix (**Section 19.4.1**) for a detailed review of the population PK analysis.

Three adolescent patients (ages 15, 16, and 17 years) with *RET*-mutant MTC enrolled in Study LIBRETTO-001 and received selpercatinib starting doses of 80 mg BID to 160 mg BID. Selpercatinib PK and safety in the adolescent patients was consistent with that observed in adult patients.

R*ET mutations and treatment response*:

FDA explored the association of RET mutations and treatment response in patients with advanced MTC included in the primary analysis (PAS, N=55) and treatment-naïve (N=88) subgroups in LIBRETTO-001. Per protocol, qualifying RET mutations (identified through documented results from local testing) included mutations known to be activating; synonymous, frameshift and nonsense mutations were excluded. The most common RET mutation in both PAS and treatment-naïve subgroups (N=143) was M918T (approximately 57.3%) in the tyrosine kinase domain, followed by mutations affecting cysteine residues within the extracellular domain (ECD) of RET (approximately 18.9%). Confirmed responses (CR or PR) were observed in PAS and treatment-naïve patients with different RET mutations, including substitutions and small insertion/deletions mapping throughout the RET protein and across

mutation types [**Table 19.16** (Appendix **19.4.6**), **Table 8.29**), supporting the proposed broad target population [advanced RET-mutant MTC]. For additional details and individual listing of mutations see Appendix **19.4.6**. Of note, a candidate companion diagnostic test is under development (NGS) and will not be available at the time of drug approval. It is unclear how qualifying RET mutations will be defined by local tests and whether/how unknown variants or variants of uncertain significance will be considered qualifying for treatment with selpercatinib in the absence of a companion diagnostic test in the post-approval setting.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

Food-Drug and pH Modifier-Drug Interactions:

The effect of food and the proton-pump inhibitor, omeprazole on selpercatinib PK was evaluated in a randomized, four period crossover study [CSR LOXO-RET-18015, Module 2.7.1.2.1] in 20 healthy subjects with a 7-day washout period. Healthy subjects received a single oral dose of 160 mg selpercatinib capsules under fasting conditions (overnight fast and continued the fast for at least 4 hours post-dose) or under fed conditions (high-fat meal) with and without coadministration of multiple doses of omeprazole. The composition of the high-fat meal was consistent with the recommendations in the FDA Food Effect Guidance for Industry. The C_{max} of selpercatinib decreased 14% after a high-fat meal as compared to that in a fasted state; the GMR% [90% CI] of the selpercatinib C_{max} was 86.24 [57.27–129.88] and the AUC_{inf} was 108.58 [81.17–145.25]. The C_{max} of selpercatinib decreased 88% with coadministration of omeprazole in the fasted state compared to selpercatinib alone in the fasted state; the GMR% [90% CI] of the selpercatinib C_{max} was 12.32 [8.14–18.66] and the AUC_{inf} was 31.28 [23.29-42.02]. The C_{max} of selpercatinib decreased 41% with coadministration of omeprazole in the fed state compared to selpercatinib alone in the fed state; the GMR% [90%CI] of the selpercatinib C_{max} was 58.62 [38.93–88.28] and the AUC_{inf} was 93.81 [70.13–125.49].

The effect of food, the proton-pump inhibitor, omeprazole and the H2 antagonist, ranitidine on selpercatinib PK was evaluated in a randomized, three period crossover study [CSR LOXO-RET-19075, Module 2.7.1.2.2] in 20 healthy subjects with a 7-day washout period. Healthy subjects received a single oral dose of 160 mg selpercatinib capsules under fasting conditions (overnight fast and continued the fast for at least 4 hours post-dose) with and without treatment with ranitidine (ranitidine dosed two hours after selpercatinib) or under fed conditions (low-fat meal) with and without coadministration of multiple doses of omeprazole. The composition of the low-fat meal was consistent with the recommendations in the FDA Food Effect Guidance for Industry. The C_{max} of selpercatinib decreased 18% with coadministration of ranitidine in the fasted state compared to selpercatinib alone in the fasted state; the GMR [90% CI] of the

selpercatinib C_{max} was 0.818 [0.680, 0.985] and the AUC_{inf} was 0.932 [0.829, 1.05]. The C_{max} of selpercatinib decreased 22% with coadministration of omeprazole in the fed state compared to selpercatinib alone in the fasted state; the GMR [90% CI] of the selpercatinib C_{max} was 0.782 [0.645, 0.949] and the AUC_{inf} was 1.00 [0.888, 1.13].

Drug-Drug Interactions

Effects of Other Drugs on Selpercatinib

CYP3A4 Inhibitors

The effects of itraconazole (a strong CYP3A4 inhibitor) on the PK of selpercatinib were evaluated in an open-label, 2-period, fixed-sequence study in healthy subjects (N = 12) with a washout period of 7 days [CSR LOXO-RET-18014, Module 2.7.2.2.4]. The systemic exposure (AUC and C_{max}) of selpercatinib increased when selpercatinib was coadministered with itraconazole (a strong CYP3A inhibitor). Following oral coadministration of 160 mg selpercatinib (capsules) with itraconazole 200 mg once daily for 7 days in healthy subjects, the GMR% [90% CI] of the AUC_{inf} of selpercatinib was 230.41 [199.05–266.70] and of the C_{max} was 130.42 [106.33–159.96] as compared to selpercatinib administered alone.

A physiological-based pharmacokinetics (PBPK) assessment of the effect of CYP3A4 moderate and strong inhibitors on selpercatinib [LOXO-DMPK-052, Module 2.7.2.2.12]predicted 2.48, 2.18, and 3.83 fold increases in AUC with the concomitant use of moderate and strong CYP3A4 inhibitors fluconazole, diltiazem, and clarithromycin, respectively.

CYP3A4 Inducers

The effects of rifampin (a strong CYP3A4 and P-gp inducer upon multiple dosing) on the PK of selpercatinib were evaluated in an open-label, 2-period, fixed-sequence study in healthy subjects (N = 12) following repeated dosing of rifampin and a single dose of selpercatinib [CSR LOXO-RET-18014, Module 2.7.2.2.4]. The systemic exposure (AUC and C_{max}) of selpercatinib decreased in subjects who were coadministered selpercatinib with rifampin. Following oral administration of rifampin (a strong CYP3A inducer) 600 mg once daily for 11 days and coadministration of a single 160 mg selpercatinib dose (capsules) to healthy subjects, the GMR% [90% CI] of the AUC_{inf} of selpercatinib was 13.31 [10.88 - 16.29] and of the C_{max} was 30.14 [21.98–41.32] as compared to selpercatinib administered alone.

A physiological-based pharmacokinetics (PBPK) assessment of the effect of CYP3A4 moderate inducers on selpercatinib [LOXO-DMPK-052, Module 2.7.2.2.12] predicted 0.53 and 0.64-fold reduction in AUC with the concomitant use of moderate CYP3A4 inducers modafinil and bosentan, respectively

P-gp Inhibitors

The effects of rifampin (a P-gp inhibitor when coadministered as a single dose) on the PK of selpercatinib were evaluated in an open-label, 2-period, fixed-sequence study in healthy subjects (N = 12) following coadministration of a single dose of rifampin with selpercatinib [CSR LOXO-RET-18014, Module 2.7.2.2.4]. The systemic exposure (AUC and C_{max}) of selpercatinib increased in subjects who were coadministered selpercatinib with a single dose of rifampin. Following oral administration of rifampin (a P-gp inhibitor upon single dosing) 600 mg once with coadministration of a single 160 mg selpercatinib dose (capsules) to healthy subjects, the GMR% [90% CI] of the AUC0-24h of selpercatinib was 106.48 [82.24 - 137.84] and of the C_{max} was 119.00% [83.58 - 169.44] as compared to selpercatinib administered alone.

Effects of Selpercatinib on Other Drugs

Effect of Selpercatinib on CYP3A4 substrates

The effects of selpercatinib on the PK of midazolam (sensitive CYP3A4 substrate) were evaluated in an open-label, fixed- sequence study in healthy subjects (N = 16) with a 48 hour washout between the first single dose of midazolam and the start of selpercatinib dosing [CSR LOXO-RET-18017, Module 2.7.2.2.5]. Healthy subjects received selpercatinib 160 mg BID for 10 days followed by coadministration of a single 2 mg dose of midazolam. The GMR% [90% CI] of the AUC_{inf} of midazolam following repeated selpercatinib dosing was 154.10 [138.86-171.00] and of C_{max} was 139.09 [116.36–166.26] as compared to midazolam administered alone. The AUC_{inf} and C_{max} of 1-hydroxymidazolam, was 127.24 [115.93–139.65] and 105.85 [88.33–126.85] respectively as compared to midazolam administered alone.

Effect of Selpercatinib on CYP2C8 substrates

The effects of selpercatinib on the PK of repaglinide (sensitive CYP2C8 substrate) were evaluated in an open-label, fixed- sequence study in healthy subjects (N = 16) with a 24 hour washout between the first single dose of repaglinide and the start of selpercatinib dosing [CSR LOXO-RET-18026, Module 2.7.2.2.6]. Healthy subjects received selpercatinib 160 mg BID for 10 days followed by coadministration of a single 0.5 mg dose of repaglinide. The GMR% [90% CI] of the AUC_{inf} of repaglinide following repeated selpercatinib dosing was 288.41 [249.06-333.98] and of C_{max} was 190.65 [152.30–238.66] as compared to repaglinide administered alone.

The Applicant's Position:

Selpercatinib can be administered with or without food.

The absorption of selpercatinib may be decreased by agents that raise gastric pH (e.g. proton pump inhibitors (PPIs), H2 blockers, antacids). If PPIs are required, take selpercatinib with food. If H2 blockers or antacids are required, take selpercatinib 2 hours before the H2 blocker or antacid.

Avoid coadministration of strong CYP3A4 inhibitors with selpercatinib. If coadministration of a strong CYP3A4 inhibitor cannot be avoided, reduce the selpercatinib dose (b) (4) After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume selpercatinib at the dose taken prior to initiating the CYP3A4 inhibitor.

Avoid coadministration of strong CYP3A4 inducers with selpercatinib. (b) (4)

Coadministration of selpercatinib with sensitive CYP3A4 substrates may increase their plasma concentrations. Avoid coadministration of selpercatinib with sensitive CYP3A4 substrates. If coadministration of sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased adverse reactions of these drugs.

Coadministration of selpercatinib with sensitive CYP3A4 substrates may increase their plasma concentrations. Avoid coadministration of selpercatinib with sensitive CYP3A4 substrates. If coadministration of sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased adverse reactions of these drugs.

No dose adjustment is recommended when co-administering selpercatinib with a P-gp inhibitor or with moderate CYP3A4 inducers

The FDA's Assessment:
Yes. There are clinically relevant drug-drug interactions between selpercatinib and acid-reducing agents (including PPIs, H2 receptor antagonists, and locally-acting antacids), moderate and strong CYP3A inhibitors and inducers, CYP2C8 substrates, and CYP3A substrates. Additional information is needed to assess the effects of selpercatinib on P-gp and BCRP substrates.
Effect of Food: FDA agrees with the Applicant's assessment that selpercatinib may be administered with or without food, unless coadministered with a PPI.

Effects of Other Drugs on Selpercatinib:

Acid-Reducing Agents: FDA agrees with the Applicant's assessment of the effect of acid-reducing agents on the PK of selpercatinib and recommendation to take selpercatinib with food when coadministered with a PPI. Based on the PK of selpercatinib in patients in Study LIBRETTO-001 (median t_{max} of 2 hrs) and results of the clinical drug interaction study with ranitidine, the timing of administration for concomitant H2 receptor antagonists and locally-acting antacids should be as follows:

- Take selpercatinib 2 hours before or 10 hours after administration of an H2 receptor antagonist.
- Take selpercatinib 2 hours before or 2 hours after administration of a locally-acting antacid.

CYP3A Inhibitors: FDA agrees with the Applicant's assessment of the effect of itraconazole on the PK of a single dose of selpercatinib in healthy volunteers.

The Applicant's initial PBPK models were updated during the review cycle to correct for overprediction in patients by reducing the fraction absorbed (fa). This change was based on the difference between the observed and the predicted C_{max} after administration of 160 mg BID. The modified model was used to predict the exposure of selpercatinib in cancer patients with and without CYP3A inhibitors. Refer to the PBPK Modeling Analysis Appendix (**Section 19.4.5**) for details.

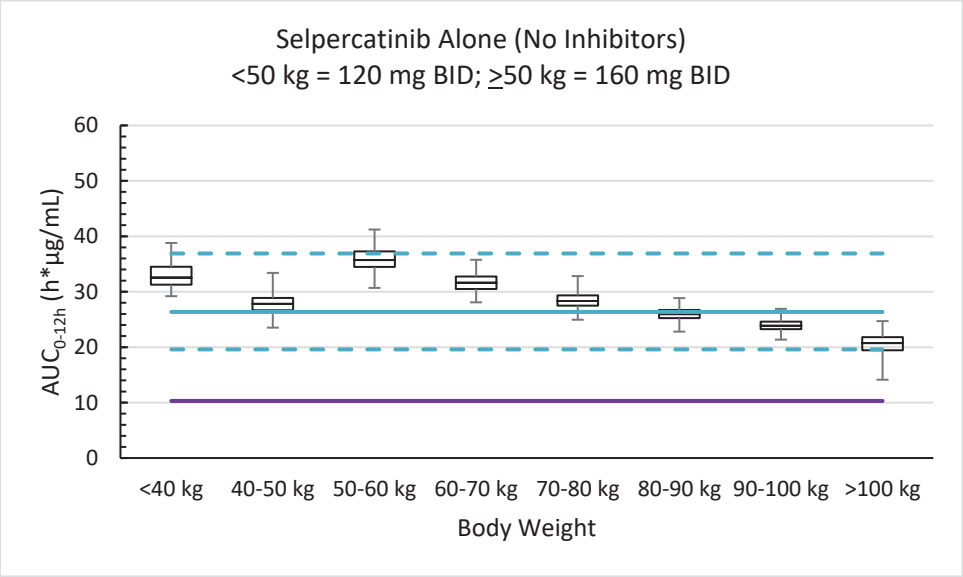
Selpercatinib dose reductions for concomitant use of moderate and strong CYP3A inhibitors were assessed based on the predicted fold-change in selpercatinib exposure from PBPK modeling and the simulated selpercatinib exposure across the body weight range for adults and adolescents from the final population PK model. Recommended dose reductions (**Table 6.5**) were identified using exposure-matching for the selpercatinib AUC. Safety of the recommended dose reductions was evaluated based on the selpercatinib C_{max} due to the concentration-dependent QT prolongation caused by selpercatinib.

Table 6.5: Recommended Dose Reductions for Selpercatinib for Concomitant Use of Strong and Moderate CYP3A Inhibitors

Current Dose of Selpercatinib	Selpercatinib Dose for Concomitant Use with Strong CYP3A Inhibitor	Selpercatinib Dose for Concomitant Use with Moderate CYP3A Inhibitor
120 mg twice daily	40 mg twice daily	80 mg twice daily
160 mg twice daily	80 mg twice daily	120 mg twice daily

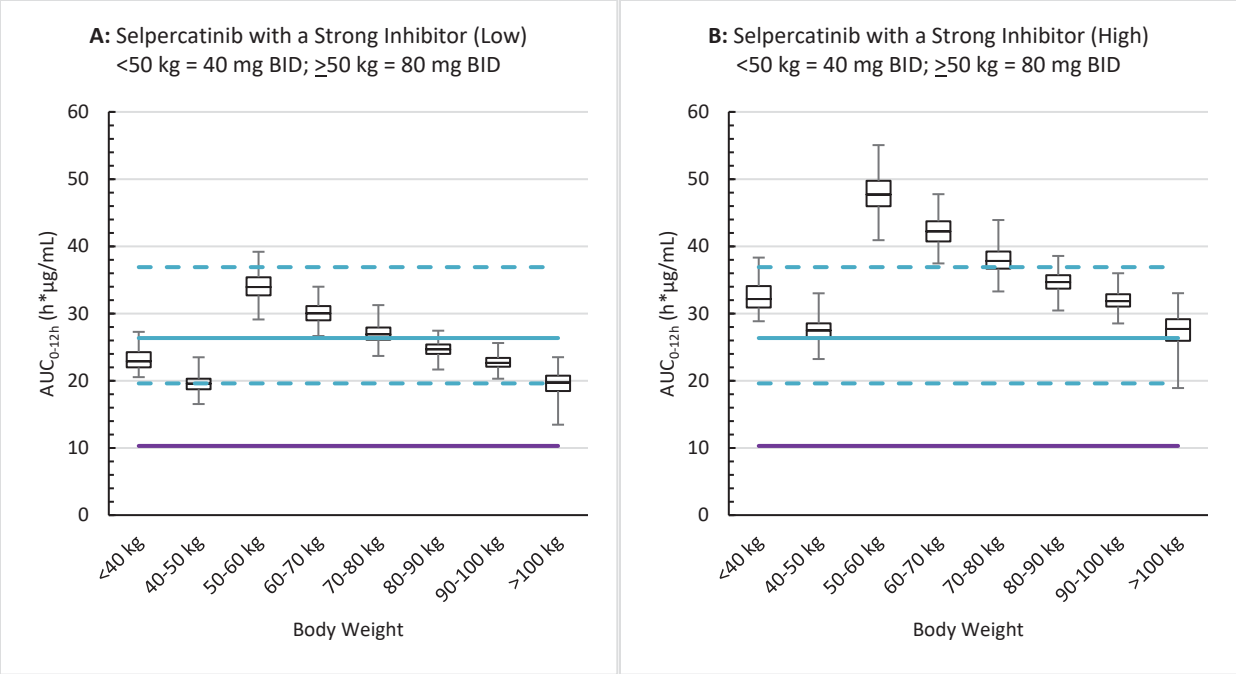
Figure 6.9 shows the simulated selpercatinib $AUC_{0\text{-}12h}$ by body weight after administration of the recommended dosage of selpercatinib alone (120 mg BID for patients with body weight <50 kg and 160 mg BID for patients with body weight ≥50 kg). Figures 6.10 and 6.11 show the simulated selpercatinib $AUC_{0\text{-}12h}$ by body weight after administration of the recommended dosage of selpercatinib per **Table 6.5** with concomitant strong (**Figure 6.10**) or moderate (**Figure 6.11**) CYP3A inhibitors. Given the variability in predictions for fold-change in exposure, figures 6.10 and 6.11 include panels for both the low (panel A) and high (panel B) ends of the predicted fold-change in exposure based on results of the updated PBPK models. Strong inhibitors were predicted to increase the AUC of selpercatinib by 126 – 226%, depending on the inhibiting drug and dose of selpercatinib. Moderate inhibitors were predicted to increase the AUC of selpercatinib by 60 – 122%, depending on the inhibiting drug and dose of selpercatinib.

Figure 6.9: Simulated Selpercatinib $AUC_{0\text{-}12h}$ After Administration of Selpercatinib Alone



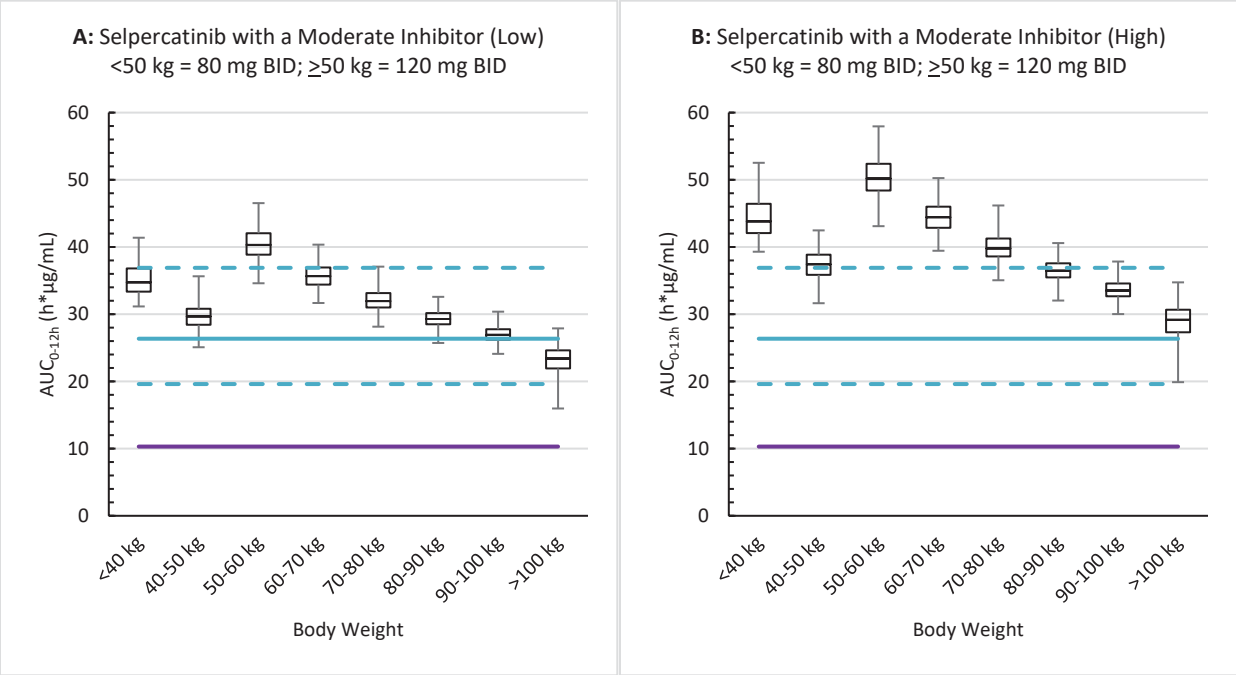
Notes: Blue lines represent the observed steady-state median (solid, 26.35 h*µg/mL) and 25th (dashed, 19.6 h*µg/mL) and 75th percentile (dashed, 36.9 h*µg/mL) $AUC_{0\text{-}12h}$ for patients treated with 160 mg BID. Purple line represents the observed steady-state median $AUC_{0\text{-}12h}$ for patients treated with 80 mg BID (10.3 µg/mL).
Source: FDA Analysis

Figure 6.10: Simulated Selpercatinib $AUC_{0\text{-}12h}$ After Administration of Selpercatinib with a Strong CYP3A Inhibitor



Notes: Blue lines represent the observed steady-state median (solid, 26.35 h*µg/mL) and 25th (dashed, 19.6 h*µg/mL) and 75th percentile (dashed, 36.9 h*µg/mL) $AUC_{0\text{-}12h}$ for patients treated with 160 mg BID. Purple line represents the observed steady-state median $AUC_{0\text{-}12h}$ for patients treated with 80 mg BID (10.3 µg/mL).
Source: FDA Analysis

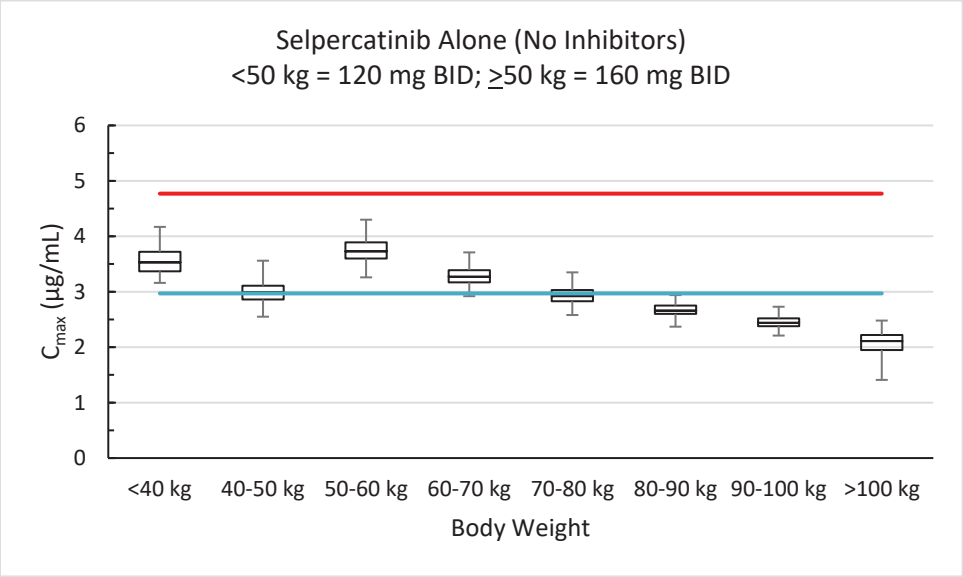
Figure 6.11: Simulated Selpercatinib AUC$_{0\text{-}12h}$ After Administration of Selpercatinib with a Moderate CYP3A Inhibitor



Notes: Blue lines represent the observed steady-state median (solid, 26.35 h*µg/mL) and 25th (dashed, 19.6 h*µg/mL) and 75th percentile (dashed, 36.9 h*µg/mL) $AUC_{0\text{-}12h}$ for patients treated with 160 mg BID. Purple line represents the observed steady-state median $AUC_{0\text{-}12h}$ for patients treated with 80 mg BID (10.3 µg/mL).
Source: FDA Analysis

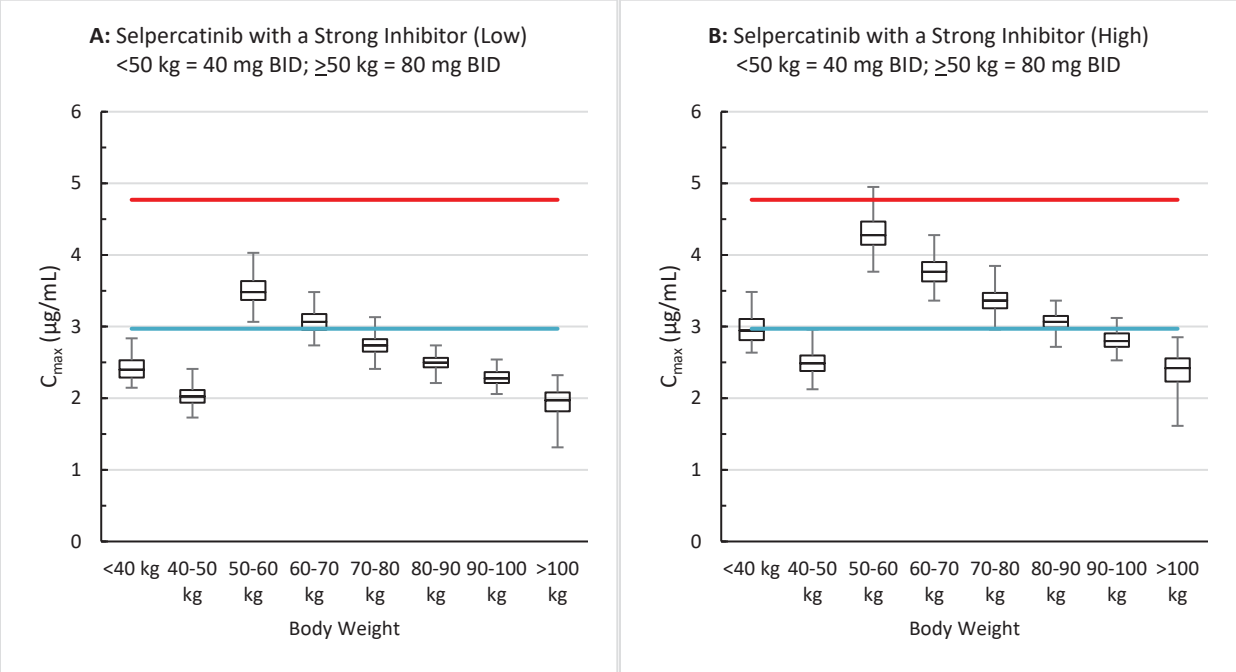
Figure 6.12 shows the simulated selpercatinib C_{max} by body weight after administration of the recommended dosage of selpercatinib alone. Figures 6.13 and 6.14 show the simulated selpercatinib C_{max} by body weight after administration of the recommended dosage of selpercatinib per **Table 6.5** with concomitant strong (**Figure 6.13**) or moderate (**Figure 6.14**) CYP3A inhibitors. Given the variability in predictions for fold-change in exposure, figures 6.13 and 6.14 include panels for both the low (panel A) and high (panel B) ends of the predicted fold-change in exposure based on results of the updated PBPK models. Strong inhibitors were predicted to increase the C_{max} of selpercatinib by 97 – 169%, depending on the inhibiting drug and dose of selpercatinib. Moderate inhibitors were predicted to increase the C_{max} of selpercatinib by 46 – 92%, depending on the inhibiting drug and dose of selpercatinib.

Figure 6.12: Simulated Selpercatinib C_{max} After Administration of Selpercatinib Alone



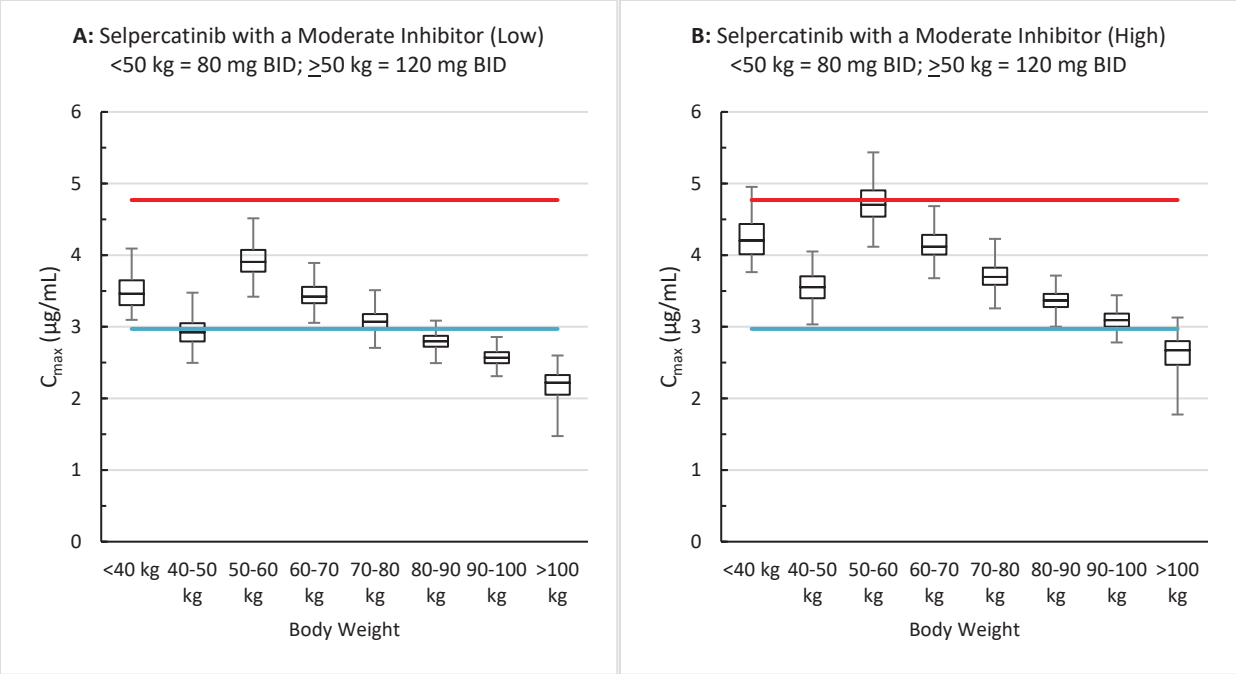
Notes: Blue line represents the observed steady-state median C_{max} for patients treated with 160 mg BID (2.97 µg/mL). Red line represents the 20 ms threshold value for QT prolongation (4.77 µg/mL).
Source: FDA Analysis

Figure 6.13: Simulated Selpercatinib C_{max} After Administration of Selpercatinib with a Strong CYP3A Inhibitor



Notes: Blue line represents the observed steady-state median C_{max} for patients treated with 160 mg BID (2.97 µg/mL). Red line represents the 20 ms threshold value for QT prolongation (4.77 µg/mL).
Source: FDA Analysis

Figure 6.14: Simulated Selpercatinib C_{max} After Administration of Selpercatinib with a Moderate CYP3A Inhibitor



Notes: Blue line represents the observed steady-state median C_{max} for patients treated with 160 mg BID (2.97 µg/mL). Red line represents the 20 ms threshold value for QT prolongation (4.77 µg/mL).
Source: FDA Analysis

CYP3A Inducers FDA agrees with the Applicant's assessment of the effect of multiple doses of rifampin on the PK of selpercatinib in healthy volunteers and the recommendation to avoid strong CYP3A inducers.

The Applicant's initial PBPK models were updated during the review cycle and an additional model to assess the effects of efavirenz (moderate CYP3A inducer) on selpercatinib was evaluated. Based on models of bosentan and efavirenz, moderate CYP3A inducers were predicted to decrease selpercatinib AUC by 40-70% and C_{max} by 34-57%. FDA therefore recommends that concomitant use of moderate CYP3A inducers should be avoided due to the potential for decreased efficacy with reduced exposure of up to 70%. Refer to the PBPK Modeling Analysis Appendix (**Section 19.4.5**) for additional detail.

Transporters: FDA agrees with the Applicant's assessment of the effect of a single dose of rifampin (P-gp inhibitor) on the PK of selpercatinib.

Effects of Selpercatinib on Other Drugs:

CYP2C8 and CYP3A Substrates: FDA agrees with the Applicant's assessment of the effect of selpercatinib on substrates of CYP2C8 and CYP3A. Selpercatinib is a moderate CYP2C8 inhibitor and a weak CYP3A inhibitor *in vivo*.

P-gp and BCRP Substrates: Selpercatinib inhibits P-gp and BCRP *in vitro*. The maximum

recommended dose (160 mg) dissolved in a 250 mL gastric volume would result in a selpercatinib gut concentration of 1,218 µM. However, selpercatinib exhibits pH-dependent solubility. Therefore, the solubility of selpercatinib in simulated fasted and fed gastrointestinal fluid was compared to the reported *in vitro* IC50s for selpercatinib inhibition of P-gp and BCRP (**Table 6.6**). In the fed condition, the gut concentration of selpercatinib may be high enough to cause clinically relevant inhibition of these transporters in the gastrointestinal tract (ratio of I_{gut}/IC50 >10). A clinical drug interaction study with a P-gp substrate will be conducted as a PMR to determine appropriate management strategies for potential drug interactions with P-gp substrates. Based on results of the P-gp study, further evaluation of the effect of selpercatinib on BCRP substrates may be warranted.

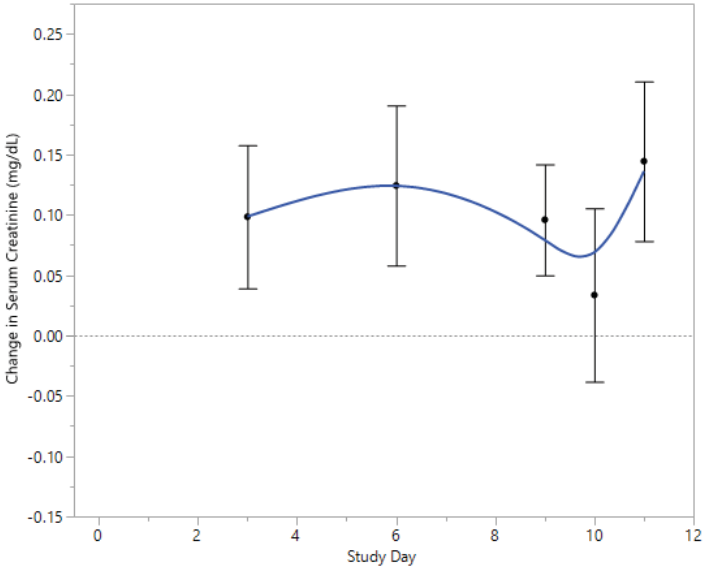
Table 6.6: Comparison of Selpercatinib IC50 *in vitro* vs Gastrointestinal Tract Concentrations

Transporter/Assay	IC50 (µM)	Selpercatinib solubility (µM)	Ratio
P-gp (quinidine)	5.4	Fasted = 13.9	2.6
	5.4	Fed = 604	111
P-gp (digoxin, MDCK)	10.7	Fasted = 13.9	1.3
	10.7	Fed = 604	56.4
P-gp (digoxin, vesicle)	45.0	Fasted = 13.9	0.3
	45.0	Fed = 604	13.4
BCRP (MDCK)	5.1	Fasted = 13.9	2.7
	5.1	Fed = 604	118
BCRP (vesicle)	22.3	Fasted = 13.9	0.6
	22.3	Fed = 604	27.1

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 10; Summary of Clinical Pharmacology Studies, Table 16

MATE1 Substrates: Selpercatinib inhibits MATE1 *in vitro* (IC50 = 0.666 µM, 350 ng/mL). In healthy volunteers enrolled in Studies LOXO-RET-18017 and -18026 (n=16 each), administration of multiple doses of selpercatinib resulted in increased serum creatinine. At steady-state (selpercatinib 160 mg BID x 10 days), the mean ± SD change in serum creatinine was 0.14 ± 0.07 mg/dL (18.0% increase over baseline, **Figure 6.15**). Similarly, in patients treated with selpercatinib in Study LIBRETTO-001, after one week on any dose of selpercatinib (20 mg QD to 240 mg BID), the mean ± SD change in serum creatinine was 0.15 ± 0.17 mg/dL (18.2% increase over baseline).

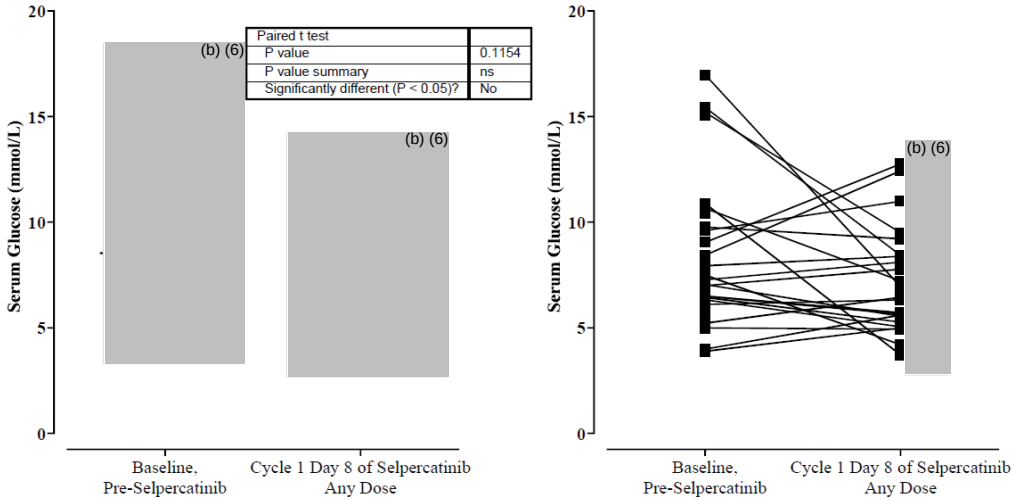
Figure 6.15: Mean Change in Serum Creatinine Over Time in Healthy Volunteers After Administration of Selpercatinib 160 mg BID



Source: FDA Analysis

To evaluate the potential for clinically significant drug interactions via MATE1 inhibition, blood glucose concentrations in patients receiving concomitant metformin (MATE1 substrate) were evaluated. There was no significant change in blood glucose relative to baseline in patients receiving concomitant metformin (**Figure 6.16**) and none of these patients experienced an adverse event of hypoglycemia.

Figure 6.16: Blood Glucose Before and After Initiation of Selpercatinib in Patients Receiving Concomitant Metformin in Study LIBRETTO-001



Source: Applicant's Response to IR dated 3 Mar 2020, Figure 1

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Primary Reviewer Team Leader

7 Sources of Clinical Data

7.1 Table of Clinical Studies

Data and the Applicant's Position:
The safety and efficacy for this NDA submission is primarily supported by LOXO-RET-17001 (LIBRETTO-001), an ongoing open-label, multicenter, first-in-human global phase ½ study of selpercatinib in patients with advanced solid tumors, including *RET* fusion-positive solid tumors, *RET*-mutant MTC, and other tumors with *RET* alterations. As of the data cutoff date, 17 June 2019, 531 patients had been treated with selpercatinib on LOXO-RET-17001. [Module 2.5.1.2 (MTC); Module 2.5.1.2 (NSCLC)]

Additional patients were treated through single-patient protocols if they were unable to travel to a study site or did not meet eligibility criteria for LOXO-RET-17001. Recently, a formal expanded access program clinical study was initiated for these patients. [Module 2.5.1.2 (MTC); Module 2.5.1.2 (NSCLC)]

In addition, a comprehensive clinical pharmacology program, inclusive of eight completed clinical pharmacology studies, was conducted in healthy subjects. Two additional clinical pharmacology studies in subjects with renal and hepatic impairment are currently ongoing. [Module 2.5.1.2 (MTC); Module 2.5.1.2 (NSCLC)]

Table 7.1 Listing of Clinical Trials Relevant to this NDA

Type of Study	Study ID	Location of Study Report	Objectives	Study Design	Dosing Regimen	Enrollment	Study Population	Duration of Treatment	Study Status; Type of Report
BA	LOXO-RET-18015	5.3.1.1	Assessments of the food effect on the PK of LOXO-292 after a high-fat meal and of the effect of a gastric pH change on the PK of LOXO-292 after multiple-doses of a PPI (omeprazole) under fasted and fed conditions in healthy adult subjects.	Single-center, open-label, randomized, 4-treatment, crossover study	160 mg, SD	20	Healthy male and female volunteers	SD	Completed; Final report
BA	LOXO-RET-18016	5.3.1.1	Absorption, metabolism, and excretion (AME) and absolute BA	Open-label, 2-part study of [^{14}C]-LOXO-292	Part 1: 160 mg [^{14}C]-LOXO-292 Part 2: 160 mg LOXO-292, oral SD followed by ~9.92 µg of [^{14}C]-LOXO-292, SD IV	12 (6 in Part 1 and 6 in Part 2)	Healthy male volunteers	SD	Completed; Final report

Table 7.1: Listing of Clinical Studies (Contd)

Type of Study	Study ID	Location of Study Report	Objectives	Study Design	Dosing Regimen	Enrollment	Study Population	Duration of Treatment	Study Status; Type of Report
PK	LOXO-RET-18057	5.3.3.1	Assessment of the safety, tolerability, and PK of single oral doses of LOXO-292 at higher dose levels than previously administered to ascertain therapeutic and supratherapeutic exposures of LOXO-292 for the thorough QT study	Single Ascending Dose study	Cohort 1: 320 mg, SD cohort 2: 640 mg, SD cohort 3: 720 mg, SD	18	Healthy male and female volunteers	SD	Completed; Final report
PK	LOXO-RET-18014	5.3.3.4	Drug-Drug interaction study of selpercatinib with itraconazole (Part 1) and rifampin (Part 2), respectively.	This was a 2-part study. Each part was conducted as an open-label, 2-period, fixed-sequence study.	160 mg, SD	24 (12 in Part 1 and 12 in Part 2)	Healthy male and female volunteers	SD	Completed; Final report
PK	LOXO-RET-18017	5.3.3.4	Drug-Drug interaction study of selpercatinib and midazolam	Open-label, 2-period, fixed-sequence study	160 mg BID for 10 days	16	Healthy male and female volunteers	10 days	Completed; Final report
PK	LOXO-RET-18026	5.3.3.4	Drug-Drug interaction study of selpercatinib and repaglinide	Open-label, 2-period, fixed-sequence study	160 mg BID for 10 days	16	Healthy male and female volunteers	10 days	Completed; Final report

Table 7.1: Listing of Clinical Studies (Contd)

Type of Study	Study ID	Location of Study Report	Objectives	Study Design	Dosing Regimen	Enrollment	Study Population	Duration of Treatment	Study Status; Type of Report
PK	LOXO-RET-19075	5.3.3.4	Drug-Drug interaction study of selpercatinib with ranitidine (Period 2) and omeprazole (Period 3)	Open-label, 3-period, fixed-sequence study	160 mg, SD in each period	20	Healthy male and female volunteers	SD	Completed; Final report
PK modeling	LOXO-292-DMPK-031	5.3.3.5	Population PK analysis and Exposure Response analysis using PK data collected in patients	Population PK modeling study.	Not applicable	Not applicable	PK data from patients	Not applicable	Completed; Final report
PK modeling	LOXO-292-DMPK-050	5.3.3.5	Population PK analysis and Exposure Response analysis using PK data collected in patients	Population PK modeling study.	Not applicable	Not applicable	PK data from patients	Not applicable	Completed; Final report
PK modeling	LOXO-292-DMPK-053	5.3.3.5	To describe a PBPK model based on in vitro, physicochemical and clinical data to predict quantitatively the effect of the presence of varying fractions of (b) (4) on the absorption and pharmacokinetic parameters of selpercatinib.	PK modeling study	Not applicable	Not applicable	PK data from healthy volunteers	Not applicable	Completed; Final report

Table 7.1: Listing of Clinical Studies (Contd)

Type of Study	Study ID	Location of Study Report	Objectives	Study Design	Dosing Regimen	Enrollment	Study Population	Duration of Treatment	Study Status; Type of Report
PK/PD	LOXO-RET-18022	5.3.4.1	Study of selpercatinib in Subjects with Mild, Moderate and Severe Hepatic Impairment	Open-label, nonrandomized, multi-center, single-dose, parallel-group study in hepatically impaired subjects and healthy-matched control subjects	160 mg, SD	38	Otherwise healthy volunteers	SD	Study conduct completed; CSR pending
PK/PD	LOXO-RET-18023	5.3.4.1	Study of selpercatinib in Subjects with Mild, Moderate and Severe Renal Impairment	Open-label, nonrandomized, multi-center, single-dose, parallel-cohort study in renally impaired subjects and healthy-matched control subjects	160 mg, SD	35**	Otherwise healthy volunteers	SD	Study conduct ongoing; CSR pending

Table 7.1: Listing of Clinical Studies (Contd)

Type of Study	Study ID	Location of Study Report	Objectives	Study Design	Dosing Regimen	Enrollment	Study Population	Duration of Treatment	Study Status; Type of Report
PK/PD	LOXO-RET-18032	5.3.4.1	Effect of selpercatinib on cardiac repolarization	Single-dose, randomized, double-blind (except for the use of moxifloxacin), placebo- and positive-controlled, 4-way crossover study.	0, 320 mg, 640 mg, SD 400 mg moxifloxacin (positive control)	32	Healthy male and female volunteers	SD	Completed; Final report
Efficacy	LOXO-RET-17001	5.3.5.2	DLT; MTD; efficacy, safety, and PK	Open-label, non-randomized PK	Escalation: Dose levels: 20 mg QD; 20 mg, 40 mg, 60 mg, 80 mg, 120 mg, 160 mg, 200 mg, 240 mg, BID Expansion: 160 mg, BID	531*	Escalation Phase: Patients (at least 12 years of age) with solid tumors Expansion Phase: Patients (at least 12 years of age) with solid tumors and RET alteration	Continuous 28-day cycles	Study ongoing; Interim report

Table 7.1: Listing of Clinical Studies (Contd)

Type of Study	Study ID	Location of Study Report	Objectives	Study Design	Dosing Regimen	Enrollment	Study Population	Duration of Treatment	Study Status; Type of Report
SPP	LOXO-RET-17003	5.3.5.2	N/A Compassionate Use	Open label	100 mg BID	1	Adult with Treatment-Refractory, Metastatic Ret-Rearranged NSCLC	158 days	Completed; Final report
SPP	LOXO-RET-18005	5.3.5.2	N/A Compassionate Use	Open label	80 mg BID (Starting Dose) 240 mg BID (Dose escalation)	1	Adult with Metastatic, RET-Fusion Positive NSCLC	203 days	Completed; Final report
SPP	LOXO-RET-18006	5.3.5.2	N/A Compassionate Use	Open label	80 mg BID (Starting Dose) 160 mg BID (Dose escalation)	1	Adult with Treatment-Refractory, Metastatic RET-Rearranged NSCLC	104 days	Completed; Final report

Table 7.1: Listing of Clinical Studies (Contd)

Type of Study	Study ID	Location of Study Report	Objectives	Study Design	Dosing Regimen	Enrollment	Study Population	Duration of Treatment	Study Status; Type of Report
SPP	LOXO-RET-18007	5.3.5.2	N/A Compassionate Use	Open label	160 mg BID	1	Adult with RET Rearranged NSCLC	56 days	Completed; Final report
SPP	LOXO-RET-18009	5.3.5.2	N/A Compassionate Use	Open label	80 mg BID (Starting Dose) 160 mg BID (Dose Escalation)	1	Adult with Treatment-Refractory, Metastatic RET-Rearranged NSCLC	152 days	Completed; Final report
SPP	LOXO-RET-18011	5.3.5.2	N/A Compassionate Use	Open label	80 mg BID	1	Adult with Treatment-Refractory, Metastatic RET-Rearranged NSCLC	60 days	Completed; Final report
SPP	LOXO-RET-18012	5.3.5.2	N/A Compassionate Use	Open label	80 mg BID	1	Adult with Treatment-Refractory, Metastatic RET-Rearranged NSCLC	19 days	Completed; Final report

Table 7.1: Listing of Clinical Studies (Contd)

Type of Study	Study ID	Location of Study Report	Objectives	Study Design	Dosing Regimen	Enrollment	Study Population	Duration of Treatment	Study Status; Type of Report
SPP	LOXO-RET-18021	5.3.5.2	N/A Compassionate Use	Open label	160 mg BID	1	Adult with Treatment-Refractory, Metastatic RET-Rearranged NSCLC	280 days	Completed; Final report
SPP	LOXO-RET-18025	5.3.5.2	N/A Compassionate Use	Open label	160 mg BID	1	Adult with RET-fusion positive thyroid cancer	64 days	Completed; Final report
SPP	LOXO-RET-18027	5.3.5.2	N/A Compassionate Use	Open label	160 mg BID	1	Pediatric patient with metastatic MTC	14 days	Completed; Final report
SPP	LOXO-RET-18041	5.3.5.2	N/A Compassionate Use	Open label	40 mg BID	1	Adult with RET-mutant MTC with Impaired Liver Function	13 days	Completed; Final report
SPP	LOXO-RET-18042	5.3.5.2	N/A Compassionate Use	Open label	160 mg BID	1	Adult with RET-Rearranged NSCLC with Central Nervous System Progression	151 days	Completed; Final report

Table 7.1: Listing of Clinical Studies (Contd)

Type of Study	Study ID	Location of Study Report	Objectives	Study Design	Dosing Regimen	Enrollment	Study Population	Duration of Treatment	Study Status; Type of Report
SPP	LOXO-RET-18045	5.3.5.2	N/A Compassionate Use	Open label	160 mg BID	1	Adult with RET-Rearranged Advanced PTC before Surgery	175 days	Completed; Final report
SPP	LOXO-RET-18050	5.3.5.2	N/A Compassionate Use	Open label	160 mg BID	1	Adult with RET-Fusion Positive Progressive NSCLC	59 days	Completed; Final report
SPP	LOXO-RET-18052	5.3.5.2	N/A Compassionate Use	Open label	40 mg BID (Starting Dose) 20 mg BID (Dose Decrease)	1	Adult with Metastatic, Progressive RET-Mutant MTC	94 days	Completed; Final report
SPP	LOXO-RET-19062	5.3.5.2	N/A Compassionate Use	Open label	80 mg BID	1	Adult with RET-fusion positive Metastatic Adenocarcinoma	0	Completed; Final report
SPP	LOXO-RET-19064	5.3.5.2	N/A Compassionate Use	Open label	160 mg BID	1	Adult RET-Fusion Positive Progressive NSCLC	17 days	Completed; Final report
SPP	LOXO-RET-19066	5.3.5.2	N/A Compassionate Use	Open label	240 mg BID (Starting Dose) 320 mg BID (Dose Escalation)	1	Adult with Metastatic RET-mutant MTC	81 days	Completed; Final report

Table 7.1: Listing of Clinical Studies (Contd)

Type of Study	Study ID	Location of Study Report	Objectives	Study Design	Dosing Regimen	Enrollment	Study Population	Duration of Treatment	Study Status; Type of Report
SPP	LOXO-RET-18018	5.3.5.2	N/A Compassionate Use	Open label	80 mg BID	1	Pediatric patient with RET-Rearranged metastatic refractory PTC	Continuous 28-day cycles	Study ongoing; Interim report
SPP	LOXO-RET-18019	5.3.5.2	N/A Compassionate Use	Open label	90 mg/m2 BID	1	Pediatric patients with Locally-Advanced RET-Fusion Positive Infantile Myofibroma	Continuous 28-day cycles	Study ongoing; Interim report
SPP	LOXO-RET-18058	5.3.5.2	N/A Compassionate Use	Open label	90 mg/m2 BID (Starting Dose) 180 mg/m2 BID (Dose escalation)	1	Pediatric patient with Metastatic RET-Fusion Positive Infantile Fibrosarcoma	Continuous 28-day cycles	Study ongoing; Interim report
SPP	LOXO-RET-19060	5.3.5.2	N/A Compassionate Use	Open label	90 mg/m2 BID	1	Pediatric patient with Locally-Advanced RET-Fusion Positive Lipofibromatosis	Continuous 28-day cycles	Study ongoing; Interim report

Table 7.1: Listing of Clinical Studies (Contd)

Type of Study	Study ID	Location of Study Report	Objectives	Study Design	Dosing Regimen	Enrollment	Study Population	Duration of Treatment	Study Status; Type of Report
SPP	LOXO-RET-19067	5.3.5.2	N/A Compassionate Use	Open label	90 mg/m^2 BID	1	Pediatric patient with Metastatic, RET-Mutant Medullary Thyroid Cancer Intolerant to Prior Inhibitors of RET	Continuous 28-day cycles	Study ongoing; Interim report

BA: bioavailability; CNS: central nervous system; DLT: dose-limiting toxicities; LOXO-292: selpercatinib; MTC: medullary thyroid cancer; MTD: maximum tolerated dose; N/A: Not Applicable; NSCLC: Non-small cell lung cancer; PBPK: physiologically based pharmacokinetic; PK: pharmacokinetics; PTC: papillary thyroid cancer; SD: single dose; SPP: Single Patient Protocol

*Enrollment as of 17-Jun-2019

** Enrollment as of 29-Oct-2019

[Module 5.2]

The FDA's Assessment:

FDA agrees with the table presented above and notes that the primary clinical study supporting the evaluation of efficacy and safety in this application is Study LOXO-RET-17001. Additional data derived from expanded access studies is not included in pooled analyses of efficacy or safety and was considered supportive.

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 LOXO-RET-17001 (LIBRETTO-001):

Trial Design

The Applicant's Description:

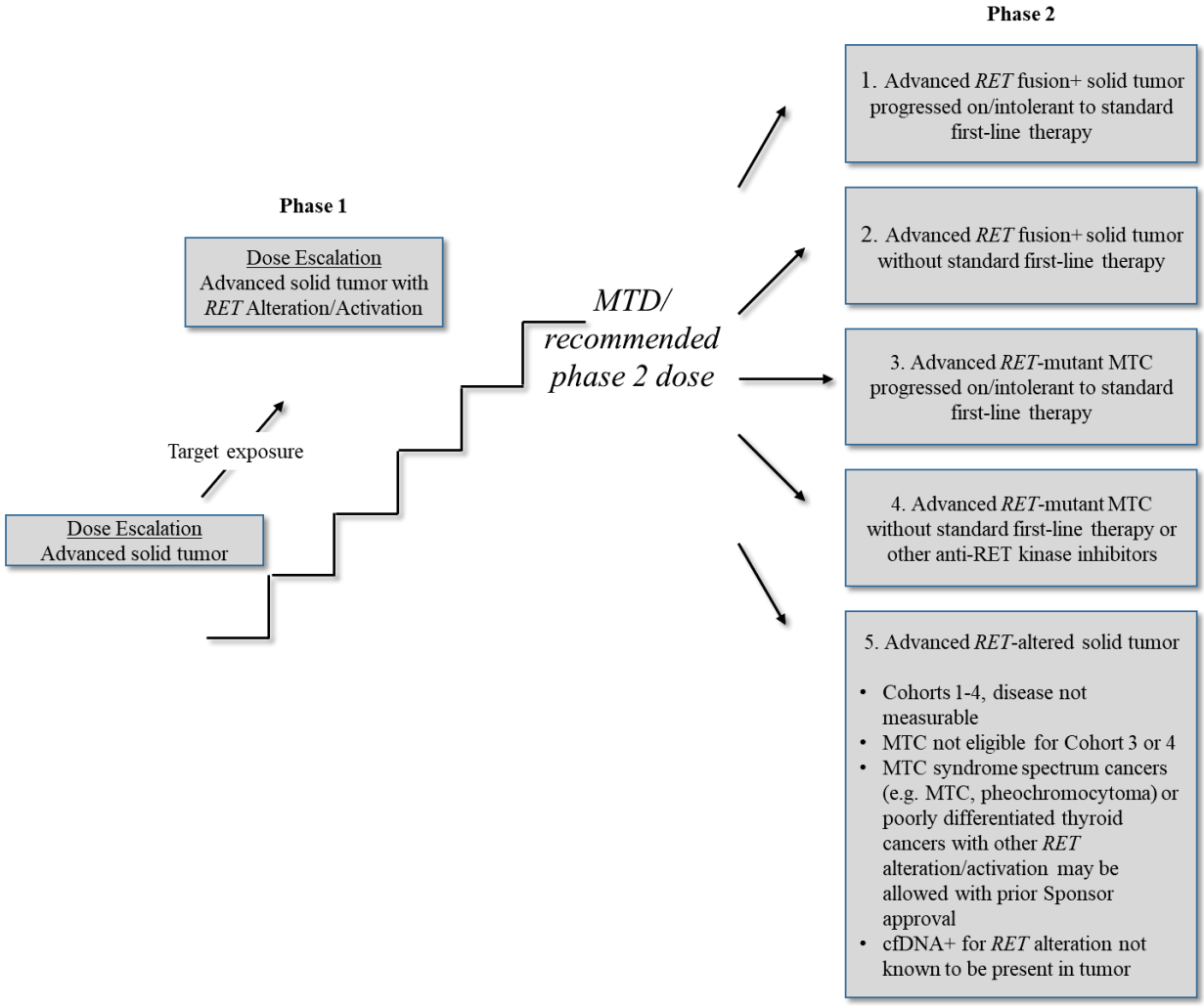
Design and Methodology [CSR Synopsis LOXO-RET-17001; CSR LOXO-RET-17001 Section 9.1]

LOXO-RET-17001 was a global, multicenter, open-label, Phase ½ study in patients with advanced solid tumors, including *RET* fusion-positive solid tumors, *RET*-mutant MTC, and other tumors with RET activation (e.g., mutations in other tumor types or other evidence of RET activation). This study is ongoing and includes two parts: Phase 1 (dose escalation) employed a "3+3" dose-escalation design and Phase 2 (dose expansion) included 5 expansion cohorts (Figure 8.1).

Selpercatinib was administered orally once daily (QD) or BID. Cycles were 28 days. Dose escalation was to proceed through the planned dose escalation cohort levels (20 mg QD, 20 mg BID, 40 mg BID, 60 mg BID, 80 mg BID, 120 mg BID, 160 mg BID, 200 mg BID, or 240 mg BID or until the maximum tolerated dose (MTD) was reached. A RP2D of 160 mg BID was selected by the Safety Review Committee (SRC) during Phase 1 of the study.

Individual patients continued selpercatinib dosing in 28-day cycles until disease progression, unacceptable toxicity, or other reasons for treatment discontinuation as outlined in Protocol Section 6.4 . Four weeks (28 days +7 days) after the last dose of study drug, all treated patients underwent a safety follow-up (SFU) assessment. All patients were also to undergo long-term follow-up (LTFU) assessments every 3 months. The Table of Assessments in provided in Table 8.1.

Figure 8.1 Study Schema



CSR LOXO-RET-17001, Figure 1

Table 8.1 LOXO-RET-17001 Assessment Schedule

	Screening	Cycle 1				Cycle 2-higher	Intra-patient Dose Escalation		EOT	SFU	LTFU
Visit Window	**Day -28 to Day -1**	**D1 ±2 Days**	**D8 ±2 Days**	**D15 ±2 Days**	**D22 [d] ±2 Days**	**±3 Days**	**D1 ±3 Days**	**D8 ±3 Days**			
Informed Consent	X										
Medical, surgical, malignancy history	X										
Molecular Pathology Report(s) describing *RET* and other alterations	X										
Archived tumor tissue or fresh biopsy	X								X		
Physical examination and ECOG or LPS	X	X	X	X		D1 C2, 3, 4, 5, etc.	X	X	X	X	
Vital signs		X [i]	X [i]	X		D1 C2, 3, 4, 5, etc. [i]		X	X	X	
12-lead ECG[j]	X	X	X			D1 C2–C6	X	X	X	X	
Urine or serum pregnancy test	X	X				D1 C2, 3, 4, 5, etc. X					
Hematology	X	X	X	X		D1 C2, 3, 4, 5, etc.	X	X	X	X	
Serum chemistries X	X	X	X	X		D1 C2, 3, 4, 5, etc.	X	X	X	X	
Liver function tests [o]						C2D15 and C3D15					
Thyroid panel [p]	X			X		D1 of odd cycles beginning with C3 (C3, 5, 7, etc.)					
Urinalysis [q]	X			X		D1 C2, 3, 4, 5, etc.			X	X	

	Screening	Cycle 1				Cycle 2-higher	Intra-patient Dose Escalation		EOT	SFU	LTFU
Visit Window	**Day -28 to Day -1**	**D1 ±2 Days**	**D8 ±2 Days**	**D15 ±2 Days**	**D22 [d] ±2 Days**	**±3 Days**	**D1 ±3 Days**	**D8 ±3 Days**			
Calcitonin, CEA (MTC only) [r]	X	X				D1 C2 and odd-numbered cycles, starting with C3 (±7 days of each radiologic disease assessment)			X		
Thyroglobulin (non-MTC thyroid cancers only) [s]	X	X	X			D1 C2 and odd-numbered cycles, starting with C3 (±7 days of each radiologic disease assessment)			X		
Serum cortisol, serum ACTH, 24-hour urine for free cortisol [t]	X	X	X			D1 C2 and odd-numbered cycles, starting with C3 (±7 days of each radiologic disease assessment)			X		
Whole blood for cfDNA analysis [u]			X			±7 days of each radiologic disease assessment			X		
Whole blood for genomic DNA	X X		X								
Disease assessment [v]	X					Every 8 weeks (±7 days) starting with D1 C3 through D1 C13. Every 12 weeks (±7 days) thereafter			X [w]		X [x]
Confirmatory disease assessment [y]						At least 4 weeks post 1st PR					
Blood sample for PK [z]			X					X			
EORTC QLQ-C30 or PedsQL [aa]						±7 days of each radiologic disease assessment			X		

X

	Screening	Cycle 1				Cycle 2-higher	Intra-patient Dose Escalation		EOT	SFU	LTFU
Visit Window	**Day -28 to Day -1**	**D1 ±2 Days**	**D8 ±2 Days**	**D15 ±2 Days**	**D22 [d] ±2 Days**	**±3 Days**	**D1 ±3 Days**	**D8 ±3 Days**			
Selpercatinib administration		→	→	→	→	→	→	→	→		
Patient dosing diary		→	→	→	→	→	→	→	→		
Patient bowel diary (MTC only) [bb]			X	X	X	D1 C2, 3, 4, 5, etc.			X		
Adverse events [cc]	→	→	→	→	→	→	→	→	→	→	
Concomitant medications [dd]	X →	→	→	→	→	→	→	→	→	→	
Survival [ee]											X

CSR LOXO-RET-17001, Table 7.

FDA Reviewer note: the list of abbreviations and footnotes below was provided by the Applicant and copied into this section by FDA after discussion with the Applicant.

Abbreviations (for Table 7 and Footnotes): ACTH = adrenocorticotropic hormone; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = cycle; C1D1 = Cycle 1 Day 1; CEA = carcinoembryonic antigen; cfDNA = circulating cell-free DNA; CR = complete response; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EOT = End of Treatment; IV = intravenous; LDH = lactate dehydrogenase; LPS = Lansky Performance Score; LTFU = Long-Term Follow-Up; MTC = medullary thyroid cancer; MRI = magnetic resonance imaging; PedsQL = Pediatric Quality of Life-Core Module; PK = pharmacokinetics; PR = partial response; QTcF = QT interval corrected for heart rate (Fridericia's formula); RBC = red blood cell; SAE = serious adverse event; SFU = Safety Follow-Up; TSH = thyroid-stimulating hormone; T3 = free triiodothyronine; T4 = free thyroxine; ULN = upper limit of normal; WBC = white blood cell; WOCBP = woman of child-bearing potential.

a. End of Treatment (EOT): +7 days of the last dose or the decision to terminate treatment.

b. Safety follow-up (SFU): 28 days (+7 days) after EOT.

c. Long-term follow-up (LTFU): approximately every 3 months (±1 month) for up to 2 years after the last dose of study drug.

d. Telephone contact for safety.

e. For all patients, anonymized/redacted report(s) to be submitted to Sponsor or designee during Screening /prior to enrollment.

f. Adequate availability of archived tumor tissue was to be confirmed, either tumor block (preferred) or ~25 × 5 um unstained slides. Patients who do not have sufficient archival tumor tissue available should undergo an optional fresh tumor biopsy, if it was considered safe to perform, prior to treatment. If sufficient archived tumor tissue was not available and a fresh biopsy cannot be safely performed, the patient may still be eligible with prior Sponsor approval. A tissue biopsy to show PD could be collected at the time of progression if it could be safely performed. If oligometastatic disease constituting progression was identified, but the patient was otherwise stable and will continue selpercatinib beyond progression, the patient may undergo an optional fresh tumor biopsy to evaluate tumor changes that may have resulted from treatment. For biopsies performed in the setting of PD, please contact the Sponsor to inform them of the planned biopsy, and whether or not therapy was continued beyond progression or discontinued (EOT).

g. Physical examination of and review of relevant systems at Screening, body weight, and height. Symptom-directed physical examinations, including measurement of weight could be performed at other time points.

h. Systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.

i. Vital signs were to be conducted as follows:

- C1D1, C1D8, Day 1 of intra-patient dose escalation and Day 8 of intra-patient dose escalation: pre-dose (up to 4 hours pre-dose, as close to dosing as possible was preferred) and post-dose at 2 hours (±15 minutes)
- Day 1 of C2-C6: post-dose at 2 hours (±15 minutes)
- All other clinic visits when neither PK or ECGs were being collected, vital signs were to be collected pre-dose (up to 4 hours pre-dose, as close to dosing as possible was preferred)

j. ECGs were to be performed during Screening (in triplicate) and during Cycle 1 at the following time points: pre-dose (triplicate, ±10 minutes, up to 4 hours pre-dose), C1D1 2 and 4 hours post-dose (triplicate, ±10 minutes), C1D8 2 and 4 hours post-dose (triplicate, ±10 minutes. In addition, triplicate ECGs were to be obtained 2 hours post-dose (±10 minutes) on C2D1, C3D1, C4D1, C5D1 and C6D1. Additional ECGs could be performed if clinically indicated. For intra-patient dose escalation, ECGs were to be performed pre-dose (triplicate, up to 4 hours pre-dose) on Day 1 of the patient's new dose, and 2 and 4 hours post-dose (triplicate, ±10 minutes) on Days 1 and 8 of the patient's new dose.

k. Repeat only if EOT reading showed treatment-emergent abnormalities.

l. For women of childbearing potential: Serum pregnancy test at Screening, serum or urine pregnancy test at Day 1 of every cycle(surgically sterilized females or those who have not had menses for at least 2 years were not required to be tested).

m. Hematology including hemoglobin, hematocrit, RBC count, WBC count with differential (neutrophils [count and percent] and lymphocytes, monocytes, eosinophils, basophils [percent]), and platelet count). For intra-patient dose escalation, if Day 1 of the new dose falls on the same day (±3 days) of a

previous hematology assessment (e.g., Day 1 of C2 and beyond), it was not necessary to repeat. Patients found to have treatment-emergent hematologic toxicity of Grades 3 or 4 were to be monitored at least weekly until resolution.

n. Serum chemistries (non-fasting), including alkaline phosphatase, albumin, ALT, AST, BUN (urea where BUN not tested), total cholesterol, creatinine, glucose, LDH, total and direct bilirubin, total protein, sodium, potassium, calcium, chloride, bicarbonate, magnesium, and phosphorus. For intra-patient dose escalation, if Day 1 of the new dose falls on the same day (±3 days) of a previous serum chemistry assessment (e.g., Day 1 of C2 and beyond), it was not necessary to repeat. Patients found to have treatment-emergent laboratory toxicity of Grades 3 or 4 were to be monitored at least weekly until resolution.

o. Collect AST, ALT, alkaline phosphatase and total and direct bilirubin on C2D15 and C3D15.

p. Thyroid-stimulating hormone (TSH), free triiodothyronine (T3), and free thyroxine (T4).

q. Complete urinalysis, including color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, protein, leukocytes, nitrites, and urobilinogen.

r. Calcitonin and CEA only for patients with a diagnosis of MTC. These were to be performed in the same laboratory to minimize intra-patient, lab-to-lab variability in their measurement.

s. Thyroglobulin only for patients with non-MTC thyroid cancers (unless not measurable due to the presence of anti-thyroglobulin antibodies). These were to be performed in the same laboratory to minimize intra-patient, lab-to-lab variability in their measurement.

t. Optional for MTC or other cancer patients with Cushing's disease related to their cancer. If performed, urine collection were to begin pre-dose.

u. Whole blood for cfDNA analysis was to be obtained at C1D1 (pre-dose), C1D15, and ±7 days following each radiologic disease assessment. Whole blood for cfDNA analysis was to be obtained at the EOT visit, even if radiologic disease assessment was not performed. If oligometastatic disease constituting progression was identified, but the patient was otherwise stable and will continue selpercatinib beyond progression, patients should have blood collected for cfDNA analysis. For whole blood collection performed in the setting of PD, please contact the Sponsor to inform them of the sample collection and whether or not therapy was continued beyond progression or discontinued (EOT).

v. Baseline disease assessment with radiographic tumor measurements using CT or MRI of chest, abdomen, and pelvis or any other areas with suspected disease involvement within 28 days of C1D1. During Phase 2, brain imaging was required at baseline for all RET fusion-positive patients, patients with a history of CNS metastases, or other patients if clinically indicated and subsequent serial scans if brain metastases were present at baseline (MRI preferred, CT with contrast was acceptable if MRI contraindicated). For each modality, IV and oral contrast were to be utilized (chest CT does not require IV contrast) unless there was a clear contraindication (e.g., decreased renal function or allergy that cannot be addressed with standard prophylactic treatments). In the absence of known or suspected disease involvement, head and neck CT/MRI scans were not required for malignancies other than those originating in the head and neck region. Other areas of scanning may also differ depending on disease type. Post-baseline scans were to be performed every 8 weeks (±7 days) for one year and every 12 weeks (±7 days) thereafter, including imaging of the chest, abdomen, and pelvis, using the same modality(ies) as used for baseline imaging assessment until PD, withdrawal of consent, or initiation of a new anticancer therapy(ies). Additionally, any studies performed at baseline that were positive for sites of disease were to be repeated at all post-baseline assessments. Additional studies could also be performed as clinically indicated. In addition, Investigators may conduct an initial tumor evaluation on C2D1 (±7 days) and a confirmatory tumor evaluation a minimum of 4

weeks (i.e., 28 days) after the first tumor evaluation that shows a CR or PR by RECIST 1.1 (or RANO, as appropriate to tumor type), if consistent with local regulatory authority requirements. In addition, an initial post baseline assessment on C2D1 (±7 days) was encouraged if consistent with regulatory guidelines. If a scan was performed on C2D1, the next scan should continue according to the schedule above (beginning at C3D1). All scans were to be collected and stored at a central facility to permit central reviewer assessment if desired. Please refer to the Site Imaging Manual for guidelines on how the various imaging studies were to be performed.

w. If not performed within the last 8 weeks.

x. Patients who discontinue study drug for reasons other than PD (e.g., AE, noncompliance, etc.) may (but for practical reasons and to minimize patient inconvenience, were not required to) undergo additional disease assessment by imaging (as specified above until PD, withdrawal of consent or initiation of a new anticancer therapy[ies]).

y. Confirmatory scans: Minimum of 4 weeks (e.g., 28 days) after the first tumor evaluation showing a CR or PR by RECIST 1.1 or RANO, as appropriate to tumor type, if permitted by regulatory authorities. The next scan should continue according to the schedule above.

z. Up to 1-hour pre-dose, and post-dose 1, 2, and 4 hours (±15 minutes) and 8 hours (±30 minutes). For intra-patient dose escalation, PK samples were to be collected pre-dose (up to 1 hour prior to dosing) and post-dose at 1, 2, and 4 hours (±15 minutes) and 8 hours (±30 minutes) on Day 8 (±3 days) of the patient's new dose. (Note: PK sampling days/times were modified with Protocol v5.0; prior to Protocol v5.0, sampling times were C1D1, C1D8, C3D1, and C5D1 at up to 1 hour pre-dose, and post-dose at 15 and 30 minutes, and 1, 2, 4, 6, and 8 hours; for intra-patient dose escalation, PK samples were collected pre-dose, and post-dose at 1, 2, 4, 6, and 8 hours on Day 8 of the patient's new dose).

aa. EORTC QLQ-C30 (patients 18 years and older) and PedsQL (patients age 12-17 years). The questionnaires were to be answered by the subject to the best of his/her ability, prior to receiving drug on C1D1 and preferably prior to learning the results of the radiologic disease assessment for subsequent cycles.

bb. Only for patients with a diagnosis of MTC and diarrhea at baseline.

cc. AEs and SAEs were to be recorded from the time that written informed consent has been obtained through the SFU Visit.

dd. Concomitant, ongoing medication(s) plus those administered within 14 days prior to the planned start of treatment.

ee. Patients were followed for survival status, date of progression, and subsequent anticancer therapy(ies) by telephone or other method.

Table 8.2 Selpercatinib Dose Levels

Dose Level	Dose Level	Frequency	Total Daily Dose
1	20 mg	QD	20 mg
2	20 mg	BID	40 mg
3	40 mg		80 mg
4	60 mg		120 mg
5	80 mg		160 mg
6	120 mg		240 mg
7	160 mg		320 mg
8	240 mg		480 mg
9	200 mg		400 mg

Abbreviations: BID = twice daily; QD = once daily; SRC = Safety Review committee; TBD = to be determined.
CSR LOXO-RET-17001, Table 2

Diagnosis and Main Criteria for Inclusion [CSR Synopsis LOXO-RET-17001]

- Patients with a locally advanced or metastatic solid tumor who progressed on or were intolerant to standard therapy, or no standard therapy exists, or in the opinion of the Investigator, were not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or declined standard therapy.
- For patients being enrolled into a specific Phase 2 dose expansion, evidence of a *RET* gene alteration in tumor (i.e., not just blood) was required (a positive germline test for a RET mutation was acceptable for patients with MTC). The *RET* alteration result was to be generated from a laboratory with Clinical Laboratory Improvement Amendments (CLIA), International Standard (ISO)/ Independent Ethics Committee (IEC), College of American Pathologists (CAP) or other similar certification.
- At least 18 years of age. For countries and sites where approved, patients as young as 12 years of age could be enrolled.
- Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 (age ≥ 16 years) or Lansky Performance Score (LPS) ≥ 40% (age < 16 years) with no sudden deterioration 2 weeks prior to the first dose of study treatment.

Dose Modification and Management Algorithms [CSR Synopsis LOXO-RET-17001; CSR LOXO-RET-17001-Appendix 16.1.1]

A RP2D of 160 mg BID was selected by the SRC during Phase 1 of the study and has been used for all patients in the Phase 2 dose expansion phase of the study (currently ongoing).

A patient who experiences a clinically significant AE (i.e., greater than Grade 2 or more than 1 grade change from baseline if baseline is Grade 2 or above) may have LOXO 292 dosing held for up to 28 days to evaluate the AE and to allow for recovery (to Grade 1 or baseline level).

Upon recovery, the patient may restart therapy if it is considered in his/her best interest to continue therapy. Upon restarting, the patient may have the dose reduced by at least one dose level (Table 8.3). If the AE does not recover to Grade 1 or less within 28 days (or baseline), the patient will have treatment permanently discontinued, unless there is a compelling clinical rationale for additional dose reduction(s) articulated by the Investigator and approved by the Sponsor. For each patient, a maximum of 2 dose reductions will be allowed, unless there is a compelling clinical rationale for additional dose reduction(s) articulated by the Investigator and approved by the Sponsor (Table 8.3).

Table 8.3 Suggested Toxicity Management During Phase 1 and Phase 2

Dose Level	Dose of LOXO-292
Starting Dose	Dose level patient enrolled to
First Dose Reduction	Reduce dose by at least one dose level
Second Dose Reduction	Reduce dose by at least one additional dose level
Third Dose Reduction and Beyond	Only permitted if there is a compelling clinical rationale articulated by the Investigator and approved by the Sponsor.

CSR LOXO-RET-17001, Appendix 16.1.1

Patients who have been dose reduced and who tolerate LOXO-292 without toxicity for at least one cycle may be re-escalated to their previous dose level with the agreement of the Investigator and the Sponsor.

Allowed Concomitant Medications [CSR LOXO-RET-17001 Section 9.4.6.1]

Allowed concomitant medications included standard supportive medications used in accordance with institutional guidelines and Investigator discretion. Examples include hematopoietic growth factors to treat neutropenia, anemia, or thrombocytopenia in accordance with American Society for Clinical Oncology guidelines (but not for prophylaxis in Cycle 1); red blood cell and platelet transfusions; anti-emetic, analgesic, and antidiarrheal medications; electrolyte repletion (e.g., calcium and magnesium) to correct low electrolyte levels; glucocorticoids (approximately 10 mg per day prednisone or equivalent, unless there was a compelling clinical rationale for a higher dose articulated by the Investigator and approved by the Sponsor), including short courses to treat asthma, chronic obstructive pulmonary disease, etc.; thyroid replacement therapy for hypothyroidism; and bisphosphonates, denosumab and other medications for the treatment of osteoporosis, prevention of skeletal-related events from bone metastases, and/or hypoparathyroidism.

Continuation of standard of care medications, including hormonal therapy for patients with prostate cancer (e.g., gonadotropin-releasing hormone [GnRH] or luteinizing hormone-releasing hormone [LHRH] agonists) and breast cancer (e.g., GnRH/LHRH agonists, aromatase inhibitors, selective estrogen receptor modulators or degraders), that the patient was on for the previous 28 days, were also allowed, provided they were not prohibited concomitant medications.

Prohibited Concomitant Medications [CSR LOXO-RET-17001 Section 9.4.6.2]

During this study, except as indicated in Section 9.4.6.1 of the protocol, patients were not allowed to receive concomitant systemic anti-cancer agents, hematopoietic growth factors for prophylaxis in Cycle 1, therapeutic monoclonal antibodies, drugs with immunosuppressant properties, or medications known to be strong inhibitors or inducers of CYP3A4 (outlined in Protocol Appendix D [Inhibitors and Inducers of CYP3A4]). Restrictions include herbal products, such as St John's wort, which could decrease the drug levels of selpercatinib. However, non-systemic (e.g., topical creams, eye drops, mouthwashes, etc.) applications were permissible. If moderate inhibitors or inducers of CYP3A4 were necessary, they were instructed to be taken with caution. If during the study, patients required initiation of treatment with strong inhibitors or inducers of CYP3A4 for clinical reasons, then the Sponsor was required to be consulted to determine whether selpercatinib was to be stopped, and therefore whether the patient was to be removed from the study.

Investigational agents (other than selpercatinib) were prohibited. No new, alternative systemic anticancer therapy was allowed prior to documentation of PD in accordance with protocol-specified disease response criteria.

The concomitant use of PPIs was prohibited, and patients were to discontinue PPIs 1 or more weeks prior to the first dose of selpercatinib (examples of PPIs were provided in Protocol Appendix E).

When concurrent use of an histamine type-2 (H2) blocking agent was necessary, e.g., ranitidine (Zantac®), famotidine (Pepcid®), or cimetidine (Tagamet®), it was required be administered only between 2 and 3 hours after the dose of selpercatinib. If not taken during this time, the dose of the H2 blocking agent was not allowed again until 2 to 3 hours after the next dose of selpercatinib.

Use of an antacid (e.g., aluminum hydroxide/magnesium hydroxide/simethicone [Maalox®] or calcium carbonate [TUMS®]), if necessary, was required to be administered 2 or more hours before and/or 2 or more hours after the dose of selpercatinib.

Any exceptions to the above were required to be approved by the Sponsor.

Treatment Compliance [CSR LOXO-RET-17001 Section 9.4.7]

Patients were required to keep a daily diary to record dosing compliance. Compliance was also assessed at each clinic visit by means of a capsule count in the returned bottle(s). Late doses (i.e., 4 or more hours after scheduled time) were to be noted in the diary. Doses that were late by more than 6 hours were to be skipped and recorded in the dosing diary as missed. Vomiting after dosing was also to be noted in the diary and a vomited dose was not to be re-dosed or replaced.

Patient Completion, Discontinuation, or Withdrawal [CSR LOXO-RET-17001 Section 9.1]

Individual patients continued selpercatinib dosing in 28-day cycles until disease progression (PD), unacceptable toxicity, or other reasons for treatment discontinuation as outlined in Protocol Section 6.4. Patients with documented PD who are tolerating treatment and, in the opinion of the Investigator, are deriving clinical benefit from continuing study treatment, may continue treatment with prior Sponsor approval. At the time a patient discontinues treatment, all safety data normally required at the EOT visit will be obtained if possible. Patients will enter LTFU where they may be required to undergo disease assessments (Table 8.1).

The FDA's Assessment:

FDA agrees with the description of Study LOXO-RET-17001 provided by the Applicant. It should be noted that the protocol permitted local treatment (palliative radiation therapy or surgery for bone metastases) with approval.

All patients underwent baseline disease assessments with CT or MRI of the chest, abdomen, and pelvis, and any other areas of suspected disease involvement. As of protocol amendment 5.0 (May 2018), all fusion-positive solid tumor patients, patients with a history of CNS metastases, or other patients if clinically indicted underwent brain imaging (MRI preferred). Prior to amendment 5.0, brain imaging was required only in patients in whom brain involvement was suspected.

Study Endpoints

The Applicant's Description:

Primary Endpoints

The primary endpoint for Phase 1 was MTD/RP2D and the primary endpoint for Phase 2 was ORR based on RECIST 1.1 or RANO, as appropriate to tumor type, assessed by independent review committee (IRC). [CSR LOXO-RET-17001, Section 8]

Secondary Endpoints

Frequency, severity, and relatedness of TEAEs and serious adverse events (SAEs), changes in laboratory parameters, plasma concentration of LOXO-292, PK parameters, ORR and other efficacy parameters, including best change in tumor size from baseline, duration of response (DOR), CNS ORR, CNS DOR, time to any and best response, and clinical benefit rate, PFS, OS. [CSR LOXO-RET-17001, Section 8]

Exploratory Endpoints

Biochemical response: changes in CEA and calcitonin for patients with MTC.

Patient Reported Outcomes (PRO) including changes from baseline in disease-related symptoms and HRQoL, as measured by EORTC QLQ-C30 (adults), PedsQL for teens (ages 13–17 years), PedsQL for children (age 12 years), and patient bowel diaries (MTC patients only). [CSR LOXO-RET-17001, Section 8]

> The FDA's Assessment:
> FDA agrees with the Applicant's description of the endpoints of Study LOXO-RET-17001. Note that the time-to-events endpoints such as PFS and OS are not interpretable in a single-arm study. Additionally, clinical benefit rate is unlikely to predict the clinical benefit and therefore it is not considered as an established endpoint for claiming efficacy.

Statistical Analysis Plan and Amendments

The Applicant's Description: [CSR LOXO-RET-17001 Appendices 16.1.1 and 16.1.9; CSR LOXO-RET-17001 Section 9.7.6]

The safety analysis was conducted on the safety analysis set which consisted of all patients who received at least one dose of selpercatinib. The primary analysis of efficacy was based on the safety analysis set unless otherwise specified.

The primary endpoint ORR was assessed using RECIST 1.1 or RANO (for patients with primary CNS tumors), as appropriate to tumor type. The estimate of the ORR was calculated based on the maximum likelihood estimator (i.e., crude proportion of patients with best overall response of CR or PR that are confirmed) and accompanied by 2- sided 95% exact binomial CI.

Secondary endpoints included DOR, PFS and OS. DOR was defined as the number of months from the start date of CR or PR (whichever response status is observed first) and subsequently confirmed, to the first date that PD is objectively documented. PFS was defined as the number of months from the date of the first dose of study drug to the earlier of documented PD or death due to any cause. Patients who were alive and without documented PD as of a data analysis cutoff date were right-censored according to the censoring methods described in the SAP. Whenever appropriate, the same censoring methods were used for DOR. OS was defined

as the number of months from the date of the first dose of study drug to the date of death, irrespective of cause.

DOR, PFS, and OS was summarized descriptively using the Kaplan-Meier method. The Kaplan-Meier estimate with 95% CI calculated using Brookmeyer and Crowley method was provided for the median. The event-free rate with the 95% CI calculated using Greenwood's formula was provided for selected time points.

In order to facilitate regulatory review of the LOXO-RET-17001 data in support of the proposed indications, data sets were created that are distinctive from those discussed in the clinical study report. The goal of the arrangement of these various data sets was to:

- maximize information through the consolidation of data from both Phase 1 and Phase 2 parts of LOXO-RET-17001.
- define groupings based on clinically meaningful distinctions, resulting in similarity of patients within a group, thus, facilitating the interpretation of results.

The inclusion criteria and statistical considerations for the primary data sets supporting the proposed indications were agreed to with the Food and Drug Administration (FDA) (MTC: 19 December 2018; NSCLC: 16 January 2019) and described in MTC-SAP [Module 5.3.5.3] and NSCLC-SAP [Module 5.3.5.3].

The FDA's Assessment:
FDA agrees with the description of the SAP. The SAP defines analysis sets which are described in detail in Table 8.5 and Table 8.6. Refer to FDA comments above on PFS, OS and clinical benefit rate.

Protocol Amendments

The Applicant's Description:

LOXO-RET-17001 protocol amendments are presented in Table 8.4.

Table 8.4 Changes to the Protocol

Version Number and Date	Major Changes to the Protocol
2.0 27 March 2017	The following revisions were made based on FDA IND review: • The starting dose was updated to 20 mg QD. • The study design was updated from rolling six to 3+3. • Dose escalation was changed to modified Fibonacci if (1) 2 or more treatment-related NCI CTCAE Grade 2 toxicities occurred within a cohort, or (2) a dose level was achieved that was consistent with causing RET target engagement. • It was noted that *RET* alterations would be identified via local, CLIA- or equivalently-approved laboratory, as long as a molecular pathology report was available.
3.0 20 July 2017	• New strengths and formulations of selpercatinib capsules—10 mg, 20 mg, and 80 mg (b) (4) —were added. • Risks were updated to include possible pancreas injury. • Eligibility age for enrolment was lowered where allowed by Ras/Ecs (Inclusion Criterion is now "At least 12 years of age"). • The required certifications for laboratories that perform molecular assays for *RET* were clarified. Fluorescence In Situ Hybridization (FISH) as the only evidence for a *RET* gene rearrangement was noted as acceptable for dose escalation, but required confirmation (e.g., by polymerase chain reaction [PCR] or next-generation sequencing [NGS]) for dose expansion. • Clarified that patients with any degree of progressive disease could be allowed to continue selpercatinib, if the patient was tolerating treatment and, in the opinion of the Investigator, the patient was deriving clinical benefit from continuing study treatment with Sponsor approval. • Clarified that selected cohorts previously declared safe by the SRC could be expanded to a total of 15 patients who have confirmed RET gene alteration status . • Inclusion Criteria for dose escalation and dose expansion were revised: ▪ If archived tumor tissue was not available prior to treatment, a fresh biopsy should be obtained, if it could be safely performed ▪ Baseline hematologic and hepatic parameters were modified in accordance with typical Phase 1 studies to reflect the patients most likely to considered for enrollment (e.g., heavily pre-treated with chemotherapy, liver involvement by their cancers). • Inclusion Criteria related to baseline TSH and calcium levels were modified and moved to Exclusion Criteria. • For dose expansion, MTC patients were to have radiographic PD (RECIST confirmation of PD was not required) within the previous 14 months (patients without radiographic PD within the previous 14 months could be enrolled with Sponsor approval).

Version Number and Date	Major Changes to the Protocol
	• Exclusion Criteria were revised: ▪ The exclusion for MTC patients with disease invading critical structures was removed since these patients are at great risk from their cancers, and may therefore benefit significantly from effective therapy. ▪ Patients with uncontrolled symptomatic hyperthyroidism or hypothyroidism and/or uncontrolled symptomatic hypercalcemia or hypocalcemia were excluded. ▪ Patients were to be instructed to discontinue treatment with PPIs 1 week (previously 2 weeks) prior to starting treatment with selpercatinib. ▪ Patients with active second malignancy other than minor treatment of indolent cancers were excluded. • Included additional guidelines for dose holds and modifications.
4.0 21 November 2017	• Patient assessments to be performed for intra-patient dose escalation were clarified. • Exclusion Criteria were revised to indicate that starting treatment with selpercatinib within less than 5 half-lives or 2 weeks of prior therapy could be permitted if considered by the Investigator to be safe and within the best interest of the patient (e.g., to minimize the acceleration of disease worsening ("flare") that may occur with acute treatment withdrawal), and with prior Sponsor approval. • The dose escalation Table was modified to be compatible with capsule strengths (10 mg, 20 mg and 80 mg) available with Protocol v3.0. • Grade 4 fatigue, asthenia, nausea or other were removed from the definition of a DLT, since these Aes were only defined for Grades 1, 2 and 3 in CTCAE 4.03. • Inclusion Criteria for dose escalation and dose expansion were revised to indicate that patients 12 to 17 years of age could be enrolled, for countries and sites where this change has been approved.
5.0 30 May 2018	• The primary purpose of this amendment was to update the trial design from a two-part Phase 1 (dose escalation and dose expansion) study to a Phase 1/Phase 2 study. In the ongoing Phase 1 (dose escalation) portion of the study, selpercatinib has shown promising early evidence of durable anti-tumor activity in patients with RET-altered cancers (e.g., RET fusion-positive cancers and RET-mutant MTC), including those with resistance to prior MKIs and those with brain metastases. While the target patient population for this study remained the same, the following substantive changes were made: ▪ RP2D of 160 mg BID was selected. ▪ Modifications were made to the composition of the cohorts in the Phase 2 (dose expansion) portion of the study and increase in sample size for each cohort. ▪ Additional objectives and endpoints were added to the Phase 2 portion of the study. ▪ The planned statistical analyses were updated as a reflection of the changes above.

Version Number and Date	Major Changes to the Protocol
	• Eligibility clarifications were made: ▪ Added definition of activating *RET* mutations that were permitted for enrollment. ▪ Added allowance of up to 6 patients with an estimated glomerular filtration rate between 15 and 30 mL/min to be enrolled with Sponsor approval. ▪ Specified prior therapies required for Cohorts 1 (*RET* fusion-positive solid tumors) and 3 (*RET*-mutant MTC) during Phase 2. ▪ Required *RET*-mutant MTC patients not previously treated with an anti-RET MKI to demonstrate radiographic progressive disease within the prior 14 months of treatment to be eligible for enrollment to Cohort 4 during Phase 2. ▪ Excluded patients with an additional validated oncogenic driver that could cause resistance to selpercatinib treatment (NSCLC patients with a second driver were previously excluded). ▪ Excluded patients previously treated with a selective RET inhibitor. ▪ Excluded patients with a clinically significant, active disease process, which makes it undesirable for the patient to participate in the trial. • PK sampling days/times were changed from the previous Protocol v4.0; ▪ Revised sampling days/times in Protocol v5.0: Day 8 of Cycle 1 at time points up to 1-hour pre-dose, and post-dose at 1, 2, 4, and 8 hours. For intra-patient dose escalation, PK samples were to be collected up to 1-hour pre-dose, and post-dose at 1, 2, 4, and 8 hours on Day 8 of the patient's new dose. ▪ Previous sampling days times in Protocol v4.0 were C1D1, C1D8, C3D1, and C5D1 at up to 1 hour pre-dose, and post-dose at 15 and 30 minutes, and 1, 2, 4, 6, and 8 hours; for intra-patient dose escalation, PK samples were collected pre-dose, and post-dose at 1, 2, 4, 6, and 8 hours on Day 8 of the patient's new dose. • Clarified the types of radiographic imaging to be performed at baseline and with each subsequent treatment. This includes baseline brain imaging in all patients with *RET* fusion-positive cancers as well as all patients with a history of CNS metastases and other patients if clinically indicated, including subsequent brain imaging in all patients with detectable brain metastases at baseline. • Clarified that a higher dose of steroids during treatment with selpercatinib was allowed if approved by the Sponsor. • Allowed local treatment with radiation and surgery during treatment with Sponsor approval and provide a recommended time of selpercatinib hold before and after such local treatment. • Added assessment of HRQoL with validated instruments, including a bowel diary for MTC patients with tumor-related diarrhea at baseline. • Clarified reporting instructions in the event of selpercatinib overdose. • Included a new liquid formulation of selpercatinib for patients who cannot swallow capsules.

Version Number and Date	Major Changes to the Protocol
	• For both Phase 1 and Phase 2, clarified that, in the event of toxicity, dose modifications were to be to the first and second prior dose levels investigated during Phase 1. • Excluded Grade 3 thrombocytopenia without clinically significant bleeding, and Grade 3 and Grade 4 lymphopenia, from the DLT definitions. • Included Assessment of tumor serum thyroglobulin levels for patients with non-MTC thyroid cancers.
6.0 11 September 2018	• Added Dose Level 9 Dose 200 mg BID (total daily dose: 400 mg) • Clarified Inclusion Criterion 6 for Phase 1: Added Lansky Performance Score (LPS) for ages under 16 years of age as an alternative method to ECOG. • Revised Inclusion Criterion 1 for Phase 2: Cohorts 1 and 3: ~~Required prior~~ **failed or intolerant to** standard **of care**; **see** ~~first-line therapies for Cohorts 1 and 3 are listed in~~ Table 4-1 **for examples**. • Revised Inclusion Criterion 9 for Phase 1 and 2: Active uncontrolled systemic bacterial, viral, or fungal infection or clinically significant, active disease process, which in the opinion of the Investigator makes ~~it undesirable~~ **the risk:benefit unfavorable** for the patient to participate in the trial. Screening for chronic conditions is not required. • Added to suggested toxicity management during Phase 1 and Phase 2: First Dose Reduction: Reduce dose by **at least** one dose level; Second Dose Reduction: Reduce dose by **at least** one additional dose level (to allow for the dose to be reduced by more than one level if felt to be in the best interest of the patient) • Study assessments: Added Liver function tests (AST, ALT, alkaline phosphatase); C2D15 and C3D15, and added C1D8 2 hours post dose vital sign • Added clarifications to Prohibited Concomitant Medications (non-systemic [e.g., topical creams, eye drops, mouthwashes, etc.]) applications were permissible for substrate of CYP3A4
7.0 18 October 2018	• Updated the clinical data to align with the Investigator's Brochure v4.0. • Increased the number of patients, sizes of cohorts (up to ~750 patients for Phase 2). • Clarified the method of reporting of Aes and SAEs that occur from date of Informed Consent to prior to first dose of study drug. • Revised Exclusion Criterion 7 for Phase 1 and Phase 2: Symptomatic primary CNS tumor, metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression. Replace previous exception with the following: ▪ Patients are eligible if neurological symptoms and CNS imaging are stable and without increase in steroid dose is stable for 14 days prior to the first dose of selpercatinib and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery (SRS). • Deleted the Per-Protocol Analysis Set and planned to use Safety Analysis Set as the alternative.

Version Number and Date	Major Changes to the Protocol
	• Added Futility Monitoring. • Clarified that all Aes that occur prior to the first dose were considered medical history unless the AE develops or worsen due to study related procedures.

CSR LOXO-RET-17001 Table 10

Protocol amendments did not have an impact on the integrity of the trial or interpretation of the results.

The FDA's Assessment:
FDA does not have additional comments regarding the description of protocol amendments.

8.1.2 LOXO-RET-17001 Study Results

Compliance with Good Clinical Practices

Data and the Applicant's Position: [CSR LOXO-RET-17001, Section 5]

LOXO-RET-17001 was conducted in accordance with:

1) Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2) The International Conference for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline [E6]
3) Applicable laws and regulations.

The FDA's Assessment:
The Applicant's statement that Study LOXO-RET-17001 was conducted accordance with GCP was reviewed in the CSR.

Financial Disclosure

The Applicant's Position: [Module 1.3.4]

Financial Disclosure information was collected for all 951 investigators and sub-investigators participating in LOXO-RET-17001. See Appendix 19.2 for detail.

The FDA's Assessment:

The applicant submitted a list of investigators and FDA forms 3454 and 3455 and appeared to adequately disclose the financial interests/ arrangements of the clinical investigators. See Appendix 19.2. The financial disclosure data does not raise concerns about the integrity of the data.

Protocol Violations/Deviations

Data and the Applicant's Position: [CSR LOXO-RET-17001 Section 10.3]

Important protocol deviations were identified prior to data cutoff and included CSR-reportable deviations related to investigational product, Inclusion or Exclusion Criteria, SAE reporting, restricted concomitant medication changes, study procedures, and informed consent.

Important protocol deviations were reported in 40 (7.5%). Overall, protocol deviations had similar incidence across the defined efficacy cohorts. The most frequently reported important protocol deviations were those relating to investigational product in 17 patients, and Inclusion Criteria and SAE reporting, each in 8 patients.

None of the protocol deviations were considered to have an effect on the safety or efficacy outcomes of the study.

The FDA's Assessment:

Important protocol deviations were defined as having met one of the following criteria: 1) a protocol deviation that could potentially affect the efficacy conclusions of the study, or 2) a protocol deviation that could potentially affect a subject's rights, safety, or well-being. Descriptions of each important protocol deviation were included in the submission and were reviewed. Protocol deviations related to investigational product included deviations related to patient compliance (dosing at incorrect frequency or missing doses), intra-patient dose escalation prior to time prescribed in the protocol, and two patients who continued treatment past progression without sponsor approval. Important protocol deviations related to study procedures included one patient who received palliative radiation prior to documentation of PD (which was not allowed per the current protocol amendment) and one patient who received palliative radiation without sponsor approval. Both patients who received radiation therapy had a best overall response of stable disease.

Protocol violations related to inclusion criteria notably included five patients whose documented RET alteration was not generated from an adequately certified laboratory (Clinical Laboratory Improvement Amendments [CLIA], International Standards/ Independent Ethics Committee [ISO/IEC], College of American Pathologists [CAP] or similar certification). By definition, the PAS includes patients with evidence of a protocol-defined RET alteration prospectively identified on the basis of a documented CLIA-certified (or equivalent ex-US) molecular pathology report. Patients (b) (6) from site #201 were included in the PAS; however all have reported protocol violations stating that the RET alteration was not generated from a laboratory with CLIA, ISO/IEC, CAP or similar certification. The sponsor clarified that the testing for these patients was conducted at a laboratory lacking CLIA-equivalent certification (though such a laboratory exists at Site #201). All of these patients were tested using

commercially available NGS testing (Illumina HiSeq2500 Hybrid Capture and ThermoFisher Ion PGM Sequencer). The sponsor chose to include these patients in the PAS given that standard NGS platforms are used in all laboratories at site #201. Improperly selected patients (patients who lack a true RET alteration but are identified as having a RET alteration by the test) would be expected not to respond. Four of five patients with this reported protocol deviation demonstrated a best response of PR, suggesting that they were not improperly selected.

Three patients did not have archival tissue or a screening biopsy. Per protocol, patients could enroll without archival tissue or a fresh biopsy with approval, but it appears this approval was not obtained for these patients.

The protocol deviations described for Study LOXO-RET-17001 are unlikely to impact the interpretation of the safety and efficacy results.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance:

Significant noncompliance to the protocol, resulting in treatment discontinuation, was observed in 1 (0.2%) patient amongst the 531 patients enrolled. [CSR LOXO-RET-17001 Table 12]

Concomitant Medications:

Most patients received concomitant medications (there were 4 patients who did not have concomitant medications reported). The most frequently reported therapeutic classes of medications were thyroid hormones (in 57.1%), natural opium alkaloids (in 37.3%), and analides (in 35.2%). [CSR LOXO-RET-17001 Section 10.5]

Rescue Medications:

Not applicable

The FDA's Assessment:
FDA agrees with the Applicant's observations regarding concomitant medications above. Antipropulsives (loperamide) was used by approximately 28% of patients across dose levels and at the recommended phase 2 dose. The most common class of antihypertensives was dihydropyridine derivatives (e.g., amlodipine) which were used by 27% of patients; followed by ACE inhibitors, which were used by 15.6% of patients, and beta blockers (13.2% of patients).

Primary Analysis of Effectiveness

For the Original NDA and the 60-Day Update, the primary analysis of effectiveness is based on the following agreements between Loxo Oncology and FDA that were incorporated into the statistical analysis plan for the *RET* fusion-positive NSCLC and *RET*-mutant MTC SCE. The most notable agreements include the following:

- The primary analysis of effectiveness for NSCLC indication would be based on the first 105 patients with RET fusion-positive NSCLC who progressed on or after receipt of platinum-based chemotherapy. The subpopulation that received prior platinum-based chemotherapy and an anti PD-1/PD-L1 antibody fall within the Breakthrough Therapy Designation (BTD) population.
- The primary analysis of effectiveness for MTC indication would be based on the first 55 patients with *RET*-mutant MTC who require systemic therapy, who have progressed following prior treatment and who have no acceptable alternative treatment options.
- Objective response rate (ORR) based on efficacy outcomes determined by an IRC would serve as the primary endpoint for efficacy. ORR would be estimated from the proportion of patients with best overall response of confirmed complete response (CR) or confirmed partial response (PR) based on RECIST version 1.1 (Eisenhauer 2009).
- Data on patients who were treatment-naïve with adequate follow-up will be included in the New Drug Application (NDA) as a separate population, these data may or may not be included in the integrated analysis population during FDA review of the NDA.

[Original NDA Module 2.7.3.3 (MTC); Original NDA Module 2.7.3.3 (NSCLC)]

***RET* Fusion Positive NSCLC and *RET* Fusion-Positive Thyroid Cancer - Analysis Sets**

The complete Statistical Analysis Plan (SAP) for *RET* fusion-positive NSCLC SCE, dated 08 August 2019, is provided in Original NDA Module 5.3.5.3. *RET* fusion-positive thyroid patients are an additional supportive analysis set for the *RET* fusion-positive NSCLC analysis. The SAP was written with consideration of the recommendations outlined in key regulatory guidance documents, including the International Conference on Harmonization (ICH) E9 guideline entitled “Guidance for Industry: Statistical Principles for Clinical Trials” (February 1998), and the US FDA Guidance for Industry entitled “Integrated Summary of Effectiveness” (US FDA 2015) and “Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics” (US FDA 2007).

A summary of analysis sets included in this NSCLC SCE are provided in Table 8.5. Additional details are provided in the SAP for *RET* fusion-positive NSCLC (Original NDA Module 5.3.5.3). For *RET* fusion-positive NSCLC, the analysis sets include a PAS, an IAS, 3 SASs, 2 additional supportive analysis sets (including one assessing *RET* fusion-positive thyroid patients), and CNS response analysis set.

Table 8.5 Description of Analysis Sets for *RET* Fusion-positive NSCLC

Analysis Set	Analysis Set Description		Number of Patients
PAS (Primary Analysis Set)	The first 105 *RET* fusion-positive NSCLC patients enrolled in Phase 1 and Phase 2 who met the following criteria: 1. Evidence of a protocol-defined qualifying and definitive *RET* fusion, prospectively identified on the basis of a documented CLIA-certified (or equivalent ex-US) molecular pathology report. Patients with a *RET* fusion co-occurring with another putative oncogenic driver, as determined at the time of study enrollment by local testing, were included. 2. Measurable disease[1] by RECIST v1.1 by investigator assessment. 3. Received 1 or more lines of prior platinum-based chemotherapy. 4. Received 1 or more doses of selpercatinib.		105
IAS (Integrated Analysis Set)	• All *RET* fusion-positive NSCLC patients treated in LOXO-RET-17001 by the data cutoff date who met PAS criteria 1-4. • Included all PAS patients and those enrolled after the 105th patient but on or before the data cutoff.		184
SASs (Supplemental Analysis Sets)	• All other *RET* fusion-positive NSCLC patients (e.g., not part of the PAS/IAS) who were treated in LOXO-RET-17001 as of the data cutoff date. • SAS1 and SAS2: met PAS criteria 1, 2 and 4 • SAS3: met PAS criteria 1 and 4 • SAS assignment was nonoverlapping, thus SAS1-3 are mutually exclusive with each other	**SAS1 (Treatment-naïve)** • No prior systemic therapy	39
		SAS2 (Prior Other Systemic Therapy) • Received prior systemic therapy other than platinum-based chemotherapy	16
		SAS3 (Non-measurable Disease) • No measurable disease[2]	14
Additional Supportive Analysis Sets	*RET* fusion-positive thyroid cancers, met PAS criteria 1 and 4		27
	RET fusion-positive tumors other than NSCLC and thyroid, met PAS criteria 1 and 4		11
CNS Response Analysis Set	All treated *RET* fusion-positive patients who met PAS criteria 1 and 4 and had investigator-assessed CNS metastases at baseline (reported as target or nontarget lesion per RECIST v1.1). These patients are described in the following 3 subsets:	CNS response in the PAS	38*
		CNS response in all patients with *RET* fusion-positive NSCLC	80*
		CNS response in patients with *RET* fusion-positive thyroid cancer or *RET* fusion-positive other tumors	10

[1] Patients without measurable disease who were enrolled in Phase 1 dose escalation were included in the PAS. Refer to the NSCLC SAP for details.
[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] Total patients in this NSCLC SCE is the sum of IAS, SAS1, SAS2, SAS3, *RET* fusion-positive Thyroid Cancer, and *RET* fusion-positive Other Tumors.

* Data updated in the 60-Day Update
Original NDA Module 2.7.3 (NSCLC) Table 6

The prespecified primary analysis of ORR was a point estimate based on the proportion of patients in the PAS with best overall response of confirmed CR or confirmed PR with a 2-sided 95% exact binomial CI using the Clopper-Pearson method. The SAP considered that the effectiveness of selpercatinib would be demonstrated if the lower limit of the 2-sided 95% CI for the point estimate of ORR exceeded 30%. DOR was summarized descriptively using the Kaplan-Meier method.

***RET*-Mutant MTC Analysis Sets**
[Module 2.7.3.3.5.1 (MTC)]

The complete SAP for *RET*-mutant MTC SCE, dated 08 August 2019, is provided in Original NDA Module 5.3.5.3. The SAP was written with consideration of the recommendations outlined in key regulatory guidance documents, including the International Conference on Harmonization (ICH) E9 guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" (February 1998) (ICH E9), and the US Food & Drug Administration Guidance for Industry entitled "Integrated Summary of Effectiveness" (US FDA 2015) and "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" (US FDA 2007).

A summary of analysis sets included in this MTC SCE are provided in Table 8.6. Additional details are provided in the SAP for *RET*-mutant MTC (Original NDA Module 5.3.5.3). For *RET*-mutant MTC, the analysis sets include a PAS, IAS and 2 supplemental analysis sets (SAS1 & SAS2).

Table 8.6 Description of Analysis Sets RET-mutant MTC

	Analysis Set Description		Number of Patients
PAS (Primary Analysis Set)	The first 55 *RET*-mutant MTC patients enrolled in Phase 1 and Phase 2 who met the following criteria: 1. Evidence of a protocol-defined qualifying and definitive *RET*-mutation prospectively identified on the basis of a documented CLIA-certified (or equivalent ex-US) molecular pathology report. Patients with a *RET* mutation co-occurring with another oncogenic driver, as determined at the time of study enrollment by local testing, were included. 2. Measurable disease[1] by RECIST v1.1 by investigator assessment. 3. Received 1 or more lines of prior therapy of cabozantinib or vandetanib. 4. Received 1 or more doses of selpercatinib.		55
IAS (Integrated Analysis Set)	• All *RET*-mutant MTC patients treated in LOXO-RET-17001 by the data cutoff date who met PAS criteria 1-4. • Included all PAS patients and those treated after the 55th patient but on or before the data cutoff.		124
SASs (Supplemental Analysis Sets)	• All other *RET*-mutant MTC patients (e.g. not part of the PAS/IAS) who were treated in LOXO-RET-17001 as of the data cutoff date. • SAS1: met PAS criteria 1, 2, and 4. • SAS2: met PAS criteria 1 and 4. • SAS assignment was nonoverlapping, thus SAS1-2 are mutually exclusive with each other	**SAS1 (cabozantinib and vandetanib naïve)** • Could have received therapies other than cabozantinib or vandetanib	88
		SAS2 (non-measurable disease) • No measurable disease[2]	14

[1] Patients without measurable disease who were enrolled in Phase 1 dose escalation were included in the PAS. See MTC SAP for details.
[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] Total patients in this MTC SCE is the sum of IAS, SAS1, SAS2 and *RET* fusion-positive thyroid cancer.
Original NDA Module 2.7.3 (NSCLC) Table 6

The prespecified primary analysis of ORR was a point estimate based on the proportion of patients in the PAS with best overall response of confirmed CR or confirmed PR with a 2-sided 95% exact binomial CI using the Clopper-Pearson method. The SAP considered that the effectiveness of selpercatinib would be demonstrated if the lower limit of the 2-sided 95% CI for the point estimate of ORR exceeded 20%. DOR was summarized descriptively using the Kaplan-Meier method.

Other RET mutated Tumors and Tumors without Known Activating RET Alterations

Of the 531 patients treated as of the Original NDA data cut of 17 June 2019, 14 patients did not fit the *RET* fusion-positive NSCLC and *RET*-mutant MTC analysis sets described above (Original NDA NSCLC SCE Module 2.7.3.3.1). These patients had other *RET* mutated tumors or tumors without known activating *RET* alterations. In the Original NDA, these patients were described in

the interim CSR. For the 60-Day Update, these patients are described in 60-Day Update SCE (NSCLC) Listing 16.2.3.2.

8.1.2.1 *RET* fusion-positive NSCLC and RET fusion-positive Thyroid Cancer Results

Patient Disposition
[Module 2.7.3.4.1 (NSCLC)]
[60-Day Update SCE (NSCLC) Table 14.1.2]

Table 8.7 and Table 8.8 present the patient disposition for the *RET* fusion-positive NSCLC efficacy population. The patient disposition for the overall safety population is presented in Section 8.2.3, Table 8.31.

Of the 253 patients with *RET* fusion-positive NSCLC in the Original NDA, 202 patients (79.8%) were still on treatment as of the Original NDA data cutoff (17 June 2019). In the 60-Day Update, 172 patients (68.0%) were still on treatment as of the 60-Day Update data cutoff (16 December 2019).

In the Original NDA, in the PAS of 105 patients with *RET* fusion-positive NSCLC, 77 patients (73.3%) were still on treatment, and 147 patients (79.9%) in the IAS were still on treatment. In the PAS, 23 patients (21.9%) stayed on treatment post progression at the discretion of the investigator. Of the 39 patients with treatment-naïve *RET* fusion-positive NSCLC (SAS1), 35 patients (89.7%) were still on treatment. In this 60-Day Update, in the PAS of 105 patients with *RET* fusion-positive NSCLC, 63 patients (60.0%) were still on treatment, and 125 patients (67.9%) in the IAS were still on treatment. In the PAS, 33 patients (31.4%) were treated post progression at the discretion of the investigator. Of the 39 patients with treatment-naïve RET fusion-positive NSCLC (SAS 1), 30 patients (76.9%) were still on treatment.

For all patients with *RET* fusion-positive NSCLC, the most common reason for discontinuation was disease progression (Original NDA n = 26/253, 10.3%, 60-Day Update n = 50/253, 19.8%). A similar proportion in the PAS also discontinued for this reason (Original NDA n = 14/105, 13.3%, 60-Day Update n = 25/105, 23.8%) (Table 8.7 and Table 8.8).

In the Original NDA, there were 11 patients with *RET* fusion-positive “other” tumors, 7 of these 11 patients (63.6%) were still on treatment as of the Original NDA data cutoff; in the 60-Day Update, 6/11 patients (54.5%) were still on treatment (60-Day Update SCE (NSCLC) Table 14.1.2).

Table 8.7 Original NDA: Patient Disposition (*RET* Fusion-positive NSCLC)

	PAS (a subset of IAS)	IAS Prior Platinum Chemo	SAS1 Treatment-naïve	SAS2 Prior Other Systemic Therapy	SAS3 Non-measurable Disease	Total
Treated	105	184	39	16	14	253
Treatment ongoing, n (%)	77 (73.3)	147 (79.9)	35 (89.7)	9 (56.3)	11 (78.6)	202 (79.8)
Treatment discontinued, n (%)	28 (26.7)	37 (20.1)	4 (10.3)	7 (43.8)	3 (21.4)	51 (20.2)
Disease progression	14 (13.3)	18 (9.8)	1 (2.6)	5 (31.3)	2 (14.3)	26 (10.3)
Adverse event	5 (4.8)	7 (3.8)	2 (5.1)	0	1 (7.1)	10 (4.0)
Withdrawal of consent	4 (3.8)	5 (2.7)	0	0	0	5 (2.0)
Death	2 (1.9)	2 (1.1)	1 (2.6)	2 (12.5)	0	5 (2.0)
Other	3 (2.9)	5 (2.7)	0	0	0	5 (2.0)
Treatment continued post-progression, n (%)	23 (21.9)	25 (13.6)	1 (2.6)	3 (18.8)	1 (7.1)	30 (11.9)
Study status continuing, n (%)	86 (81.9)	160 (87.0)	37 (94.9)	12 (75.0)	11 (78.6)	220 (87.0)
Study status discontinued, n (%)	19 (18.1)	24 (13.0)	2 (5.1)	4 (25.0)	3 (21.4)	33 (13.0)
Withdrawal of consent	6 (5.7)	8 (4.3)	1 (2.6)	0	2 (14.3)	11 (4.3)
Death	13 (12.4)	16 (8.7)	1 (2.6)	4 (25.0)	1 (7.1)	22 (8.7)

Source: Original NDA Module 2.7.3 (NSCLC) Table 7

Table 8.8 60-Day Update: Patient Disposition (*RET* Fusion-positive NSCLC)

	PAS (a subset of IAS)	IAS Prior Platinum Chemo	SAS1 Treatment-naïve	SAS2 Prior Other Systemic Therapy	SAS3 Non-measurable Disease	Total
Treated	105	184	39	16	14	253
Treatment ongoing, n (%)	63 (60.0)	125 (67.9)	30 (76.9)	8 (50.0)	9 (64.3)	172 (68.0)
Treatment discontinued, n (%)	42 (40.0)	59 (32.1)	9 (23.1)	8 (50.0)	5 (35.7)	81 (32.0)
Disease progression	25 (23.8)	34 (18.5)	6 (15.4)	6 (37.5)	4 (28.6)	50 (19.8)
Adverse event	5 (4.8)	11 (6.0)	2 (5.1)	0	1 (7.1)	14 (5.5)
Withdrawal of consent	6 (5.7)	7 (3.8)	0	0	0	7 (2.8)
Death	2 (1.9)	3 (1.6)	1 (2.6)	2 (12.5)	0	6 (2.4)
Other	4 (3.8)	4 (2.2)	0	0	0	4 (1.6)

	PAS (a subset of IAS)	IAS Prior Platinum Chemo	SAS1 Treatment-naïve	SAS2 Prior Other Systemic Therapy	SAS3 Non-measurable Disease	Total
Treatment continued post-progression, n (%)	33 (31.4)	42 (22.8)	5 (12.8)	5 (31.3)	1 (7.1)	53 (20.9)
Study status continuing, n (%)	70 (66.7)	138 (75.0)	37 (94.9)	10 (62.5)	10 (71.4)	195 (77.1)
Study status discontinued, n (%)	35 (33.3)	46 (25.0)	2 (5.1)	6 (37.5)	4 (28.6)	58 (22.9)
Withdrawal of consent	12 (11.4)	16 (8.7)	1 (2.6)	1 (6.3)	2 (14.3)	20 (7.9)
Death	23 (21.9)	30 (16.3)	1 (2.6)	5 (31.3)	2 (14.3)	38 (15.0)

Source: 60-Day Update SCE (NSCLC) Table 14.1.2

Table 8.9 presents the patient disposition for the *RET* fusion-positive thyroid cancer efficacy population. The patient disposition for the overall safety population is presented in Section 8.2.3, Table 8.31. Of the 27 patients with *RET* fusion-positive thyroid cancer in the Original NDA, 23/27 patients (85.2%) were still on treatment as of the Original NDA data cutoff; and 21/27 patients (77.8%) were still on treatment as of the 60-Day Update data cutoff.

Table 8.9 Original NDA: Patient Disposition (*RET* Fusion-positive Thyroid Cancer)

	Original NDA	60-Day Update
Treated	**27**	**27**
Treatment Ongoing, n (%)	23 (85.2)	21 (77.8)
Discontinuation, n (%)	4 (14.8)	6 (22.2)
Disease Progression	1 (3.7)	3 (11.1)
Adverse Event	1 (3.7)	1 (3.7)
Non-compliance	1 (3.7)	1 (3.7)
Withdrawal of Consent	1 (3.7)	1 (3.7)
Treated Post-progression, n (%)	5 (18.5)	6 (22.2)
Study Status Continuing, n (%)	25 (92.6)	22 (81.5)
Study Status Discontinued, n (%)	2 (7.4)	5 (18.5)
Withdrawal of Consent	1 (3.7)	1 (3.7)
Death	1 (3.7)	4 (14.8)

Source: Original NDA Module 2.7.3 (NSCLC) Table 8; 60-Day Update SCE (NSCLC) Table 14.1.2

The FDA's Assessment:

FDA confirmed the analysis above provided by the Applicant. Note that validation of the Applicant's analysis results by FDA was performed only for the patient population of primary

interest including the PAS and SAS1 for RET Fusion-positive NSCLC and RET-Mutant MTC, and CNS response analysis set-PAS in RET Fusion-positive NSCLC patients.

FDA also requested that the Applicant provide an analysis of treatment post-progression given the significant number of patients who received treatment following progression. An assessment of whether patients subsequently responded was not possible based on the data collected by the sponsor, but the following Table demonstrates the time on treatment post-progression for patients with NSCLC, MTC, and for all patients in the safety database as of the data cut-off of December 17, 2019.

Table 8.10: Time on Treatment Post-Progression (Applicant's Analysis)

	***RET*-mutant MTC (n = 299)**	***RET* fusion-positive NSCLC (n = 329)**	**Overall Safety (n= 702)**
No. of Subjects Treated Post Progression*	31	55	99
Time on Treatment Post Progression (months)			
Mean	4.3	3.5	3.9
Standard Deviation	5.6	4.0	4.5
Median	2.2	2.4	2.3
Min, Max	0.2, 22.7	0.1, 22.3	0, 22.7

*Subjects (b) (6) and (b) (6) were indicated to have treatment post progression, but were excluded from this analysis due to treatment discontinuation occurring on the same day as disease progression

Demographic Characteristics

The median age of the population across all patients with *RET* fusion-positive NSCLC was 61 years and encompassed a wide range (23–86 years) (Table 8.11). For PAS patients, 50% were between the age of 45 and 64 years. There were more females than males. The majority (51%) of *RET* fusion-positive NSCLC patients were white, with a high proportion of patients identified as Asian (41%). Body weight had a median of 64.0 kg and ranging from 38.85 to 148 kg. The median body mass index (BMI) was 23.6 kg/m^2 and likewise displayed a wide range from 15.7 to 45.3 kg/m^2. Most patients had a baseline Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 (98%), and 70% were never smokers.

The demographic characteristics of patients with *RET* fusion-positive thyroid cancer were similar to those of patients with *RET* fusion-positive NSCLC, although there were more males than females and a lower proportion of Asian patients (Table 8.11). [Module 2.7.3.4.2 (NSCLC)]

Table 8.11 Demographics for *RET* fusion-positive NSCLC and *RET* fusion-positive thyroid cancer

	RET Fusion-positive NSCLC						*RET* fusion-positive Thyroid N = 27	*RET* fusion-positive Other Tumors N = 11
	PAS (a subset of IAS) N = 105	IAS Prior Platinum Chemo N = 184	SAS1 Treatment-naïve N = 39	SAS2 Prior Other Systemic Therapy N = 16	SAS3 Non-measurable Disease N = 14	Total N = 253		
Age, years								
Median	61.0	62.0	61.0	58.5	60.0	61.0	54.0	54.0
Range	23-81	23-81	23-86	47-71	44-80	23-86	20-88	31-76
Overall age group, n (%)								
18-44 years	17 (16.2)	26 (14.1)	4 (10.3)	0	1 (7.1)	31 (12.3)	7 (25.9)	4 (36.4)
45-64 years	52 (49.5)	89 (48.4)	18 (46.2)	12 (75.0)	7 (50.0)	126 (49.8)	11 (40.7)	4 (36.4)
65-74 years	30 (28.6)	54 (29.3)	13 (33.3)	4 (25.0)	5 (35.7)	76 (30.0)	5 (18.5)	2 (18.2)
≥ 75 years	6 (5.7)	15 (8.2)	4 (10.3)	0	1 (7.1)	20 (7.9)	4 (14.8)	1 (9.1)
Sex, n (%)								
Male	43 (41.0)	79 (42.9)	17 (43.6)	6 (37.5)	6 (42.9)	108 (42.7)	14 (51.9)	8 (72.7)
Female	62 (59.0)	105 (57.1)	22 (56.4)	10 (62.5)	8 (57.1)	145 (57.3)	13 (48.1)	3 (27.3)
Race, n (%)								
White	55 (52.4)	86 (46.7)	28 (71.8)	11 (68.8)	5 (35.7)	130 (51.4)	20 (74.1)	10 (90.9)
Black	5 (4.8)	9 (4.9)	3 (7.7)	0	0	12 (4.7)	1 (3.7)	0
Asian	40 (38.1)	82 (44.6)	7 (17.9)	5 (31.3)	9 (64.3)	103 (40.7)	2 (7.4)	0
Other/Missing	5 (4.8)	7 (3.8)	1 (2.6)	0	0	8 (3.2)	4 (14.8)	1 (9.1)
Ethnicity, n (%)								
Hispanic or Latino	4 (3.8)	4 (2.2)	0	1 (6.3)	1 (7.1)	6 (2.4)	3 (11.1)	1 (9.1)
Not Hispanic or Latino	98 (93.3)	175 (95.1)	38 (97.4)	15 (93.8)	13 (92.9)	241 (95.3)	22 (81.5)	10 (90.9)
Missing	3 (2.9)	5 (2.7)	1 (2.6)	0	0	6 (2.4)	2 (7.4)	0
Height (cm)								
n	103	181	38	16	14	249	25	11
Median	164.0	164.0	167.0	160.0	166.0	165.0	170.0	175.0
Range	149-188	143-192	149-182	150-181	149-178	143-192	148-197	158-190
Body weight (kg)								

	RET Fusion-positive NSCLC						*RET* fusion-positive Thyroid N = 27	*RET* fusion-positive Other Tumors N = 11
	PAS (a subset of IAS) N = 105	IAS Prior Platinum Chemo N = 184	SAS1 Treatment-naïve N = 39	SAS2 Prior Other Systemic Therapy N = 16	SAS3 Non-measurable Disease N = 14	Total N = 253		
n	104	183	39	16	14	252	27	11
Median	64.00	64.00	72.00	57.60	62.10	64.0	78.30	76.00
Range	42.20-148.00	38.85-148.00	45.60-130.50	48.60-109.5	46.90-106.8	38.85-148.0	41.30-121.4	48.10-100.90
Body mass index, kg/m²								
n	103	181	38	16	14	249	25	11
Median	23.15	23.31	25.63	23.31	21.84	23.57	25.28	24.82
Range	17.3-43.7	15.7-45.3	18.3-45.2	17.8-37.0	19.4-40.7	15.7-45.3	17.3-51.8	18.3-32.2
Baseline ECOG, n (%)								
0	31 (29.5)	66 (35.9)	19 (48.7)	3 (18.8)	6 (42.9)	94 (37.2)	8 (29.6)	3 (27.3)
1	72 (68.6)	114 (62.0)	20 (51.3)	12 (75.0)	8 (57.1)	154 (60.9)	16 (59.3)	7 (63.6)
2	2 (1.9)	4 (2.2)	0	1 (6.3)	0	5 (2.0)	3 (11.1)	1 (9.1)
Smoking history, n (%)								
Never smoked	75 (71.4)	125 (67.9)	29 (74.4)	11 (68.8)	11 (78.6)	176 (69.6)	21 (77.8)	8 (72.7)
Former smoker	29 (27.6)	55 (29.9)	9 (23.1)	5 (31.3)	3 (21.4)	72 (28.5)	6 (22.2)	2 (18.2)
Current smoker	1 (1.0)	4 (2.2)	1 (2.6)	0	0	5 (2.0)	0	0
Missing	0	0	0	0	0	0	0	1 (9.1)

Analysis set definitions: PAS = Primary Analysis Set; IAS = Prior Platinum Chemotherapy; SAS1 = Treatment-naïve; SAS2 = Prior Other Systemic Therapy; SAS3 = Non-measurable Disease.
Note: For *RET* fusion-positive NSCLC, the PAS includes the first 105 patients of the IAS. The Total column is the sum of the IAS, SAS1, SAS2, and SAS3.
Source: Module 2.7.3 (NSCLC) Table 9; Module 5.3.5.3 ISE (NSCLC) Table 14.2.1

Baseline Disease Characteristics

For *RET* fusion-positive NSCLC PAS patients, the median time from diagnosis was 30.1 months. Most patients (98%) in the PAS had metastatic disease at enrollment, 80% were diagnosed as stage 4, and 36% had CNS metastasis at baseline. Next generation sequencing (NGS) on tumor samples (81%) was the most common method of determining *RET* fusion status. These features were similar across the other analysis sets [Original NDA Module 2.7.3.4.2 (NSCLC); 60-Day Update SCE (NSCLC) Tables 14.2.2, 14.2.4]

Tumor histologies in patients with *RET* fusion-positive thyroid cancer included papillary (n = 21), poorly differentiated (n = 3), anaplastic (n = 2), and Hurthle cell (n = 1) (Table 8.12). The median time from diagnosis for *RET* fusion-positive thyroid cancer was 92.3 months (Table 8.12). The majority of patients (100%) had metastatic disease and had a baseline ECOG score of 0 or 1, and were never smokers (**Error! Reference source not found.**). [Original NDA Module 2.7.3.4.2 (NSCLC); 60-Day Update SCE (NSCLC) Tables 14.2.1, 14.2.2, 14.2.4]

Table 8.12 Original NDA and 60-Day Update: Baseline Disease Characteristics for *RET* Fusion-positive NSCLC and *RET* Fusion-positive Thyroid Cancer

	***RET* Fusion-positive NSCLC**						***RET* Fusion-positive Thyroid N = 27**	***RET* Fusion-positive Other Tumors N = 11**
	PAS (a subset of IAS) N = 105	**IAS Prior Platinum Chemo N = 184**	**SAS1 Treatment -naïve N = 39**	**SAS2 Prior Other Systemic Therapy N = 16**	**SAS3 Non-measurable Disease N = 14**	**Total N = 253**		
Primary tumor type, n (%)								
NSCLC	105 (100)	184 (100)	39 (100)	16 (100)	14 (100)	253 (100)	0	0
Papillary Thyroid	0	0	0	0	0	0	21 (77.8)	0
Poorly Differentiated Thyroid	0	0	0	0	0	0	3 (11.1)	0
Anaplastic Thyroid	0	0	0	0	0	0	2 (7.4)	0
Hurthle Cell Thyroid	0	0	0	0	0	0	1 (3.7)	0
Pancreatic	0	0	0	0	0	0	0	4 (36.4)
Salivary	0	0	0	0	0	0	0	2 (18.2)
Carcinoid	0	0	0	0	0	0	0	1 (9.1)
Colon	0	0	0	0	0	0	0	1 (9.1)
Rectal Neuroendocrine	0	0	0	0	0	0	0	1 (9.1)
Small intestine	0	0	0	0	0	0	0	1 (9.1)
Xantho-granuloma	0	0	0	0	0	0	0	1 (9.1)
Stage at diagnosis, n (%)								
I, IA, IB	1 (1.0)	2 (1.1)	0	1 (6.3)	1 (7.1)	4 (1.6)	0	0
II, IIA, IIB	0	2 (1.1)	1 (2.6)	1 (6.3)	2 (14.2)	6 (2.4)	1 (3.7)	0
IIIA, IIIB	3 (2.9)	10 (5.4)	0	0	0	10 (4.0)	0	0
IIIC	0	0	1 (2.6)*	0	0	1 (0.4)*	0	0
IV	84 (80.0)	121 (65.8)	31 (79.5)*	10 (62.5)	8 (57.1)	170 (67.2)*	16 (59.3)	7 (63.6)
IVA	9 (8.6)	18 (9.8)	2 (5.1)	1 (6.3)	1 (7.1)	22 (8.7)	0	1 (9.1)
IVB	4 (3.8)	18 (9.8)	2 (5.1)	1 (6.3)	2 (14.3)	23 (9.1)	1 (3.7)	0

	RET Fusion-positive NSCLC						*RET* Fusion-positive Thyroid N = 27	*RET* Fusion-positive Other Tumors N = 11
	PAS (a subset of IAS) N = 105	IAS Prior Platinum Chemo N = 184	SAS1 Treatment -naïve N = 39	SAS2 Prior Other Systemic Therapy N = 16	SAS3 Non-measurable Disease N = 14	Total N = 253		
IVC	4 (3.8)	13 (7.1)	1 (2.6)	2 (12.5)	0	16 (6.3)	8 (29.6)	2 (18.2)
Missing	0	0	1 (2.6)	0	0	1 (0.4)	1 (3.7)	1 (9.1)
Time from diagnosis, months								
Median	30.10	24.20	2.00	7.15	19.50	18.40	92.30	17.40
Range	1.5-142.3	1.5-164.8	0.7-8.1	2.0-112.5	7.4-223.7	0.7-223.7	2.6-401.7	4.1-74.2
History of metastatic disease, n (%)								
Yes	103 (98.1)	179 (97.3)	39 (100)	16 (100)	14 (100)	248 (98.0)	27 (100)	11 (100)
No	2 (1.9)	5 (2.7)	0	0	0	5 (2.0)	0	0
Time from diagnosis of metastatic disease, months								
Median	20.40	19.50	1.60	7.15	10.65	12.50	53.10	4.90
Range	1.5-100.8	1.0-108.1	0.0-8.1	2.0-75.5	0.4-91.1	0-108.1	1.9-344.9	3.0-74.2
At least 1 measurable lesion by investigator, n (%)								
Yes	104 (99.0)	183 (99.5)	39 (100)	16 (100)	0	238 (94.1)	26 (96.3)	9 (81.8)
No	1 (1.0)	1 (0.5)	0	0	14 (100)	15 (5.9)	1 (3.7)	2 (18.2)
Sum of diameters at baseline by investigator, mm								
Median	60.0	54.7	70.0	78.0	0	57.6	54.0	90.0
Range	10.2-248.2	10.0-297.0	15.0-191.0	20.0-249.6	0-0	10.0-297.0	11.0-156.4	26.0-229.0
CNS metastases at baseline by investigator, n (%)								
Yes	38 (36.2)*	61 (33.2)*	7 (17.9)	10 (62.5)	2 (14.3)	80 (31.6)*	7 (25.9)	3 (27.3)
No	67 (63.8)*	123 (66.8)*	32 (82.1)	6 (37.5)	12 (85.7)	173 (68.4)*	20 (74.1)	8 (72.7)

Analysis Set definitions: PAS = Primary Analysis Set; IAS = Prior Platinum Chemotherapy; SAS1 = Treatment-naïve; SAS2 = Prior Other Systemic Therapy; SAS3 = Non-measurable Disease.
Note: For *RET* fusion-positive NSCLC, the PAS includes the first 105 patients of the IAS. The Total column is the sum of the IAS, SAS1, SAS2, and SAS3.
Source: 60-Day Update SCE (NSCLC) Tables 14.2.2, 14.2.4
* Data updated in 60-Day Update

In both the Original NDA and the 60-Day Update, among *RET* fusion-positive NSCLC patients, the most common fusion partner was KIF5B, followed by CCDC6 and then NCOA4. For patients with *RET* fusion-positive thyroid cancers, CCDC6 was the most common partner. [Original NDA Module 2.7.3.4.2 (NSCLC); 60-Day Update Table 14.2.5]

The FDA's Assessment:

FDA agrees with Applicant's results provided above; however, refer to FDA comment in

Section-8.1.2.1 (page -185) regarding the validation of efficacy results by FDA for the different analysis population presented in this AA.

FDA requested information regarding the two patients in the NSCLC PAS who did not have a history of metastatic disease. These patients had Stage IV disease at the time of enrollment.

***RET* Fusion-Positive NSCLC Efficacy Data**

[Original NDA Module 2.5.4.2 (NSCLC); 60-Day Update SCE (NSCLC) Tables 14.3.1.1, 14.3.1.2, 14.3.1.3, 14.3.1.4, 14.3.3.1, 14.3.3.2, 14.3.3.3, 14.3.3.4, 14.3.6.1.1, 14.3.6.3.1, 14.3.7.1.1]

Primary Analysis Set: Patients Who Received 1 or More Lines of Prior Platinum-based Therapy

The *RET* fusion-positive NSCLC PAS is a prospectively defined population of patients consisting of the first 105 patients consecutively enrolled to LOXO-RET-17001 who had received prior platinum-based chemotherapy. The PAS was powered to rule out a lower bound of ORR of 30%, a threshold deemed clinically meaningful and consistent with the estimated response rates seen with approved targeted therapies in genetically-defined NSCLC patient populations who have failed prior therapies.

In the *RET* fusion-positive NSCLC PAS in the Original NDA, the ORR was 61.9% (65/105; 95% CI: 51.9, 71.2) by IRC and 65.7% (69/105; 95% CI: 55.8, 74.7) by investigator assessment (Table 8.13). In the 60-Day Update, the ORR was 63.8% (67/105; 95% CI 53.9, 73.0) by IRC assessment, and 69.5% (73/105; 95% CI 59.8, 78.1) by investigator assessment. In the Original NDA, the Kaplan-Meier estimate for median DOR was 12.5 months (95% CI: 10.3, NE), with median DOR follow-up of 8.1 months and 17/65 (26%) events observed, by IRC assessment. The median DOR by investigator assessment was 20.3 months (95% CI: 13.8, 24.0), with median DOR follow-up of 8.0 months and 16/69 (23%) events observed. At the time of the data cutoff for this 60-Day Update the median DOR by IRC increased to 17.5 months (95% CI: 12.0, NE), with 23/67 (34.3%) events observed and median DOR follow-up of 12.1 months. The median DOR by investigator assessment was 20.3 months (95% CI: 15.6, 24.0), with median DOR follow-up of 14.8 months and 28/73 (38.4%) events observed.

A waterfall plot illustrating the best change in tumor size per RECIST v1.1 based on IRC assessment is shown below Figure 8.2 and Figure 8.3. The Kaplan-Meier plot of DOR based on IRC assessment is shown in Figure 8.4 and Figure 8.5.

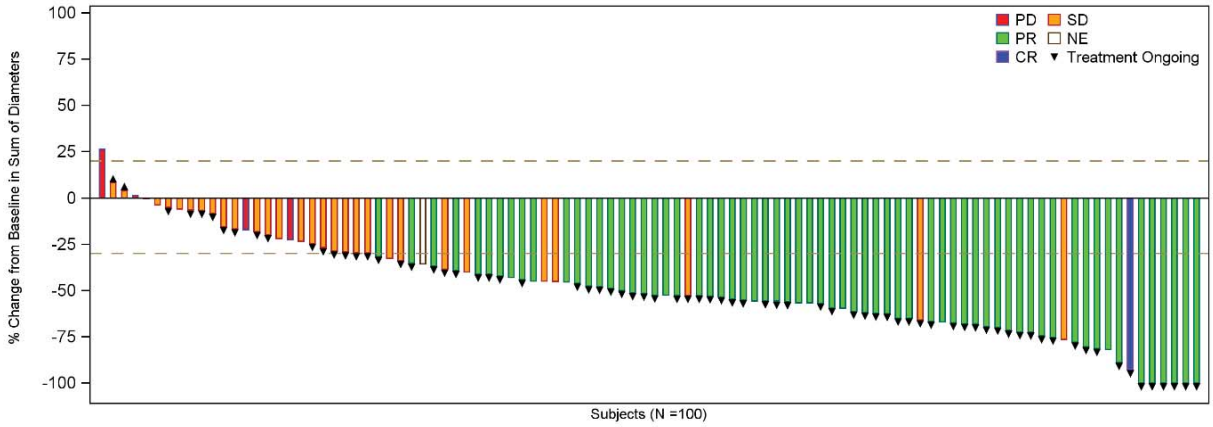
Table 8.13 Original NDA and 60-Day Update: Objective Response Rate and Duration of Response for *RET* Fusion-positive NSCLC Primary Analysis Set

	Original NDA		60-Day Update	
	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment
No. of Patients	**105**	**105**	**105**	**105**
Best Overall Response, n (%)				
Complete response	1 (1.0)	2 (1.9)	2 (1.9)	2 (1.9)
Partial response	64 (61.0)	67 (63.8)	65 (61.9)	71 (67.6)
Objective Response Rate (confirmed CR/PR), n (%)				
ORR	65 (61.9)	69 (65.7)	67 (63.8)	73 (69.5)
(95% confidence interval)	(51.9, 71.2)	(55.8, 74.7)	(53.9, 73.0)	(59.8, 78.1)
Duration of Response, months				
Median (95% confidence interval)	12.5 (10.3, NE)	20.3 (13.8, 24.0)	17.5 (12.0, NE)	20.3 (15.6, 24.0)
Minimum, Maximum	1.8+, 20.2+	1.9+, 24.0	1.9+, 26.2+	1.3+, 26.0+
Duration of Response, n (%)				
< 6 months	31 (47.7)	23 (33.3)	13 (19.4)	11 (15.1)
≥ 6 – 12 months	27 (41.5)	31 (44.9)	30 (44.8)	28 (38.4)
≥ 12 – 18 months	4 (6.2)	7 (10.1)	20 (29.9)	24 (32.9)
≥ 18 – 24 months	3 (4.6)	8 (11.6)	3 (4.5)	9 (12.3)
≥ 24 months	0	0	1 (1.5)	1 (1.4)
Response Status, n (%)				
Disease progression	16 (24.6)	14 (20.3)	21 (31.3)	26 (35.6)
Died before disease progression	1 (1.5)	2 (2.9)	2 (3.0)	2 (2.7)
Censored	48 (73.8)	53 (76.8)	44 (65.7)	45 (61.6)
Duration of Response Follow-up, months				
Median	8.1	8.0	12.1	14.8

Median DOR and DOR follow-up estimated using the Kaplan-Meier method

Source: Original NDA Module 2.7.3 (NSCLC) Table 18, Table 22; 60-Day Update Tables 14.3.1.1; 14.3.1.2, 14.3.3.1, 14.3.3.2

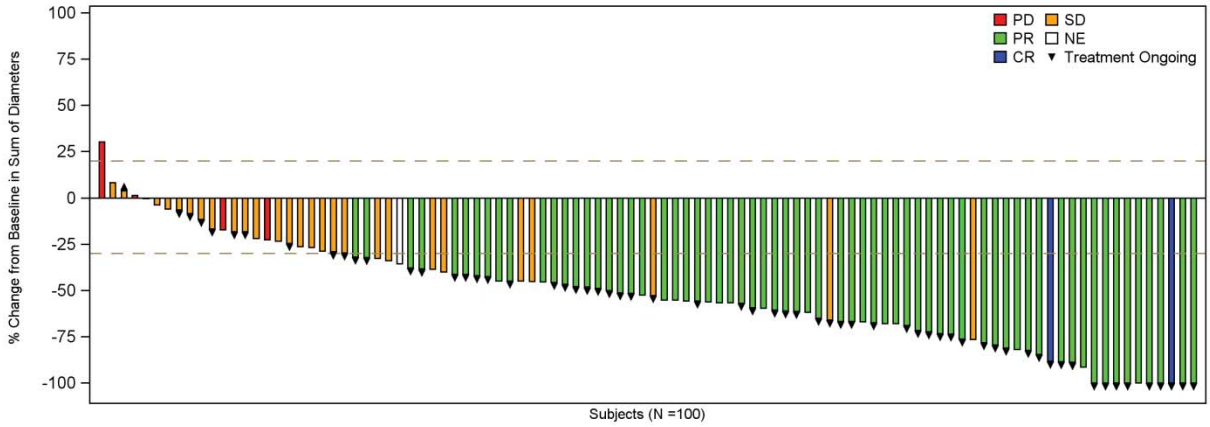
Figure 8.2 Original NDA: Waterfall Plot of Best Change in Tumor Burden Based on IRC Assessment – Primary Analysis Set



Note: Five subjects not shown due to two having non-target lesions only and three with no post-baseline target lesion measurements.

Source: Original NDA Module 5.3.5.3 SCE (NSCLC) Figure 14.2.1

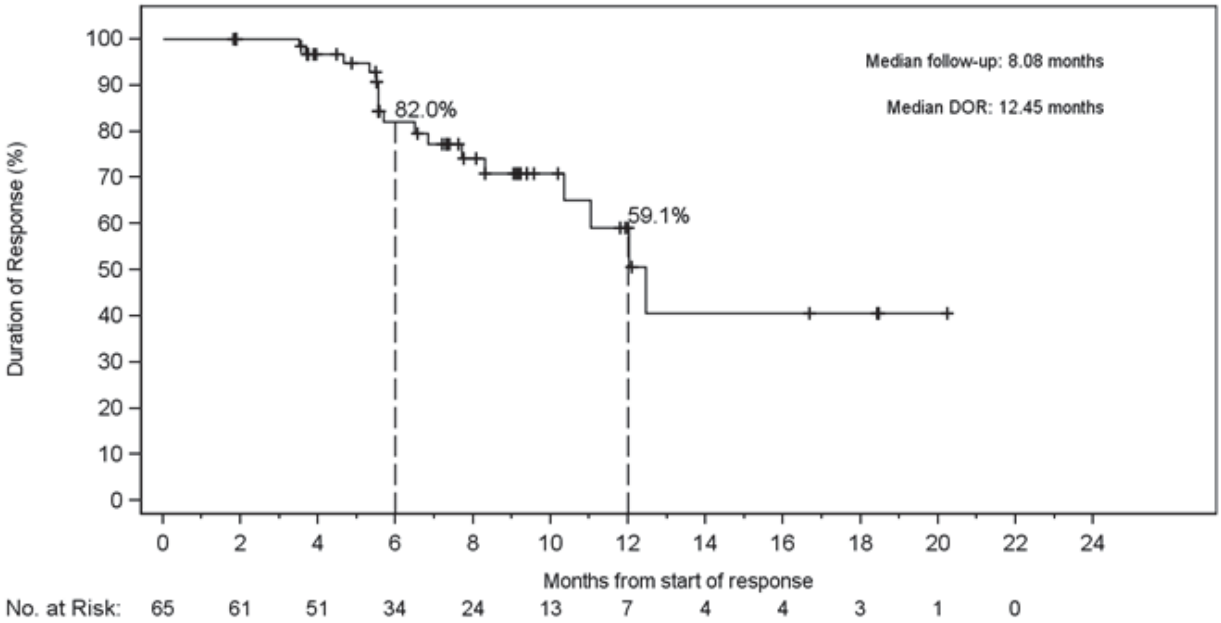
Figure 8.3 60-Day Update: Waterfall Plot of Best Change in Tumor Burden Based on IRC Assessment – Primary Analysis Set



Note: Five subjects not shown due to two having non-target lesions only and three with no post-baseline target lesion measurements.

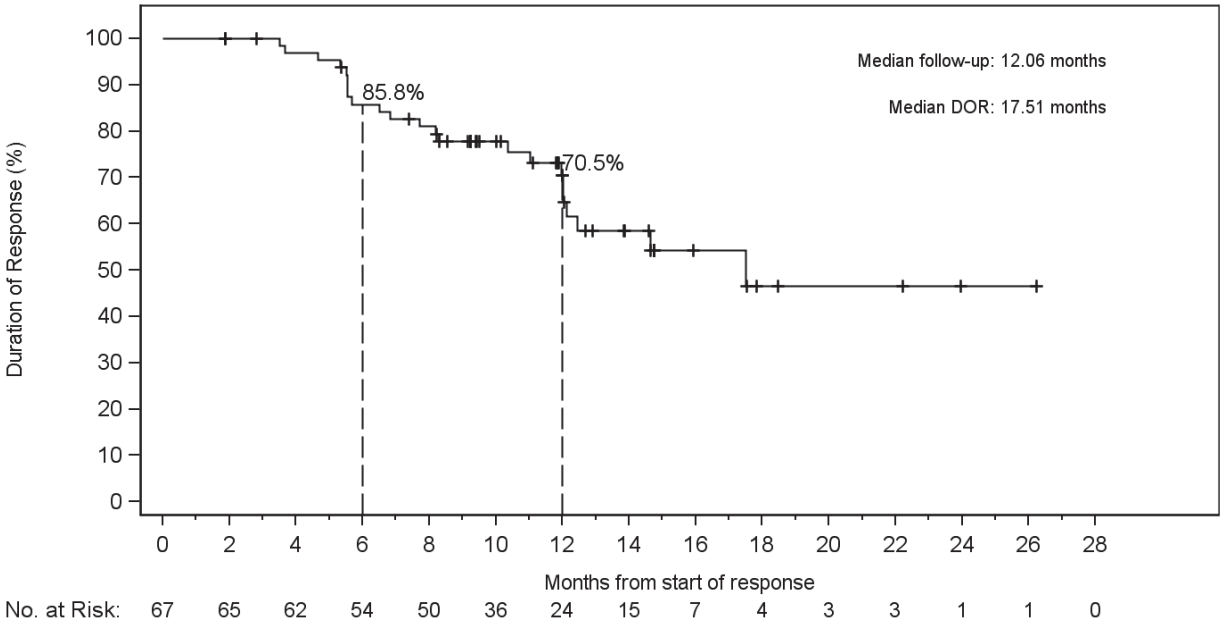
Source: 60-Day Update SCE (NSCLC) Figure 14.2.1

Figure 8.4 Original NDA: Kaplan-Meier Plot of Duration of Response Based on IRC Assessment – Primary Analysis Set



Source: Original NDA Module 5.3.5.3 SCE (NSCLC) Figure 14.3.1

Figure 8.5 60-Day Update: Kaplan-Meier Plot of Duration of Response Based on IRC Assessment – Primary Analysis Set



Source: 60-Day Update SCE (NSCLC) Figure 14.3.1

Approximately 25–40% of NSCLC patients develop brain metastasis. In the PAS for the Original NDA, 37 patients had CNS metastases at baseline, who were in turn referred for a prospectively defined IRC-based CNS assessment.

At the 60-Day Update, 1 additional PAS patient was identified to have CNS metastases per investigator at baseline, making a total of 38 PAS patients with CNS metastases at baseline. Consistent with the Original NDA, there were 11 patients with measurable CNS disease by IRC. The CNS ORR in these 11 patients was 90.9% (10/11; 95% CI: (58.7, 99.8), including 3 CRs (27.3%) and 7 PRs (63.6%) (60-Day Update SCE (NSCLC) Table 14.3.6.1.1). CNS ORR was similar for patients who received brain radiation more than 2 months prior to the start of selpercatinib treatment (80% (4/5; 95% CI: 28.4, 99.5) and patients who did not receive any prior brain radiation therapy (100% (6/6); 95% CI: 54.1, 100.0) (60-Day Update SCE (NSCLC) Table14.3.6.3.1). The median CNS DOR was 10.1 months (95% CI: 6.7, NE) (60-Day Update SCE (NSCLC) Table 14.3.7.1.1).

Integrated Analysis Set

In addition to the PAS, the IAS is comprised of all *RET* fusion-positive NSCLC patients who have received 1 or more lines of prior platinum-based chemotherapy, including the first 105 patients in the PAS. As of the data cutoff for the Original NDA, a total of 184 IAS patients had been treated with selpercatinib. As of the 16 December 2019 data cutoff for this 60-Day Update the ORR in the IAS was 56.5% (104/184; 95% CI: 49.0, 63.8) by IRC and 62.5% (115/184; 95% CI: 55.1, 69.5) by Investigator (60-Day Update SCE (NSCLC) Tables 14.3.1.3, 14.3.1.4).

Supplemental Analysis Set 1 - Patients Who Were Treatment-naïve

As of the 17 June 2019 data cutoff for the Original NDA, a total of 39 treatment-naïve *RET* fusion-positive NSCLC patients (the SAS 1) had been treated with selpercatinib. Of these 39 patients, 13 patients had at least 6 months follow up from the first dose of selpercatinib and were characterized for efficacy. As of the 60-Day Update, all 39 treatment-naïve *RET* fusion-positive NSCLC patients have been evaluated for response and had the opportunity to be followed for at least 6 months from first dose.

In the Original NDA, the ORR was 92.3% (12/13; 95% CI: 64.0, 99.8) by both IRC and investigator assessment. In this 60-Day Update, the ORR was 84.6% (33/39; 95% CI: 69.5, 94.1) by both IRC and investigator assessment (Table 8.14). In the Original NDA, the median DOR by IRC was not reached (95% CI: 6.4, NE), with median DOR follow-up of 7.5 months and 3/12 (25%) events observed; the median DOR by investigator assessment was not reached (95% CI: 8.3, NE), with median DOR follow-up of 8.2 months and 2/12 (17%) events observed. In the 60-Day Update,

the median DOR by IRC and by investigator assessment was not reached (95% CI: 12.0, NE), with median DOR follow-up of 7.4 months and 7/33 (21.2%) events observed (Table 8.14).

A waterfall plot illustrating the best change in tumor size per RECIST v1.1 based on IRC assessment is shown below Figure 8.6 and Figure 8.7. The Kaplan-Meier plot of DOR based on IRC assessment is shown in Figure 8.8 and Figure 8.9.

Table 8.14 Original NDA and 60-Day Update: Objective Response Rate and Duration of Response for Treatment-Naive *RET* Fusion-positive NSCLC

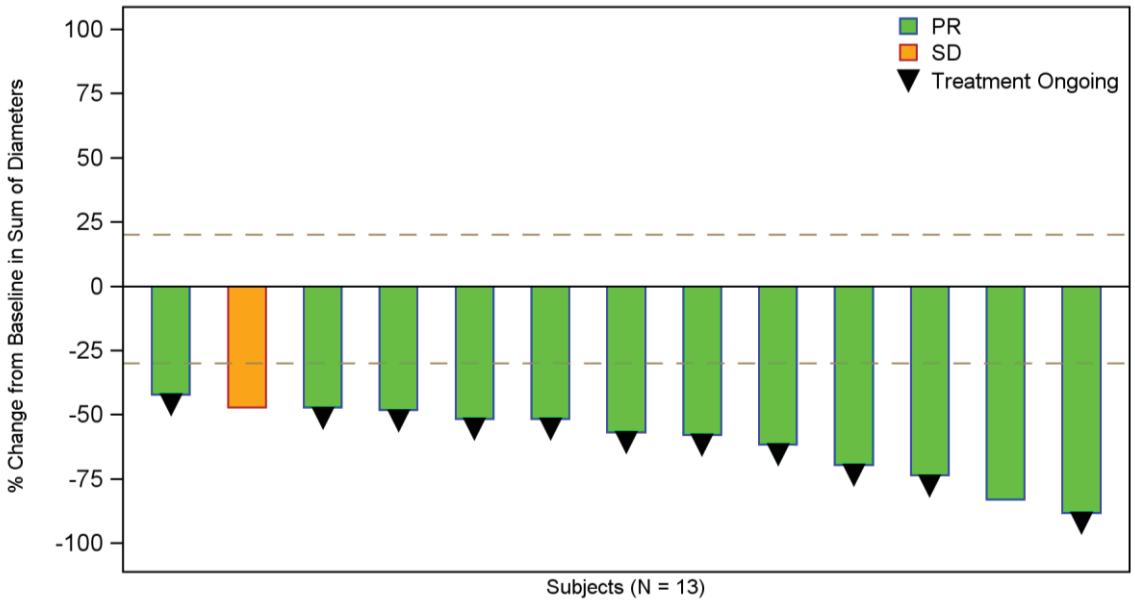
	Original NDA		60-Day Update	
	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment
No. of patients	39	39	39	39
No. of eligible[#] patients	13	13	39	39
Best Overall Response, n (%)				
Complete response	0	1 (7.7)	0	1 (2.6)
Partial response	12 (92.3)	11 (84.6)	33 (84.6)	32 (82.1)
Objective Response Rate (confirmed CR/PR), n (%)				
ORR	12 (92.3)	12 (92.3)	33 (84.6)	33 (84.6)
(95% CI)	(64.0, 99.8)	(64.0, 99.8)	(69.5, 94.1)	(69.5, 94.1)
Duration of Response, months				
No. of patients with response	12	12	33	33
Median (95% CI)	NE (6.4, NE)	NE (8.3, NE)	NE (12.0, NE)	NE (12.0, NE)
Minimum, Maximum	3.7+, 14.5+	4.0+, 14.5+	1.9+, 20.0+	3.5+, 20.0+
Duration of Response, n (%)				
< 6 months	3 (25.0)	4 (33.3)	14 (42.4)	13 (39.4)
≥ 6 – 12 months	8 (66.7)	7 (58.3)	14 (42.4)	13 (39.4)
≥ 12 – 18 months	1 (8.3)	1 (8.3)	4 (12.1)	6 (18.2)
≥ 18 – 24 months	0	0	1 (3.0)	1 (3.0)
Response Status (n, %)				
Disease progression	3 (25.0)	2 (16.7)	7 (21.2)	7 (21.2)
Censored	9 (75.0)	10 (83.3)	26 (78.8)	26 (78.8)
Duration of Response Follow-up, months				
Median	7.5	8.2	7.4	7.4

Median DOR and DOR follow-up estimated using the Kaplan-Meier method

[#] Eligible patients include 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 SCE SAP)

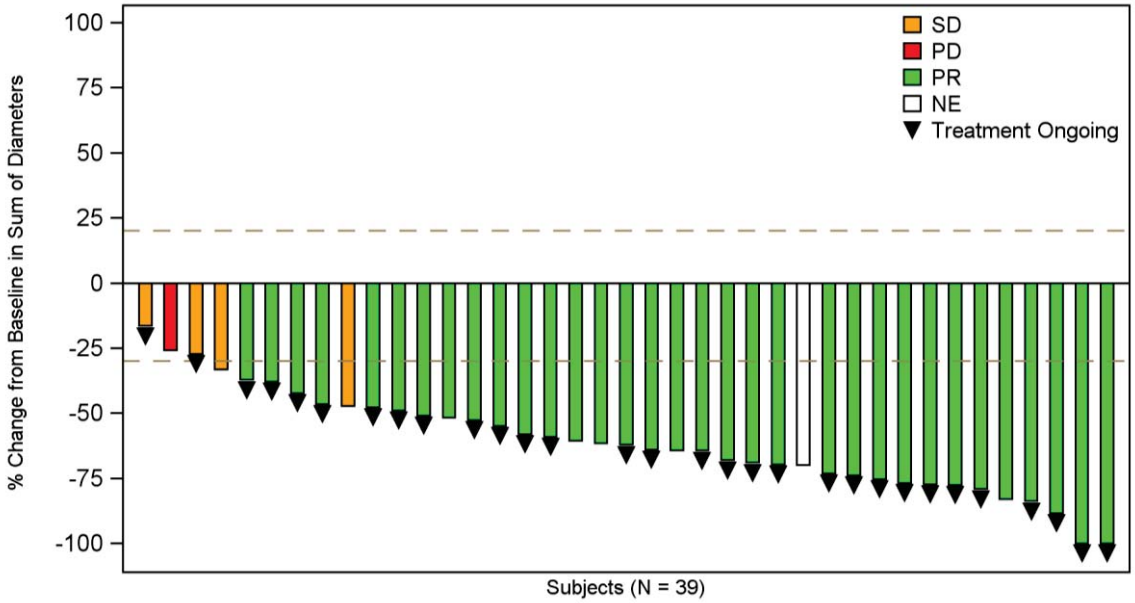
Source: Original NDA Module 2.5 (NSCLC) Table 4; 60-Day Update SCE (NSCLC) Tables 14.3.1.3, 14.3.1.4, 14.3.3.3, 14.3.3.4

Figure 8.6 Original NDA: Waterfall Plot of Best Change in Tumor Burden Based on IRC Assessment – Treatment-naive *RET* Fusion-positive NSCLC Patients with ≥ 6 Months Follow-up



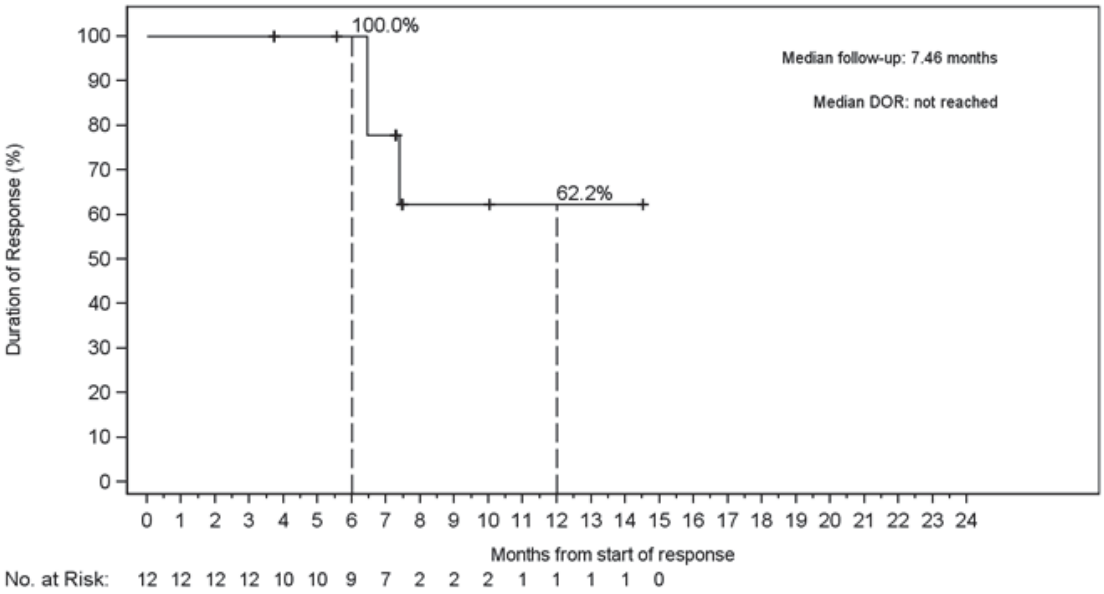
Source: Original NDA Module 5.3.5.3 SCE (NSCLC) Figure 14.2.3

Figure 8.7 **60-Day Update: Waterfall Plot of Best Change in Tumor Burden Based on IRC Assessment –Treatment-naive *RET* Fusion-positive NSCLC Patients**



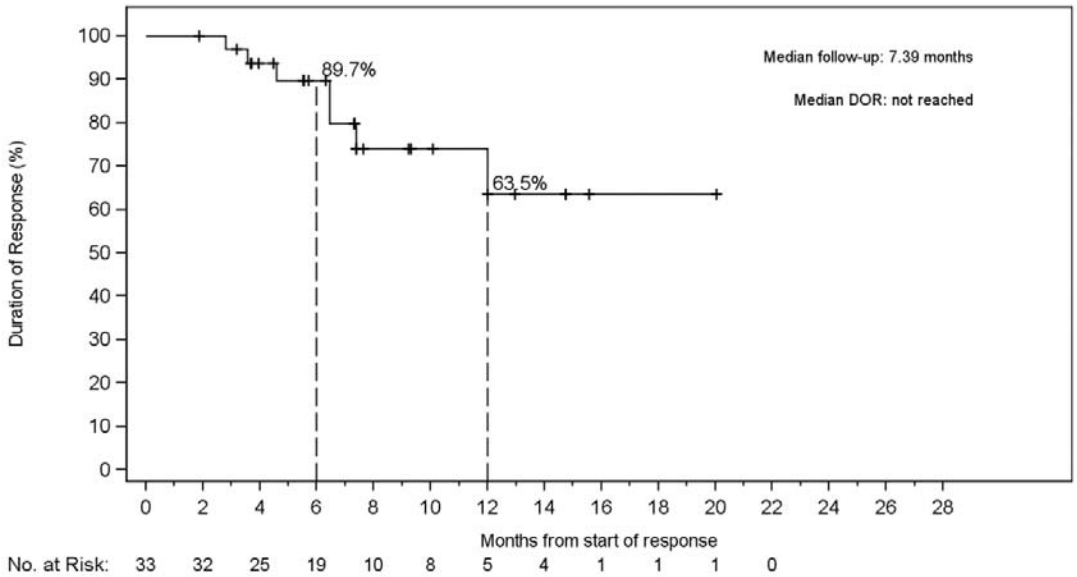
Source: 60-Day Update SCE (NSCLC) Figure 14.2.3

Figure 8.8 **Original NDA: Kaplan-Meier Plot of Duration of Response Based on IRC Assessment –Treatment-naïve *RET* Fusion-positive NSCLC with ≥ 6 Months Follow-up**



Source: Original NDA Module 5.3.5.3 SCE (NSCLC) Figure 14.3.3

Figure 8.9 60-Day Update: Kaplan-Meier Plot of Duration of Response Based on IRC Assessment –Treatment-naïve *RET* Fusion-positive NSCLC



Source: 60-Day Update SCE (NSCLC) Figure 14.3.3

The FDA's Assessment:

FDA agrees with applicant's results provided above. FDA has following additional comments regarding the efficacy results presented:

- Given the small number of patients who had CNS metastases at baseline per IRC (n=11) the results pertaining to CNS ORR should be interpreted cautiously.
- Note that results for durability of responses, categorized as < 6 months, ≥ 6 – 12 months, ≥ 12 – 18 months, and ≥ 18 – 24 months, as presented in the current and subsequent sections, are based on observed durations and not KM estimate.
- [redacted] (b) (4) The duration of response was described by the number of patients who had responses of at least 6 months in duration.

RET Fusion-Positive Thyroid Cancer Efficacy Data
[60-Day Update SCE (NSCLC) Tables 14.3.1.3, 14.3.1.4, 14.3.3.3, 14.3.3.4]

As of the 17 June 2019 data cutoff date for the Original NDA, 27 patients with *RET* fusion-positive thyroid cancer had been treated with selpercatinib, of whom 19 had received a prior systemic therapy other than RAI (hereafter referred to as "previously treated"). Histology for these 19 patients included papillary (n = 13), poorly differentiated (n = 3), anaplastic (n = 2), and Hurthle cell (n = 1).

The other 8 patients (all papillary) received no other prior systemic therapy other than RAI (hereafter referred to as "systemic therapy naïve").

Table 8.15 summarizes the histology and prior systemic therapy of patients with *RET* fusion-positive thyroid cancer.

Table 8.15 Original NDA and 60-Day Update: Histology and Prior Therapy in *RET* Fusion-positive Thyroid Cancer

Histology	Previously Treated[1]	Systemic Therapy Naïve[2]
Papillary	13	8
Poorly Differentiated	3	0
Anaplastic	2	0
Hurthle Cell	1	0
Total	19	8

[1] ≥ 1 systemic therapy in addition to RAI
[2] No prior systemic therapy other than RAI
Source: Original NDA Module 2.7.3 (NSCLC) Table 39 and Module 5.3.5.3 SCE (NSCLC) Table 14.2.2; 60-Day Update SCE (NSCLC) Table 4.2.2

As of the 17 June 2019 data cutoff for the Original NDA, a total of 15 of the 19 previously treated *RET* fusion-positive thyroid cancer patients, and 3 of the 8 systemic therapy naïve RET fusion-positive thyroid cancer patients had at least 6 months follow-up from first selpercatinib dose and were characterized for efficacy (Table 8.16 and Table 8.17). As of the 60-Day Update, all 19 previously treated *RET* fusion-positive thyroid cancer patients and all 8 systemic therapy naïve RET fusion-positive thyroid cancer patients have been evaluated for response and had the opportunity to be followed for at least 6 months follow up from first dose.

In the Original NDA, for the 15 patients with previously treated *RET* fusion-positive thyroid cancer, the ORR was 86.7% (13/15; 95% CI: 59.5, 98.3) by IRC and 66.7% (10/15; 95% CI: 38.4, 88.2) by investigator (Table 8.16). In this 60-Day Update, for the 19 patients with previously treated RET fusion-positive thyroid cancer, the ORR was 78.9% (15/19; 95% CI: 54.4, 93.9) by

IRC, and was 57.9% (11/19; 95% CI: 33.5, 79.7) by Investigator. In the Original NDA, the median DOR by IRC was not reached (95% CI: 7.6 months, NE), median DOR follow-up of 12.1 months and 3/13 (23%) events observed; the median DOR by investigator assessment was not reached (95% CI: 4.7 months, NE), with median DOR follow-up of 14.8 months and 2/10 (20%) events observed. In the 60-Day Update, the median DOR by IRC was 18.4 months (15/19; 95% CI: 7.6, NE), with median DOR follow-up of 17.5 months and 6/15 (40.0%) events observed; the median DOR by investigator assessment was not reached (95% CI: 9.5, NE), with median DOR follow-up of 17.5 months and 3/11 (27.3%) events observed.

In the Original NDA, for the 3 patients with treatment naïve *RET* fusion-positive thyroid cancer, the ORR was 100% (3/3; 95% CI: 29.2, 100.0) by IRC and 67% (2/3; 95% CI: 9.4, 99.2) by investigator assessment; all responders by IRC were still in response by both the IRC and investigator (Table 8.17). In the 60-Day Update, for the 8 patients with treatment naïve *RET* fusion-positive thyroid cancer, the ORR was 100% (8/8; 95% CI: 63.1, 100) by IRC, and was 75.0% (6/8; 95% CI: 34.9, 96.8) by Investigator. All responders were still in response by both the IRC and investigator.

A waterfall plot illustrating the best change in tumor size per RECIST v1.1 based on IRC assessment is shown below in

Figure 8.10 and Figure 8.11. The Kaplan-Meier plot of DOR based on IRC assessment is shown in Figure 8.12 and Figure 8.13.

Table 8.16 Original NDA and 60-Day Update: Objective Response Rate and Duration of Response for Previously Treated *RET* Fusion-positive Thyroid Cancer[1]

	Original NDA		60-Day Update	
	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment
No. of patients	19	19	19	19
No. of eligible# patients	15	15	19	19
Best Overall Response, n (%)				
Complete response	0	0	1 (5.3)	0
Partial response	13 (86.7)	10 (66.7)	14 (73.7)	11 (57.9)
Objective Response Rate (confirmed CR/PR), n (%)				
ORR	13 (86.7)	10 (66.7)	15 (78.9)	11 (57.9)
(95% confidence interval)	(59.5, 98.3)	(38.4, 88.2)	(54.4, 93.9)	(33.5, 79.7)
Duration of Response, months				

	Original NDA		60-Day Update	
	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment
No. of patients with response	13	10	15	11
Median (95% confidence interval)	NE (7.6, NE)	NE (4.7, NE)	18.4 (7.6, NE)	NE (9.5, NE)
Minimum, Maximum	1.9+, 17.2+	3.8+, 18.4+	1.9, 24.0+	4.7, 24.0+
Duration of Response, n (%)				
< 6 months	3 (23.1)	3 (30.0)	2 (13.3)	1 (9.1)
≥ 6 – 12 months	5 (38.5)	3 (30.0)	6 (40.0)	5 (45.5)
≥ 12 – 18 months	5 (38.5)	3 (30.0)	4 (26.7)	2 (18.2)
≥ 18 – 24 months	0	1 (10.0)	3 (20.0)	3 (27.3)
≥ 24 months	0	0	0	0
Response Status, n (%)				
Disease progression	3 (23.1)	2 (20.0)	4 (26.7)	3 (27.3)
Died	0	0	2 (13.3)	0
Censored	10 (76.9)	8 (80.0)	9 (60.0)	8 (72.7)
Duration of Response Follow-up, months				
Median	12.1	14.8	17.5	17.5

Median DOR and DOR follow-up estimated using the Kaplan-Meier method

[#] Eligible patients include 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).

[1] ≥ 1 systemic therapy in addition to RAI

Source: Original NDA Module 2.7.3 (NSCLC) Tables 40 and 41; 60-Day Update SCE (NSCLC) Tables 14.3.1.3, 14.3.1.4, 14.3.3.3, 14.3.3.4

Table 8.17 Original NDA and 60-Day Update: Objective Response Rate and Duration of Response for Systemic Therapy Naïve *RET* Fusion-positive Thyroid Cancer[1]

	Original NDA		60-Day Update	
	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment
No. of patients	8	8	8	8
No. of eligible[#] patients	3	3	8	8
Best Overall Response, n (%)				
Complete response	1 (33.3)	0	1 (12.5)	0

	Original NDA		60-Day Update	
	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment
Partial response	2 (66.7)	2 (66.7)	7 (87.5)	6 (75.0)
Objective Response Rate (confirmed CR/PR), n (%)				
ORR	3 (100)	2 (66.7)	8 (100)	6 (75.0)
(95% confidence interval)	(29.2, 100)	(9.4, 99.2)	(63.1, 100)	(34.9, 96.8)
Duration of Response, months				
No. of patients with response	3	2	8	6
Median (95% confidence interval)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Minimum, Maximum	3.7+, 8.5+	7.6+, 8.5+	3.9+, 13.0+	3.9+, 13.0+
Duration of Response, n (%)				
< 6 months	2 (66.7)	0	2 (25.0)	2 (33.3)
≥ 6 – 12 months	1 (33.3)	2 (100)	5 (62.5)	2 (33.3)
≥ 12 – 18 months	0	0	1 (12.5)	2 (33.3)
Response Status, n (%)				
Disease progression	0	0	0	0
Censored	3 (100)	2 (100)	8 (100)	6 (100)
Duration of Response Follow-up, months				
Median	5.6	8.0	8.8	7.7

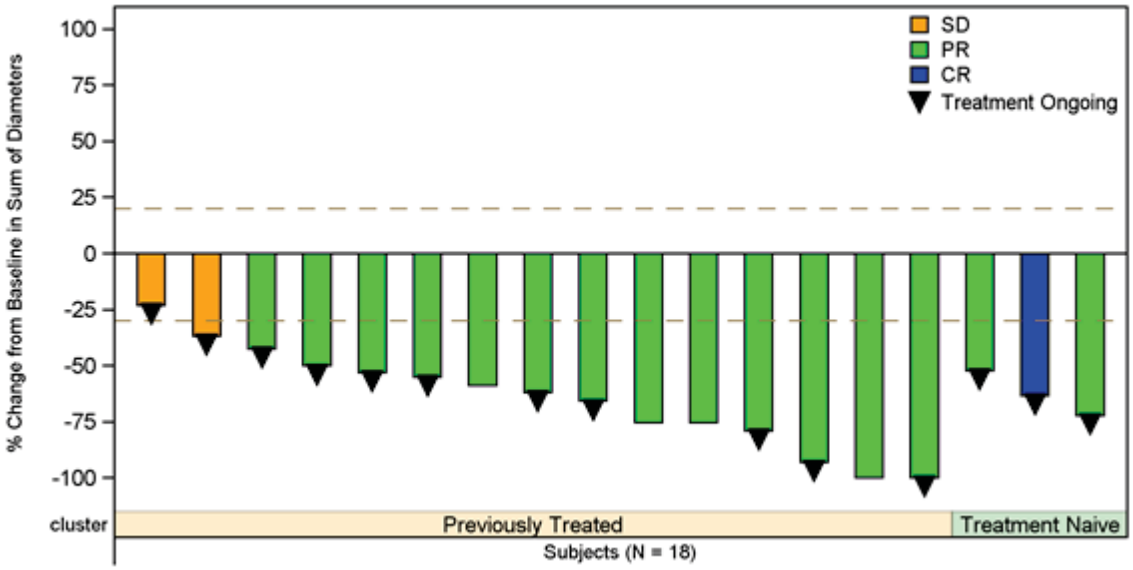
Median DOR and DOR follow-up estimated using the Kaplan-Meier method

[#] Eligible patients include 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).

[1] No prior systemic therapy other than RAI

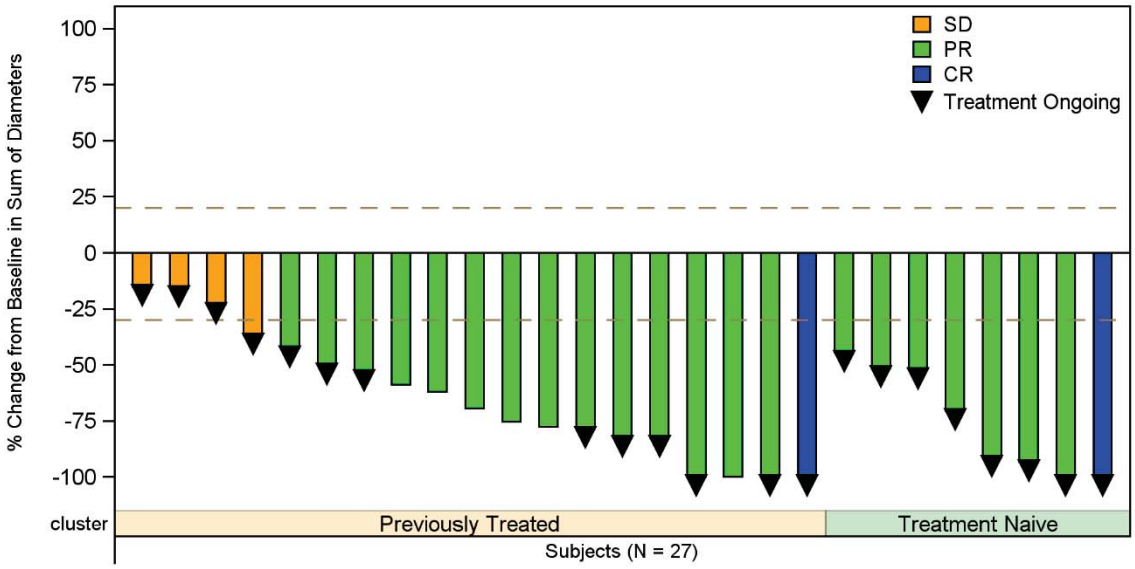
Source: Original NDA Module 2.7.3 (NSCLC) Tables 40 and 41; 60-Day Update SCE (NSCLC) Tables 14.3.1.3, 14.3.1.4, 14.3.3.3, 14.3.3.4

Figure 8.10 Original NDA: Waterfall Plot of Best Change in Tumor Burden Based on IRC Assessment – *RET* Fusion-positive Thyroid Cancer Patients with ≥ 6 Months Follow-up



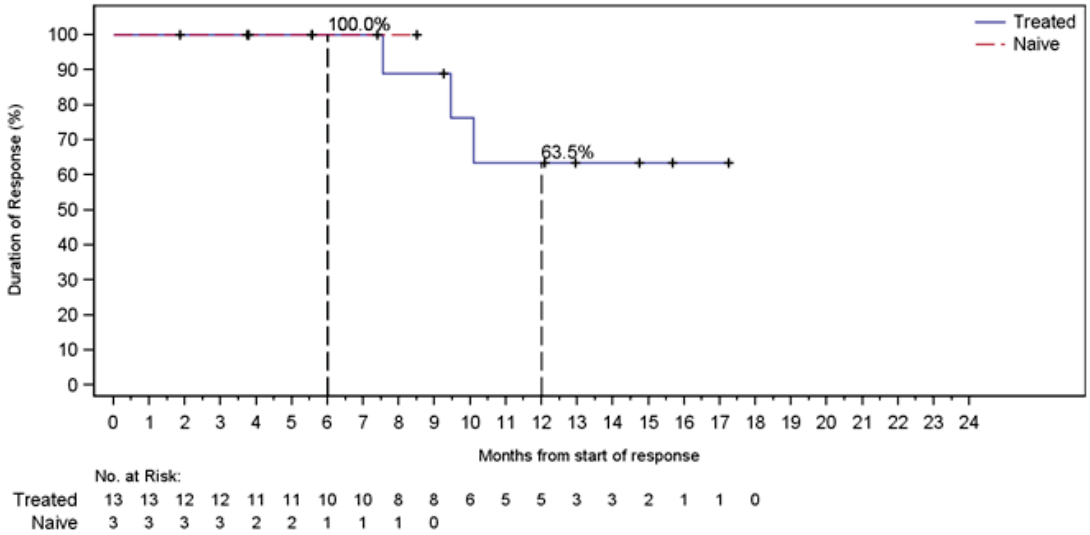
Source: Original NDA Module 5.3.5.3 SCE (NSCLC) Figure 14.2.3

Figure 8.11 60-Day Update: Waterfall Plot of Best Change in Tumor Burden Based on IRC Assessment – *RET* Fusion-positive Thyroid Cancer Patients



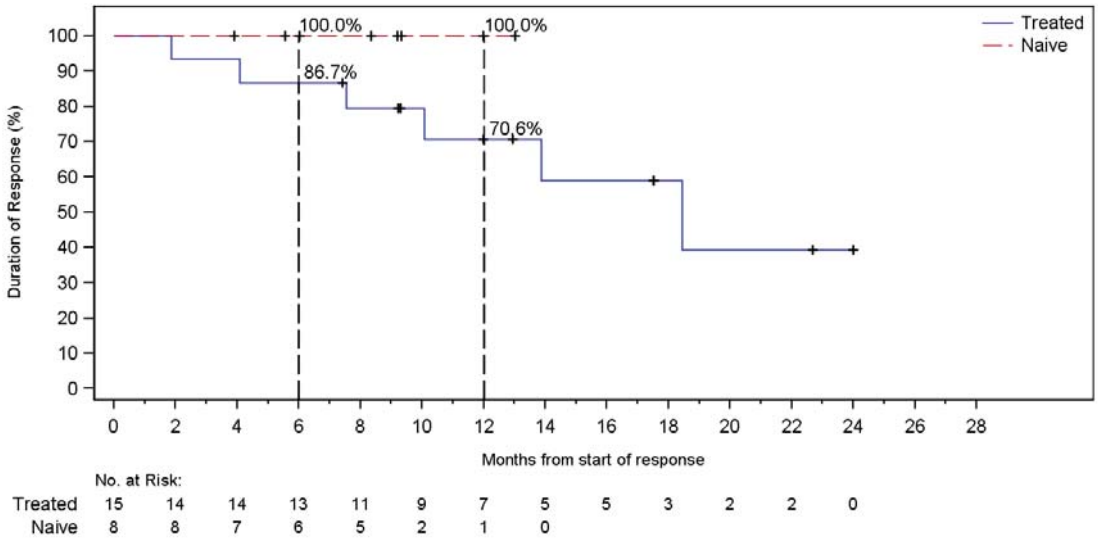
Source: 60-Day Update SCE (NSCLC) Figure 14.2.3

Figure 8.12 Original NDA: Kaplan-Meier Plot of Duration of Response Based on IRC Assessment – *RET* Fusion-positive Thyroid Cancer Patients with ≥ 6 Months Follow-up



Source: Original NDA Module 5.3.5.3 SCE (NSCLC) Figure 14.3.3

Figure 8.13 60-Day Update: Kaplan-Meier Plot of Duration of Response Based on IRC Assessment – *RET* Fusion-positive Thyroid Cancer Patients



Source: 60-Day Update SCE (NSCLC) Figure 14.3.3

The FDA's Assessment:

Overall, patients with RET fusion-positive thyroid cancer had received a range of 1 – 7 prior therapies and a median of three prior therapies.

The majority of the patients had received radioactive iodine and were deemed inappropriate candidates for further RAI for one of the following reasons:

- No iodine update on post-RAI scan
- Received a cumulative RAI dose of ≥ 600 mCI
- Demonstrated one or more measurable lesions that progressed (per RECIST 1.1) within 12 months of 131I therapy, despite demonstration of radioiodine avidity at the time of pre- or post-treatment scan
- FDG avidity demonstrated on PET CT and investigator judgement that patients with FDG-avid tumors do not respond to RAI
- Active brain metastases
- Patient received 515 mCi RAI and had abnormal PFTs and concern for radiation fibrosis
- Unknown (includes one patient with "previously treated" disease)

The subset of patients termed "previously treated" includes patients who received RAI and a subsequent therapy (n=16) and those who were ineligible for RAI and received systemic therapy (n=3). Reasons for not receiving RAI included anaplastic histology and not having undergone thyroidectomy due to widespread metastatic disease. The most common histology in this group was PTC (n=13). All but one patient with PTC received at least one prior TKI, including the TKIs approved in this population: sorafenib (n=4), lenvatinib (5) or both (n=1). Other therapies included cabozantinib (n=1), vandetanib (n=1), anti-PD-1 therapy (n=3) and other therapies.

Prior therapies received by patients with anaplastic thyroid cancer (n=2) included prior taxane chemotherapy (both patients) and prior radioactive iodine (one patient). The remainder of patients had Hurthle cell (n=1) and poorly-differentiated (n=3) histologies; all of these patients had had prior systemic therapy, 75% had had prior cancer surgery, and 50% had prior radiation therapy. 75% had prior treatment with a kinase inhibitor (including sorafenib, lenvatinib, or other), and 50% had prior chemotherapy.

FDA notes that Table 8.16 originally contained an error. An updated table was provided by the Applicant and replaced by FDA.

Additional comments regarding the efficacy results presented:

- Note that results for durability of responses, categorized as < 6 months, ≥ 6 – 12 months, and ≥ 12 – 18 months, are based on observed durations and not KM estimate.
- (b) (4)

(b) (4)

The duration of response was described by the number of patients who had responses of at least 6 months in duration.

ORR and DOR by Subpopulations [Original NDA Module 2.7.3.5.1.5 (NSCLC); 60-Day Update Tables 14.3.1.1, 14.3.3.1, 14.3.9.1, 14.3.9.3]

ORR and DOR was analyzed by several demographic variables using IRC assessment (Table 8.18). The ORR and DOR by age was similar in both the Original NDA and the 60-Day Update. Females had a moderately higher response rate than males, and the DOR was not reached in both the Original NDA and 60-Day Update, whereas males had a median DOR of 12.5 months. The ORR and DOR by race also appeared largely similar as presented in Table 8.18.

Table 8.18 Original NDA and 60-Day Update: ORR and DOR by Demographics Based on IRC Assessment

	Original NDA				60-Day Update			
	N	Responders	ORR, % (95% CI)	DOR, months (Range)	N	Responders	ORR, % (95% CI)	DOR, months (Range)
Overall	105	65	61.9 (51.9, 71.2)	12.45 (1.8+, 20.2+)	105	67	63.8 (53.9, 73.0)	17.51 (1.9+, 26.2+)
Age								
< 65 years	69	46	66.7 (54.3, 77.6)	12.02 (1.9+, 20.2+)	69	46	66.7 (54.3, 77.6)	17.51 (1.9+, 26.2+)
≥ 65 years	36	19	52.8 (35.5, 69.6)	12.45 (1.8+, 18.5+)	36	21	58.3 (40.8, 74.5)	14.65 (4.7, 24.0+)
Sex								
Male	43	21	48.8 (33.3, 64.5)	12.45 (3.6+, 12.5)	43	23	53.5 (37.7, 68.8)	12.45 (1.9+, 14.8+)
Female	62	44	71.0 (58.1, 81.8)	NR (1.8+, 20.2+)	62	44	71.0 (58.1, 81.8)	NR (1.9+, 26.2+)
Race								
White	55	35	63.6 (49.6, 76.2)	12.02 (1.9+, 20.2+)	55	36	65.5 (51.4, 77.8)	17.51 (1.9+, 26.2+)
Asian	40	23	57.5 (40.9, 73.0)	10.35 (1.8+, 10.4)	40	24	60.0 (43.3, 75.1)	NR (1.9+, 14.8+)
Other	10	7	70.0 (34.8, 93.3)	NR (3.5, 11.9+)	10	7	70.0 (34.8, 93.3)	14.65 (3.5, 14.8+)

Source: Original NDA Module 5.3.5.3 SCE (NSCLC) Tables 14.3.1.1, 14.3.3.1, 14.3.9.1; 60-Day Update SCE (NSCLC) Tables 14.3.1.1, 14.3.3.1, 14.3.9.1

ORR and DOR by fusion partner are presented in Table 8.19. In both the Original NDA and the 60-Day Update, responses were seen in almost all fusion partners with the exception of CCDC88C and TRIM24. However, both fusion partners only had 1 patient each, making it challenging to draw conclusions.

ORR and DOR by type of molecular test are also presented in Table 8.19. In both the Original NDA and the 60-Day Update, ORR and DOR were similar across all types of tests.

Table 8.19 Original NDA and 60-Day Update: ORR and DOR by *RET* Fusion Partner and Type of Molecular Assay Based on IRC Assessment

	Original NDA				60-Day Update			
	N	Responders	ORR, % (95% CI)	DOR, months (Range)	N	Responders	ORR, % (95% CI)	DOR, months (Range)
Overall	105	65	61.9 (51.9, 71.2)	12.45 (1.8+, 20.2+)	105	67	63.8 (53.9, 73.0)	17.51 (1.9+, 26.2+)
RET Fusion Partner								
KIF5B	59	33	55.9 (42.4, 68.8)	12.45 (1.8+, 18.5+)	59	34	57.6 (44.1, 70.4)	NR (1.9+, 24.0+)
CCDC6	24	18	75.0 (53.3, 90.2)	11.04 (1.9+, 12.0+)	24	19	79.2 (57.9, 92.9)	14.65 (1.9+,17.8+)
NCOA4	2	1	PR, NE	NR (8.3+)	2	1	PR, NE (NA)	NR (13.86+)
Other	8	4	50.0 (15.7, 84.3)	NR (5.6, 9.2+)	8	4	50.0 (15.7, 84.3)	10.17 (5.6, 14.6+)
KIAA1468	2	0	SD, SD	Not applicable	2	0	SD, SD	Not applicable
ARHGAP12	1	1	PR	NR (9.2+)	1	1	PR	NR (14.6+)
CCDC88C	1	0	SD	Not applicable	1	0	SD	Not applicable
CLIP1	1	1	PR	5.55 (5.6)	1	1	PR	5.55 (5.6)
PRKAR1A	1	1	PR	NR (9.1+)	1	1	PR	12.02 (12.0)
RBPM and DOCK1	1	1	PR	8.31 (8.3)	1	1	PR	8.31 (8.3)
TRIM24	1	0	SD	Not applicable	1	0	SD	Not applicable
Unknown	12	9	75.0 (42.8, 94.5)	NR (3.7, 20.2+)	12	9	75.0 (42.8, 94.5)	12.12 (3.7, 26.2+)
Type of Molecular Assay								
NGS on blood or plasma	8	6	75.0 (34.9, 96.8)	11.04 (4.5+, 12.5)	9	6	66.7 (29.9, 92.5)	9.61 (4.7, 14.7)
NGS on tumor	86	51	59.3 (48.2, 69.8)	NR (1.8+, 18.5+)	85	53	62.4 (51.2, 72.6)	NR (1.9+, 24.0+)
PCR	2	2	PR, PR	NR (3.9+, 7.4+)	2	2	PR, PR	NR (9.2+, 14.8+)
FISH	9	6	66.7 (29.9, 92.5)	6.83 (3.7, 20.2+)	9	6	66.7 (29.9, 92.5)	9.48 (3.7, 26.2+)

Source: Original NDA Module 5.3.5.3 SCE (NSCLC) Tables 14.3.1.1, 14.3.3.1, 14.3.9.1, 14.3.9.3; 60-Day

Update SCE (NSCLC) Tables 14.3.1.1, 14.3.3.1, 14.3.9.1, 14.3.9.3

ORR and DOR by number of prior therapy or type of prior therapy are presented in Table 8.20. In patients with 1–2 prior therapies, the ORR in the Original NDA was lower than patients with 3 or more therapies. This trend continued in the 60-Day Update. In both the Original NDA and the 60-Day Update, the ORR for patients with or without prior anti-PD-1/PD-L1 therapy or prior MKI therapy did not appear different. With longer follow-up, some subgroups had a median DOR changed from reached to not reached and vice versa, likely due to a change in the number of events and duration of follow-up for each subgroup.

Table 8.20 Original NDA and 60-Day Update: ORR and DOR by Number and Type of Prior Therapy Based on IRC Assessment

	Original NDA				60-Day Update			
	N	Responders	ORR, % (95% CI)	DOR, months (Range)	N	Responders	ORR, % (95% CI)	DOR, months (Range)
Overall	105	65	61.9 (51.9, 71.2)	12.45 (1.8+, 20.2+)	105	67	63.8 (53.9, 73.0)	17.51 (1.9+, 26.2+)
Number of Prior Therapies								
1-2	46	23	50.0 (34.9, 65.1)	NR (3.5, 18.5+)	46	27	58.7 (43.2, 73.0)	17.51 (1.9+,18.5+)
3+	59	42	71.2 (57.9, 82.2)	12.0 (1.8+, 20.2+)	59	40	67.8 (54.4, 79.4)	NR (1.9+, 26.2+)
Prior Anti-PD-1/PD-L1 Therapy								
Yes	58	38	65.5 (51.9, 77.5)	12.45 (1.8+, 20.2+)	58	38	65.5 (51.9, 77.5)	NR (1.9+,26.2+)
No	47	27	57.4 (42.2, 71.7)	NR (3.5, 18.4+)	47	29	61.7 (46.4, 75.5)	17.51 (2.8+,24.0+)
Prior Multikinase Inhibitor								
Yes	50	32	64.0 (49.2, 77.1)	12.45 (3.6+, 20.2+)	50	32	64.0 (49.2,77.1)	NR (1.9+,26.2+)
No	55	33	60.0 (45.9, 73.0)	12.02 (1.8+, 18.5+)	55	35	63.64 (49.64, 76.2)	17.51 (1.9+,18.5+)

Source: Original NDA Module 5.3.5.3 SCE (NSCLC) Tables 14.3.1.1, 14.3.3.1, 14.3.9.1; 60-Day Update SCE (NSCLC) Tables 14.3.1.1, 14.3.3.1, 14.3.9.1

The ORR and DOR by other baseline disease characteristics are presented in Table 8.21. The ORR was trending higher in both in the Original NDA and the 60-Day Update in patients with a ECOG 0 than patients with ECOG 1-2. In addition, the DOR remained consistent for both

subpopulations between the two data cutoffs. ORR by smoking status was largely similar. DOR was 7.7 and 11.0 months at the Original NDA and 60-Day Update, respectively, for smokers, and not reached for non-smokers. ORR and DOR by metastatic disease at baseline was difficult to characterize due to the low number of patients. ORR for patients with CNS metastasis at baseline was largely similar in both the Original NDA and the 60-Day Update.

Table 8.21 Original NDA and 60-Day Update: Duration of Response by Additional Baseline Disease Characteristics Based on IRC Assessment

	Original NDA				60-Day Update			
	N	Responders	ORR, % (95% CI)	DOR, months (Range)	N	Responders	ORR, % (95% CI)	DOR, months (Range)
Overall	105	65	61.9 (51.9, 71.2)	12.45 (1.8+, 20.2+)	105	67	63.8 (53.9, 73.0)	17.51 (1.9+, 26.2+)
ECOG								
0	31	22	71.0 (52.0, 85.8)	NR (1.9+, 20.2+)	31	23	74.2 (55.4, 88.1)	NR (7.4+, 20.2+)
1-2	74	43	58.1 (46.1, 69.5)	11.04 (1.8+, 18.5+)	74	44	59.5 (47.4, 70.7)	12.12 (1.9+, 24.0+)
Smoking Status								
Never Smoked	75	48	64.0 (52.1, 74.8)	NR (1.8+, 20.2+)	75	50	66.7 (54.8, 77.1)	NR (1.9+, 26.2+)
Smoker	30	17	56.7 (37.4, 74.5)	7.72 (1.9+, 18.4+)	30	17	56.7 (37.4, 74.5)	11.04 (3.7, 24.0+)
Any Metastatic Disease								
Yes	103	63	61.2 (51.1, 70.6)	12.45 (1.8+, 20.2+)	103	65	63.1 (53.0,72.4)	17.51 (1.9+, 26.2+)
No	2	2	PR, PR	NR (3.7+, 3.9+)	2	2	PR, PR	NR (9.2+)
CNS Metastasis at Baseline by Investigator								
Yes	37	22	59.5 (42.1, 75.3)	NR (3.6+, 18.5+)	38	24	63.2 (46.0, 78.2)	17.51 (1.9+, 24.0+)
No	68	43	63.2 (50.7, 74.6)	12.02 (1.8+, 20.2+)	67	43	64.2 (51.5, 75.5)	NR (1.9+, 26.2+)

Source: Original NDA Module 5.3.5.3 SCE (NSCLC) Tables 14.3.1.1, 14.3.3.1, 14.3.9.1; 60-Day Update SCE (NSCLC) Tables 14.3.1.1, 14.3.3.1, 14.3.9.1

The FDA's Assessment:

FDA agrees with applicant's results; however, results for the subgroups with small sample size, such as subgroup of patients with certain *RET* fusion partner, type of

molecular assay, and with no metastatic disease, the estimated medians may not adequately characterize the DOR results.

Preliminary responses were observed in exploratory subgroups of *RET* fusion-positive thyroid cancer of non-papillary histology (n=6) included in the *RET* fusion-positive thyroid efficacy population; partial responses occurred in patients with anaplastic (1 of 2 patients), Hurthle cell (1 of 1 patient), and poorly-differentiated (2 of 3 patients) histologies. However, given that there are too few patients in each of these histological subgroups other than papillary thyroid cancer, the results should be interpreted with caution.

8.1.2.2 *RET*-mutant MTC Results

Patient Disposition
[[Original NDA Module 2.7.3.4.1 (MTC); 60-Day Update SCE (MTC) Tables 14.1.2]

Table 8.22 and Table 8.23 present patient disposition for *RET*-mutant MTC.

Of the 226 patients with *RET*-mutant MTC in the Original NDA, 200 patients (88.5%) were still on treatment as of the Original NDA data cutoff (17 June 2019) and 186 patients (82.3%) were still on treatment as of this 60-Day Update (data cutoff 16 December 2019).

In the Original NDA, in the PAS of 55 patients with *RET*-mutant MTC, 40 patients (72.73%) were still on treatment, and 102 patients (82.3%) in the IAS were still on treatment; 13 patients (23.6%) stayed on treatment post-progression at the discretion of the investigator. In the 60-Day Update, 37 patients (67.3%) were still on treatment, and 92 patients (74.2%) in the IAS were still on treatment; 17 patients (30.9%) stayed on treatment post-progression at the discretion of the investigator.

Of the 88 patients with cabozantinib/vandetanib-naïve *RET*-mutant MTC (SAS1) in the Original NDA, 84 patients (95.5%) were still on treatment; in the 60-Day Update, 81 patients (92.0%) were still on treatment. For all patients with *RET*-mutant MTC, the most common reason for discontinuation was disease progression in the Original NDA (12/226, 5.3%) and also in the 60-Day Update (18/226, 8.0%). A similar trend was observed in patient discontinuation due to disease progression within PAS in the Original NDA (7/55, 12.7%) and also in the 60-Day Update (9/55, 16.4%) (Table 8.23).

Table 8.22 Original NDA: Patient Disposition for *RET*-mutant MTC

	PAS (a subset of IAS)	IAS Prior cabozantinib or vandetanib	SAS1 cabozantinib/ vandetanib-naïve	SAS2 Non-measurable Disease	Total
Treated	55	124	88	14	226
Treatment ongoing, n (%)	40 (72.7)	102 (82.3)	84 (95.5)	14 (100)	200 (88.5)
Treatment discontinued, n (%)	15 (27.3)	22 (17.7)	4 (4.5)	0	26 (11.5)
Disease progression	7 (12.7)	11 (8.9)	1 (1.1)	0	12 (5.3)
Adverse event	2 (3.6)	3 (2.4)	3 (3.4)	0	6 (2.7)
Withdrawal of consent	1 (1.8)	3 (2.4)	0	0	3 (1.3)
Death	2 (3.6)	2 (1.6)	0	0	2 (0.9)
Other	3 (5.5)	3 (2.4)	0	0	3 (1.3)
Treated post-progression, n (%)	13 (23.6)	16 (12.9)	0	0	16 (7.1)
Study status continuing, n (%)	43 (78.2)	106 (85.5)	87 (98.9)	14 (100)	207 (91.6)
Study status discontinued, n (%)	12 (21.8)	18 (14.5)	1 (1.1)	0	6 (2.7)
Withdrawal of consent	3 (5.5)	6 (4.8)	0	0	6 (2.7)
Lost to follow-up	1 (1.8)	1 (0.8)	0	0	1 (0.4)
Death	8 (14.5)	11 (8.9)	1 (1.1)	0	12 (5.3)

Source: Original NDA Module 2.7.3 (MTC) Table 7

Table 8.23 60-Day Update: Patient Disposition for *RET*-mutant MTC

	PAS (a subset of IAS)	IAS Prior cabozantinib or vandetanib	SAS1 cabozantinib/ vandetanib-naïve	SAS2 Non-measurable Disease	Total
Treated	55	124	88	14	226
Treatment ongoing, n (%)	37 (67.3)	92 (74.2)	81 (92.0)	13 (92.9)	186 (82.3)
Treatment discontinued, n (%)	18 (32.7)	32 (25.8)	7 (8.0)	1 (7.1)	40 (17.7)
Disease progression	9 (16.4)	17 (13.7)	1 (1.1)	0	18 (8.0)
Adverse event	4 (7.3)	7 (5.6)	4 (4.5)	0	11 (4.9)
Intercurrent Illness Compromising Ability to Fulfill Protocol Requirements	0	1 (0.8)	0	0	1 (0.4)
Requirement for Alternative Treatment per Investigator	0	0	1 (1.1)	1 (7.1)	2 (0.9)

	PAS (a subset of IAS)	IAS Prior cabozantinib or vandetanib	SAS1 cabozantinib/ vandetanib-naïve	SAS2 Non-measurable Disease	Total
Withdrawal of consent	1 (1.8)	2 (1.6)	1 (1.1)	0	3 (1.3)
Death	2 (3.6)	3 (2.4)	0	0	3 (1.3)
Other	2 (3.6)	2 (1.6)	0	0	2 (0.9)
Treated post-progression, n (%)	17 (30.9)	25 (20.2)	3 (3.4)	0	28 (12.4)
Study status continuing, n (%)	41 (74.5)	99 (79.8)	85 (96.6)	14 (100.0)	198 (87.6)
Study status discontinued, n (%)	14 (25.5)	25 (20.2)	3 (3.4)	0	28 (12.4)
Withdrawal of consent	3 (5.5)	6 (4.8)	1 (1.1)	0	7 (3.1)
Lost to follow-up	1 (1.8)	1 (0.8)	0	0	1 (0.4)
Death	10 (18.2)	18 (14.5)	2 (2.3)	0	20 (8.8)

Source: 60-Day Update SCE (MTC) Table 14.1.2

Demographic Characteristics

The efficacy analyses evaluated the same patients in the Original NDA and the 60-Day Update efficacy population; therefore the demographics and baseline characteristics were the same in the 60-Day Update and in the Original NDA with a few data updates as noted in the tables below.

The median age across all patients with *RET*-mutant MTC in the Original NDA and the 60-Day Update was 58 years and encompassed a wide range (15–90 years) (Table 8.24). For PAS patients, 49% were between the ages of 45 and 64 years. There were more males than females. The majority (88%) of *RET*-mutant MTC patients were white. Body weight had a median of 72.0 kg and ranging from 26.8 to 176.8 kg. The median BMI was 23.5 kg/m^2 and likewise displayed a wide range from 11.6 to 59.1 kg/m^2. Most patients had a baseline Eastern Cooperative Oncology Group (ECOG) of 0 or 1 (95%). [Original NDA Module 2.7.3.4.2 (MTC)]

Table 8.24 Original NDA and 60-Day Update: Demographics for *RET*-mutant MTC

	***RET*-mutant MTC**				
	PAS (a subset of IAS) N = 55	**IAS Prior cabozantinib or vandetanib N = 124**	**SAS1 cabozantinib/ vandetanib-naïve N = 88**	**SAS2 Non-measurable Disease N = 14**	**Total N = 226**
Age, years					

	RET-mutant MTC				
	PAS (a subset of IAS) N = 55	**IAS** Prior cabozantinib or vandetanib N = 124	**SAS1** cabozantinib/ vandetanib-naïve N = 88	**SAS2** Non-measurable Disease N = 14	**Total** N = 226
Median	57.0	57.5	58.0	60.5	58
Range	17-84	17-90	15-82	30-74	15-90
Overall age group, n (%)					
<18 years	1 (1.8)	1 (0.8)	2 (2.3)	0	3 (1.3)
18–44 years	9 (16.4)	21 (16.9)	20 (22.7)	5 (35.7)	46 (20.4)
45–64 years	27 (49.1)	59 (47.6)	43 (48.9)	6 (42.9)	108 (47.8)
65–74 years	12 (21.8)	32 (25.8)	14 (15.9)	3 (21.4)	49 (21.7)
≥ 75 years	6 (10.9)	11 (8.9)	9 (10.2)	0	20 (8.8)
Sex, n (%)					
Male	36 (65.6)	81 (65.3)	58 (65.9)	9 (64.3)	148 (65.5)
Female	19 (34.5)	43 (34.7)	30 (34.1)	5 (35.7)	78 (34.5)
Race, n (%)					
White	49 (89.1)	111 (89.5)	75 (85.2)*	13 (92.9)	199 (88.1)*
Black	1 (1.8)	2 (1.6)	1 (1.1)*	0	3 (1.3)*
Asian	0	1 (0.8)	4 (4.5)	1 (7.1)	6 (2.7)
Other/Missing	5 (9.1)	10 (8.1)	8 (9.1)	0	18 (8.0)
Ethnicity, n (%)					
Hispanic or Latino	4 (7.3)	9 (7.3)	2 (2.3)	1 (7.1)	12 (5.3)
Not Hispanic or Latino	50 (90.9)	111 (89.5)	84 (95.5)	13 (92.9)	208 (92.0)
Missing	1 (1.8)	4 (3.2)	2 (2.3)	0	6 (2.7)
Body weight (kg)					
Median	74.00	70.15	76.20	73.30	72.00
Range	42.30-176.80	36.50-176.80	26.80-148.30	48.10-110.70	26.80-176.80
Height (cm)					
n	55	120*	83	14	217*
Median	173.0	170.5*	172.0	174.5	172.0*
Range	150-196	150-196	150-199	159-203	150-203
Body mass index, kg/m^2					
n	55	120*	83	14	217*
Median	24.24	23.02*	24.85	24.93	23.55
Range	16.4-59.1	15.2-59.1	11.6-49.6	17.9-35.3	11.6-59.1
Baseline ECOG, n (%)					
0	11 (20.0)	31 (25.0)	43 (48.9)	8 (57.1)	82 (36.3)
1	41 (74.5)	84 (67.7)	42 (47.7)	6 (42.9)	132 (58.4)
2	3 (5.5)	9 (7.3)	3 (3.4)	0	12 (5.3)

Analysis set definitions: PAS = Primary Analysis Set; IAS = Prior Cabozantinib or Vandetanib; SAS1 = Cabozantinib/vandetanib-naïve; SAS2 = Non-measurable Disease.

Note: For *RET*- mutant MTC, the PAS includes the first 55 patients from IAS. The "Total" column is the sum of the IAS, SAS1, and SAS2.

Source: 60-Day Update SCE (MTC) Table 14.2.1
* Data updated in 60-Day Update

The FDA's Assessment:

FDA agrees with Applicant's results provided above. Refer to FDA comment in Section-8.1.2.1 (page -185) regarding the validation of results by FDA for the different analysis populations presented in this AA.

Baseline Disease Characteristics

For *RET*-mutant MTC PAS patients, the median time from diagnosis was 65.3 months (Table 8.25). Most patients (98%) in the PAS patients had metastatic disease at enrollment, 60% were diagnosed as stage 4. Next generation sequencing (NGS) on tumor samples was the most common method of determining *RET* mutation status. Almost all PAS patients had abnormal calcitonin levels and CEA levels at baseline.

As expected with MTC patients, the median calcitonin (4761.0 pg/mL) was elevated and ranging from 1 to 200,000 pg/ml. Similarly, the median CEA was 93.00 ng/mL ranging from 1.0 to 14515 ng/ml (Table 8.25). These features were similar across the other analysis sets.

The median time from diagnosis for all RET-mutant MTC patients was 59.8 months (Table 8.25). Among all RET-mutant MTC patients, the most common mutation was M918T, followed by extracellular cysteine mutations. [Original NDA Module 2.7.3.4.2 (MTC)].

Table 8.25 Original NDA and 60-Day Update: Baseline Disease Characteristics for *RET*-mutant MTC

Characteristic	*RET*-mutant MTC				
	PAS (a subset of IAS) N = 55	**IAS Prior cabozantinib or vandetanib N = 124**	**SAS1 cabozantinib/ vandetanib-naïve N = 88**	**SAS2 Non-measurable Disease N = 14**	**Total N = 226**
Primary Tumor Type, n (%)					
Medullary Thyroid Cancer	55 (100)	124 (100)	88 (100)	14 (100)	226 (100)
Stage at Initial Diagnosis, n (%)					
I	0	1 (0.8)	0	0	1 (0.4)
II	0	0	2 (2.3)	0	2 (0.9)
IIB	0	0	1 (1.1)	0	1 (0.4)
III	1 (1.8)	2 (1.6)	0	0	2 (0.9)
IIIA	1 (1.8)	1 (0.8)	0	0	1 (0.4)
IV	33 (60.0)	65 (52.4)*	42 (47.7)	6 (42.9)	113 (50.0)*
IVA	6 (10.9)	11 (8.9)	7 (8.0)	2 (14.3)	20 (8.8)
IVB	0	2 (1.6)	2 (2.3)	1 (7.1)	5 (2.2)
IVC	12 (21.8)	39 (31.5)*	31 (35.2)	5 (35.7)	75 (33.2)*
Missing	2 (3.6)	3 (2.4)	3 (3.4)	0	6 (2.7)
Time from Diagnosis, months					
Median	65.3	61.9	56.40	56.10	59.80
Range	3.3-417.9	3.3-454.6	1.4-522.8	5.3-428.7	1.4-522.8

Characteristic	*RET*-mutant MTC				
	PAS (a subset of IAS) N = 55	**IAS Prior cabozantinib or vandetanib N = 124**	**SAS1 cabozantinib/ vandetanib-naïve N = 88**	**SAS2 Non-measurable Disease N = 14**	**Total N = 226**
History of Metastatic Disease, n (%)					
Yes	54 (98.2)	123 (99.2)*	88 (100)*	13 (92.9)	224 (99.1)*
No	1 (1.8)	1 (0.8)*	0	1 (7.1)	2 (0.9)*
Time from Diagnosis of Metastatic Disease, months					
Median	43.35	50.00	44.55	35.20	48.10
Range	3.3-299.9	0.5-299.9	0.5-522.8	6.9-321.1	0.5-522.8
Presence of Diarrhea at Baseline, n (%)					
Yes	33 (60.0)	77 (62.1)	55 (62.5)*	7 (50.0)	139 (61.5)*
No	22 (40.0)	47 (37.9)	33 (37.5)*	7 (50.0)	87 (38.5)*
Calcitonin (pg/ml)					
n	54	123	88	14	225
Median	6364.5	4969.0	4956.5	3821.2	4761.0
Range	66-169521	1-200000	51-151354	185-82106	1-200000
CEA (ng/ml)					
n	55	124	87	14	225
Median	151.90	133.55	61.80	31.45	93.00
Range	2.3-12412.0	1.7-12412.0	1.0-14515.0	3.5-551.2	1.0-14515.0
Tumor Burden (At least one measurable lesion per Investigator), n (%)					
Yes	53 (96.4)	122 (98.4)	86 (97.7)	0	208 (92.0)
No	2 (3.6)	2 (1.6)	2 (2.3)	14 (100)	18 (8.0)

Analysis set definitions: PAS = Primary Analysis Set; IAS = Prior Cabozantinib or Vandetanib; SAS1 = Cabozantinib/vandetanib-naïve; SAS2 = Non-measurable Disease.
Note: For *RET*- mutant MTC, the PAS includes the first 55 patients from IAS. The "Total" column is the sum of the IAS, SAS1, and SAS2.
Source: 60-Day Update SCE (MTC) Tables 14.2.1; 14.2.2; 14.2.4
* Data updated in 60-Day Update

The FDA's Assessment:

FDA agrees with Applicant's results provided above.

RET-Mutant MTC Efficacy Data

[Original NDA Module 2.5.4.2 (MTC); 60-Day Update SCE (MTC) Tables 14.3.1.1, 14.3.1.2, 14.3.1.3, 14.3.1.4, 14.3.3.1, 14.3.3.2, 14.3.3.3, 14.3.3.4, 14.3.8.1]

Primary Analysis Set: Patients Who Received 1 or More Lines of Prior Cabozantinib or Vandetanib

The *RET*-mutant MTC PAS is a prospectively defined population of patients consisting of the first 55 patients consecutively enrolled to LOXO-RET-17001 who had received prior cabozantinib or vandetanib. The PAS was powered to rule out a lower bound of ORR of 20%, a threshold deemed clinically meaningful and consistent with the estimated response rates seen with approved therapies.

In the *RET*-mutant MTC PAS in the Original NDA, the ORR was 63.6% (35/55; 95% CI: 49.6, 76.2) by IRC and 52.7% (29/55; 95% CI: 38.8, 66.3) by investigator assessment (Table 8.26). In the 60-Day Update, the ORR was 69.1% (38/55; 95% CI 55.2, 80.9) by IRC assessment, and 61.8% (34/55; 95% CI 47.7, 74.6) by investigator assessment. In the Original NDA, the Kaplan-Meier estimate for median DOR by IRC assessment was not reached (95% CI: NE, NE), with median DOR follow-up of 9.2 months and 4/35 (11%) events observed. The median DOR by investigator assessment was not reached (95% CI: 11.1 months, NE), with median DOR follow-up of 10.6 months and 6/29 (21%) events observed. In the 60-Day Update the median DOR by IRC assessment was not reached (95% CI: 19.1, NE), with median DOR follow-up of 14.1 months and 6/38 (15.8%) events observed. The median DOR by investigator assessment was not reached (95% CI: 18.4, NE), with 9/34 (26.5%) events observed and median DOR follow-up of 14.8 months.

A waterfall plot illustrating the best change in tumor size per RECIST v1.1 based on IRC assessment is shown below Figure 8.14 and Figure 8.15. The Kaplan-Meier plot of DOR based on IRC assessment is shown in Figure 8.16 and Figure 8.17.

Table 8.26 Original NDA and 60-Day Update: Objective Response Rate and Duration of Response for *RET*-mutant MTC Primary Analysis Set

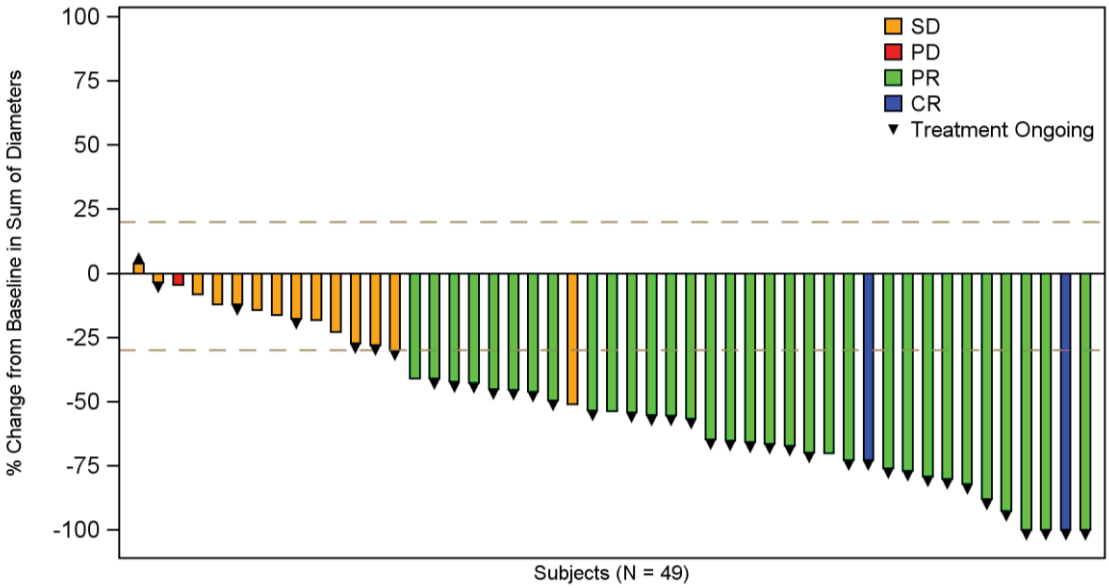
	Original NDA		60-Day Update	
	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment
No. of patients	55	55	55	55
Best Overall Response, n (%)				
Complete response	3 (5.5)	3 (5.5)	5 (9.1)	3 (5.5)
Partial response	32 (58.2)	26 (47.3)	33 (60.0)	31 (56.4)
Objective Response Rate (confirmed CR/PR), n (%)				
ORR	35 (63.6)	29 (52.7)	38 (69.1)	34 (61.8)
(95% CI)	(49.6, 76.2)	(38.8, 66.3)	(55.2, 80.9)	(47.7, 74.6)
Duration of Response, months				
Median (95% CI)	NE (NE, NE)	NE (11.1, NE)	NE (19.1, NE)	NE (18.4, NE)
Minimum, Maximum	2.8+, 18.4+	1.9+, 17.3+	2.8+, 24.0+	2.8+, 23.1+
Duration of Response, n (%)				
< 6 months	13 (37.1)	10 (34.5)	9 (23.7)	9 (26.5)

	Original NDA		60-Day Update	
	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment
≥ 6 to 12 months	16 (45.7)	13 (44.8)	8 (21.1)	8 (23.5)
≥ 12 to 18 months	5 (14.3)	6 (20.7)	14 (36.8)	10 (29.4)
≥ 18 to 24 months	1 (2.9)	0	7 (18.4)	7 (20.6)
Response Status, n (%)				
Disease progression	4 (11.4)	6 (20.7)	6 (15.8)	9 (26.5)
Censored	31 (88.6)	23 (29.3)	32 (84.2)	25 (73.5)
Duration of Response Follow-up, months				
Median	9.2	10.6	14.1	14.8

Median DOR and DOR follow-up estimated using the Kaplan-Meier method

Source: Original NDA Module 2.5 (MTC) Table 3 and Module 2.7.3 (MTC) Tables 18 and 22; 60-Day Update SCE (MTC) Tables 14.3.1.1, 14.3.1.2, 14.3.3.1, 14.3.3.2

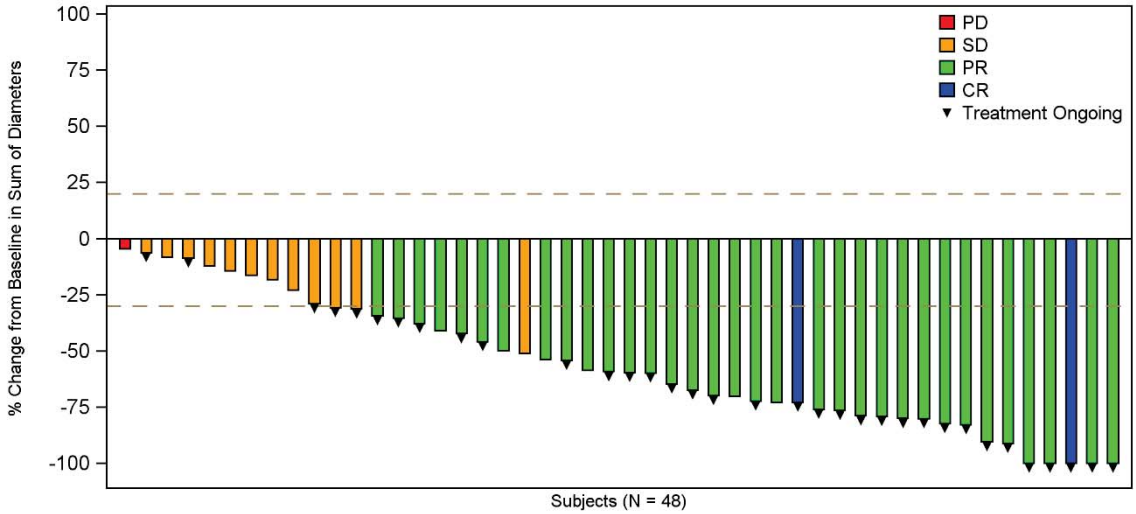
Figure 8.14 Original NDA: Waterfall Plot of Best Change in Tumor Burden Based on IRC Assessment – *RET*-mutant MTC Primary Analysis Set



Note: Six subjects not shown due to four having non-target lesions only and two with no post-baseline target lesion measurements.

Source: Original NDA Module 5.3.5.3 SCE (MTC) Figure 14.2.1

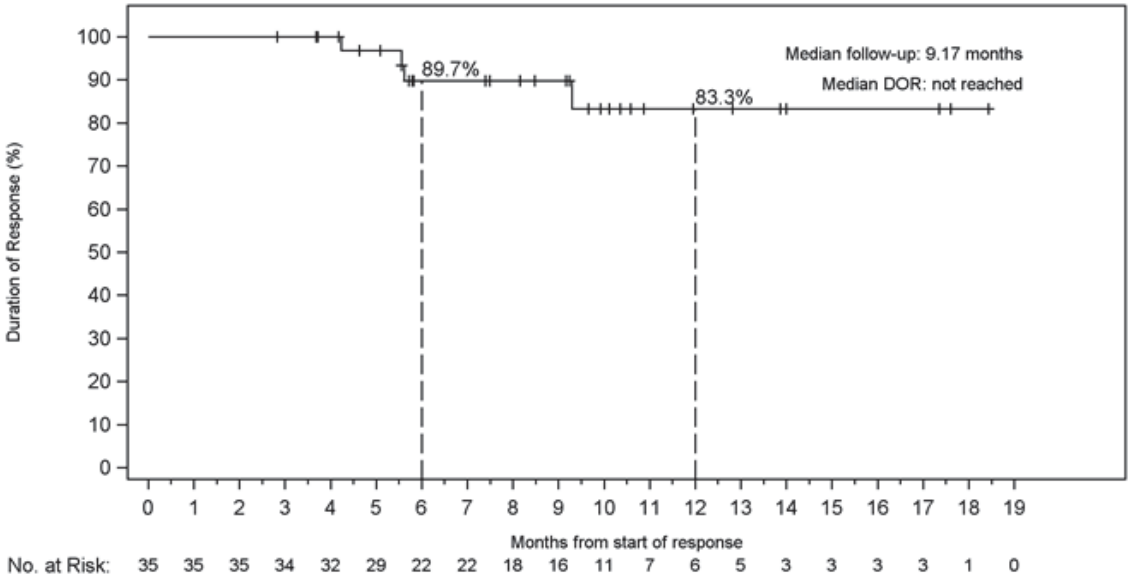
Figure 8.15 60-Day Update: Waterfall Plot of Best Change in Tumor Burden Based on IRC Assessment – *RET*-mutant MTC Primary Analysis Set



Note: Seven subjects not shown due to five having non-target lesions only and two with no post-baseline target lesion measurements. Patient (b) (6) was updated to have non-target lesions only at the 60-Day Update.

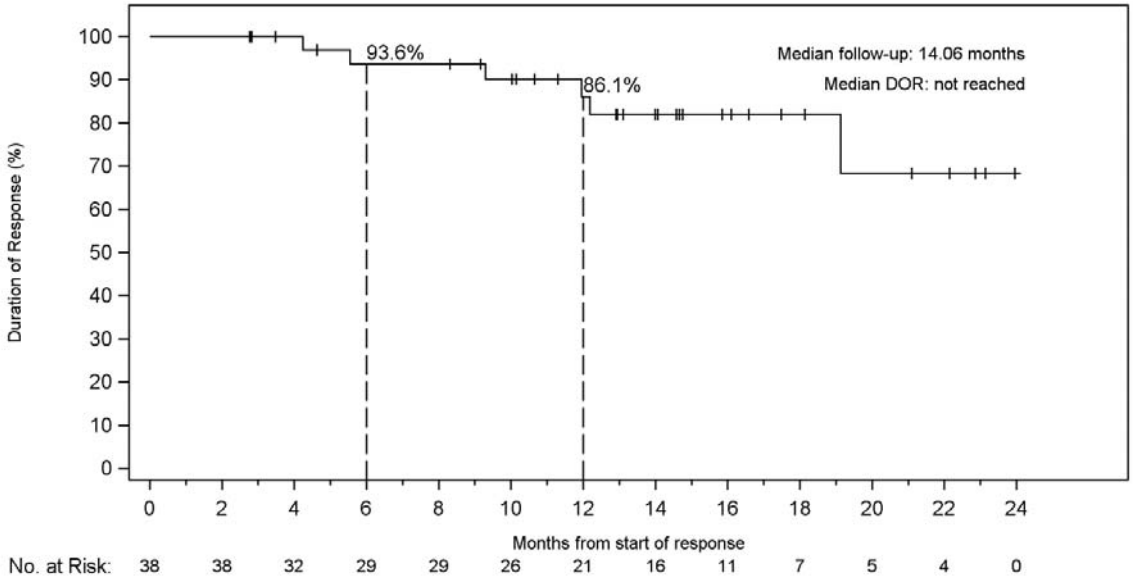
Source: 60-Day Update Figure 14.2.1

Figure 8.16 Original NDA: Kaplan-Meier Plot of Duration of Response Based on IRC Assessment – *RET*-mutant MTC Primary Analysis Set



Source: Original NDA Module 5.3.5.3 SCE (MTC) Figure 14.3.1

Figure 8.17 60-Day Update: Kaplan-Meier Plot of Duration of Response Based on IRC Assessment – *RET*-mutant MTC Primary Analysis Set



Source: 60-Day Update Figure 14.3.1

Biochemical response rates were evaluated for calcitonin and CEA and was defined as ≥ 50% decrease for ≥ 4 weeks (Wells et al. 2012). At the 60-Day Update, the biochemical response rates were 91% (95% CI: 79.7, 96.9) for calcitonin and 66% (95% CI: 51.7, 78.5) for CEA (60-Day Update SCE (MTC) Tables 14.3.6.1, 14.3.6.2).

Integrated Analysis Set

In addition to the PAS, the IAS is comprised of all *RET*-mutant MTC who have received 1 or more lines of cabozantinib or vandetanib, including the first 55 patients in the PAS. As of the 17 June 2019 data cutoff for the Original NDA, a total of 124 IAS patients had been treated with selpercatinib. Of these 124 patients, 82 patients had the opportunity to be followed for at least 6 months from the first dose of selpercatinib and were characterized for efficacy. In the Original NDA, the ORR was 59% (48/82; 95% CI: 47.1, 69.3) by IRC assessment and 48% (39/82; 95% CI: 36.4, 58.9) by investigator assessment (Original NDA SCE (MTC) Module 2.7.3.5.2). As of the 60-Day Update, all 124 patients have been evaluated for response and the opportunity to be followed for at least 6 months from first dose. In the 60-Day Update, the ORR was 67.7% (84/124; 95% CI: 58.8, 75.9) by IRC assessment (60-Day Update SCE (MTC) Table 14.3.1.3) and 58.9 % (73/124; 95% CI: 49.7, 67.6) by investigator assessment (60-Day Update SCE (MTC) Table14.3.1.4).

Supplemental Analysis Set 1 - Patients Who Were Cabozantinib/Vandetanib-Naïve

As of the 17 June 2019 data cutoff for the Original NDA, a total of 88 cabozantinib/vandetanib-naïve *RET*-mutant MTC patients had been treated with selpercatinib. Of these 88 patients, 44 patients had the opportunity to be followed for at least 6 months from the first dose of selpercatinib and are characterized for efficacy. As of the 60-Day Update, all 88 patients have been evaluated for response and had the opportunity to be followed for at least 6 months from first dose.

In the Original NDA, the ORR in these patients was 70.5% (31/44; 95% CI: 54.8, 83.2) by IRC assessment and 65.9% (29/44; 95% CI: 50.1, 79.5) by investigator assessment (Table 8.27). As of the 60-Day Update, all 88 patients have been evaluated for response and followed for at least 6 months from first dose. In this 60-Day Update, the ORR was 72.7% (64/88; 95% CI: 62.2, 81.7) by IRC assessment, and was 67.0% (59/88; 95% CI: 56.2,76.7) by investigator assessment. In the Original NDA, the median DOR by IRC was not reached (95% CI: NE, NE), with median DOR follow-up of 7.2 months and 2/31 (6.5%) events observed. The median DOR by investigator assessment was not reached (95% CI: NE, NE), with median DOR follow-up of 7.4 months and 0/29 (0%) events observed. In the 60-Day Update, the median DOR by IRC assessment and also by investigator assessment was 22.0 months (95% CI: NE, NE); median DOR follow-up by IRC assessment was 7.8 months with 3/64 (4.7%) events observed; median DOR follow-up by investigator assessment was 8.0 months with 2/59 (3.4%) events observed.

A waterfall plot illustrating the best change in tumor size per RECIST v1.1 based on IRC assessment is shown below Figure 8.18 and Figure 8.19. The Kaplan-Meier plot of DOR based on IRC assessment is shown in Figure 8.20 and Figure 8.21.

Table 8.27 Original NDA and 60-Day Update: Objective Response Rate and Duration of Response for Cabozantinib/Vandetanib-naïve *RET*-mutant MTC

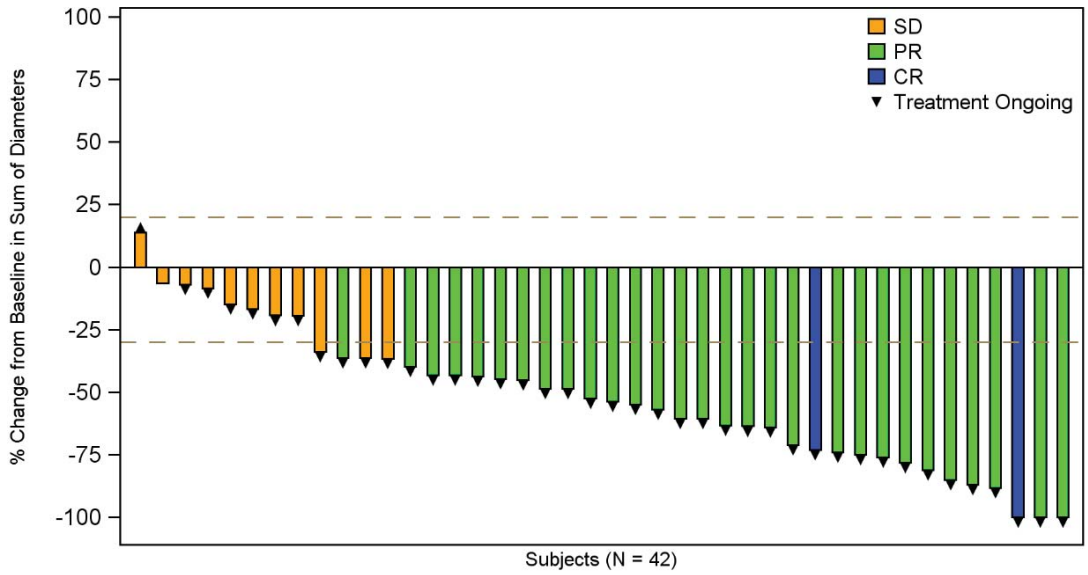
	Original NDA		60-Day Update	
	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment
No. of patients	88	88	88	88
No. of eligible# patients	44	44	88	88
Best Overall Response, n (%)				
Complete response	2 (4.5)	1 (2.3)	10 (11.4)	3 (3.4)
Partial response	29 (65.9)	28 (63.6)	54 (61.4)	56 (63.6)

	Original NDA		60-Day Update	
	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment
Objective Response Rate (confirmed CR/PR), n (%)				
ORR	31 (70.5)	29 (65.9)	64 (72.7)	59 (67.0)
(95% CI)	(54.8, 83.2)	(50.1, 79.5)	(62.2, 81.7)	(56.2,76.7)
Duration of Response, months				
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	21.95 (NE,NE)	21.95 (NE, NE)
Minimum, Maximum	1.9+, 15.9+	1.8+, 15.7+	1.8+, 21.9	1.8+, 21.9
Duration of Response, n (%)				
< 6 months	17 (54.8)	14 (48.3)	25 (39.1)	21 (35.6)
≥ 6 to 12 months	11 (34.5)	11 (37.9)	24 (37.5)	24 (40.7)
≥ 12 to 18 months	3 (9.7)	4 (13.8)	13 (20.3)	10 (16.9)
≥ 18 to 24 months	0	0	2 (3.1)	4 (6.8)
Response Status, n (%)				
Disease progression	2 (6.5)	0	3 (4.7)	2 (3.4)
Died	0	0	1 (1.6)	1 (1.7)
Censored	29 (93.5)	29 (100)	60 (93.8)	56 (94.9)
Duration of Response Follow-up, months				
Median	7.2	7.4	7.8	8.0

Median DOR and DOR follow-up estimated using the Kaplan-Meier method

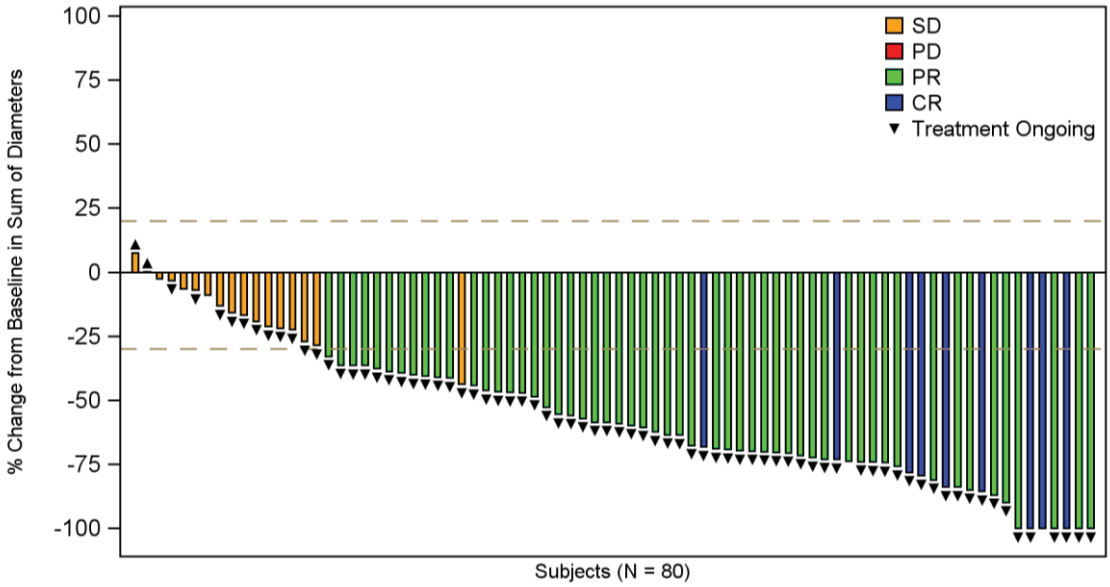
[#] Eligible patients include all patients in the analysis set who have the opportunity to be followed for at least 6 months from the first dose of selpercatinib to the data cutoff date (per *RET* fusion-positive NSCLC SCE SAP).
Source: Original NDA Module 2.5 (MTC) Table 4; 60-Day Update SCE (MTC) Tables 14.3.1.3, 14.3.1.4, 14.3.3.3, 14.3.3.4

Figure 8.18 Original NDA: Waterfall Plot of Best Change in Tumor Burden Based on IRC Assessment – Cabozantinib/Vandetanib-naïve *RET*-mutant MTC Patients with ≥ 6 Months Follow-up



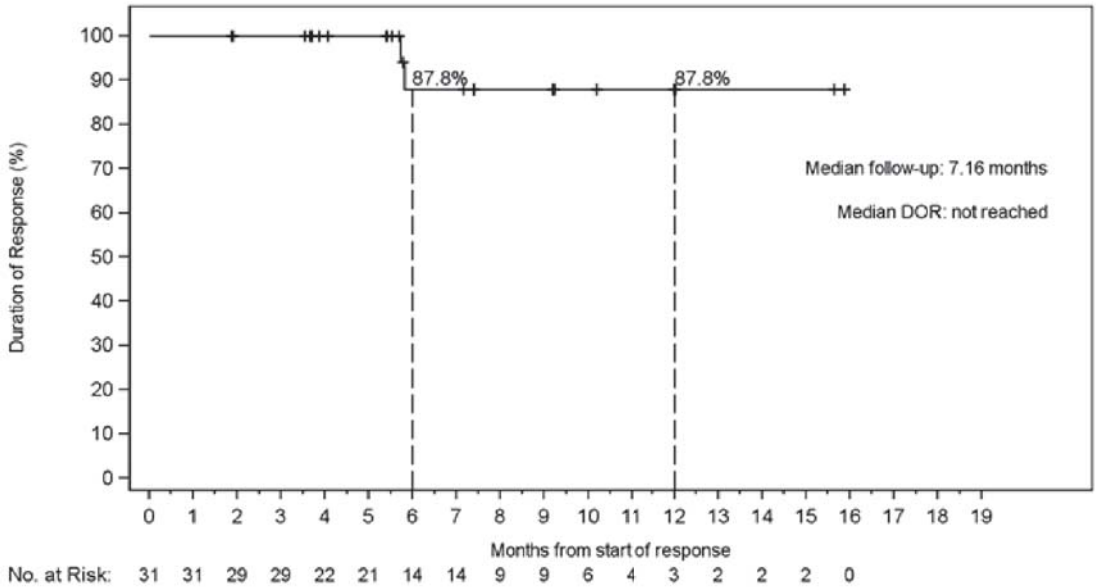
Note: Two subjects not shown due to one having non-target lesions only and one with no post-baseline target lesion measurements.
Source: Original NDA Module 5.3.5.3 SCE (MTC) Figure 14.2.3

Figure 8.19 60-Day Update: Waterfall Plot of Best Change in Tumor Burden Based on IRC Assessment – Cabozantinib/Vandetanib-naïve *RET*-mutant MTC Patients



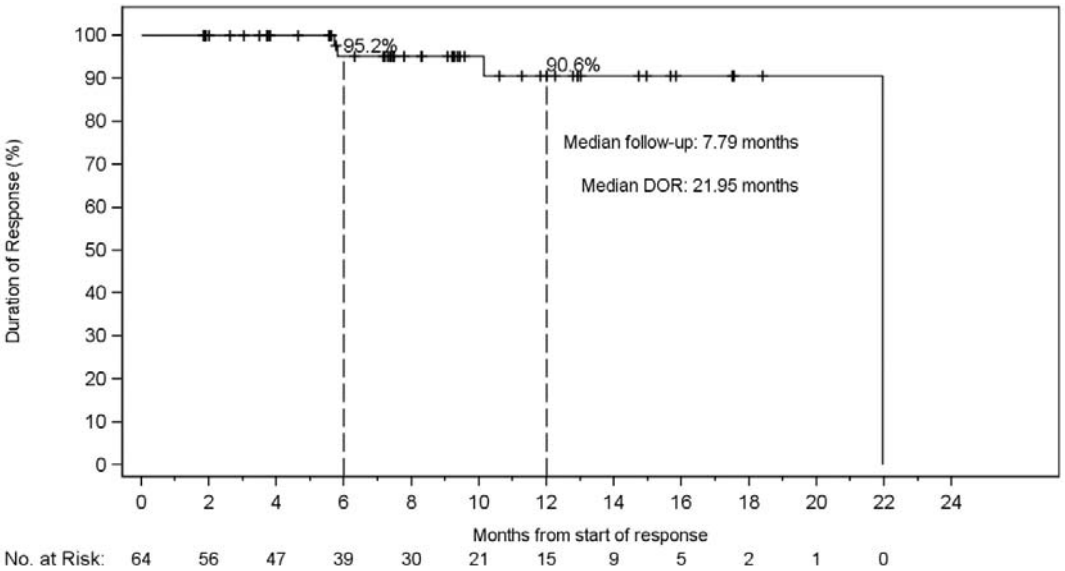
Note: Eight subjects not shown due to six having non-target lesions only and two with no post-baseline target lesion measurements.
Source: 60-Day Update SCE (MTC) Figure 14.2.3

Figure 8.20 Original NDA: Kaplan-Meier Plot of Duration of Response Based on IRC Assessment – Cabozantinib/Vandetanib-naïve *RET*-mutant MTC Patients with ≥ 6 Months Follow-up



Source: Original NDA Module 5.3.5.3 SCE (MTC) Figure 14.3.3

Figure 8.21 **60-Day Update: Kaplan-Meier Plot of Duration of Response Based on IRC Assessment – Cabozantinib/Vandetanib-naïve *RET*-mutant MTC Patients**



Source: 60-Day Update SCE (MTC) Figure 14.3.3

The FDA's Assessment:

FDA agrees with Applicant's results provided above. Please refer to the Additional comments regarding the efficacy results presented:

- Note that results for durability of responses, categorized as < 6 months, ≥ 6 – 12 months, and ≥ 12 – 18 months, are based on observed durations and not KM estimate.
- (b) (4) The duration of response was described by the number of patients who had responses of at least 6 months in duration.

ORR and DOR by Subpopulations
[Original NDA Module 2.7.3.5.1.5 (MTC); 60-Day Update Tables 14.3.1.1, 14.3.3.1, 14.3.8.1]

ORR and DOR were analyzed by several demographic variables using IRC assessment (Table 8.28). The ORR was consistent across all subgroups in both the Original NDA and the 60-Day Update. In the Original NDA, the DOR for all subsets was not reached. For the 60-Day Update, the DOR for all subsets was also not reached with the exception of females, who had a median DOR of 19.1 months.

Table 8.28 Original NDA and 60-Day Update: ORR and DOR by Demographics Based on IRC Assessment – *RET*-mutant MTC Primary Analysis Set

	Original NDA				60-Day Update			
	N	Responders	ORR, % (95% CI)	DOR, months (Range)	N	Responders	ORR, % (95% CI)	DOR, months (Range)
Overall	55	35	63.6 (49.6, 76.2)	NR (2.8+, 18.4+)	55	38	69.1 (55.2, 80.9)	NR (2.8+, 23.1+)
Age								
< 65 years	37	23	62.2 (44.8, 77.5)	NR (2.8+, 18.4+)	37	25	67.6 (50.2, 82.0)	NR (2.8+, 24.0+)
≥ 65 years	18	12	66.7 (41.0, 86.7)	NR (3.7+, 12.0+)	18	13	72.2 (46.5, 90.3)	NR (3.5+, 17.5+)
Sex								
Male	36	23	63.9 (46.2, 79.2)	NR (2.8+, 18.4+)	36	25	69.4 (51.9,83.7)	NR (2.8+, 24.0+)
Female	19	12	63.2 (38.4, 83.7)	NR (4.2+, 14.0+)	19	13	68.4 (43.5, 87.4)	19.1 (2.8+, 19.1)
Race								
White	49	31	63.3 (48.3, 76.4)	NR (2.8+, 18.4+)	49	34	69.4 (54.6, 81.8)	NR (2.8+, 24.0+)
Other	6	4	66.7 (22.3, 95.7)	NR (5.9+, 17.4+)	6	4	66.7 (22.3, 95.7)	NR (2.8+, 23.0+)
ECOG								
0	11	8	72.7 (39.0, 94.0)	NR (4.2, 14.0+)	11	8	72.7 (39.0, 94.0)	19.1 (4.2, 22.1+)
1-2	44	27	61.4 (45.5, 75.6)	NR (2.8+, 18.4+)	44	30	68.2 (52.4, 81.4)	NR (2.8+, 24.0+)
Any Metastatic Disease								
Yes	54	34	63.0 (48.7, 75.7)	NR (2.8+, 18.4+)	54	37	68.5 (54.5, 80.5)	NR (2.8+, 24.0+)
No	1	1	PR	NR (10.6+)	1	1	PR	NR (16.1+)

NR: Not reached
Source: Original NDA Module 2.7.3 (MTC) Table 23 and Module 5.3.5.3 SCE (MTC) Tables 14.3.1.1,

14.3.3.1, 14.3.8.1; 60-Day Update Tables 14.3.1.1, 14.3.3.1, 14.3.8.1

ORR and DOR by type of *RET* mutation are presented in Table 8.29. Responders were observed in all types of *RET* mutations including M918T, extracellular cysteine mutations, V804M/L, and others. The DOR was not reached in all 4 subgroups in both the Original NDA and the 60-Day Update.

ORR and DOR by type of molecular test are also presented in Table 8.29. Responders were observed in all categories. NGS on tumor had a slightly higher ORR than PCR in both the Original NDA and 60-Day Update. The DOR in all subgroups was not reached.

Table 8.29 Original NDA and 60-Day Update: ORR and DOR by RET Mutation Type and Type of Molecular Assay Based on IRC Assessment – *RET*-mutant MTC Primary Analysis Set

	Original NDA				60-Day Update			
	N	Responders	ORR, % (95% CI)	DOR, months (Range)	N	Responders	ORR, % (95% CI)	DOR, months (Range)
Overall	55	35	63.6 (49.6, 76.2)	NR (2.8+, 18.4+)	55	38	69.1 (55.2, 80.9)	NE (2.8+, 24.0+)
RET Mutation Type								
M918T	33	19	57.6 (39.2, 74.5)	NR (2.8+, 17.6+)	33	21	63.6 (45.1, 79.6)	19.1 (2.8+, 23.1+)
Extra-cellular Cysteine Mutation	7	5	71.4 (29.0, 96.3)	NR (3.7+, 12.0+)	7	5	71.4 (29.0, 96.3)	NR (2.8+, 18.1+)
V804M/ L[1]	5	3	60.0 (14.7, 94.7)	NR (9.7+, 17.4+)	5	3	60.0 (14.7, 94.7)	NR (14.8+, 22.9+)
Other	10	8	80.0 (44.4, 97.5)	NR (3.7+, 18.4+)	10	9	90.0 (55.5, 99.8)	NR (3.5+, 24.0+)
Type of *RET* Molecular Assay								
NGS on Blood or Plasma	2	1	PR, SD	NR (2.8+)	2	1	PR, SD	NR (2.8+)
NGS on Tumor	43	28	65.1 (49.1, 79.0)	NR (3.7+, 18.4+)	43	31	72.1 (56.3, 84.7)	NR (2.8+, 24.0+)
PCR	9	5	55.6 (21.2, 86.3)	NR (3.7+, 17.4+)	9	5	55.6 (21.2, 86.3)	NR (9.2+, 23.0+)
Other	1	1	PR	NR (5.6)	1	1	PR	5.6

NR: Not reached
[1] Patient has either V804M or V804L mutation
Source: Original NDA Module 2.7.3 (MTC) Table 24 and Module 5.3.5.3 SCE (MTC)Tables 14.3.1.1, 14.3.3.1, 14.3.8.1; 60-Day Update Tables 14.3.1.1, 14.3.3.1, 14.3.8.1

ORR and DOR by number of prior therapy or type of prior therapy are presented in Table 8.30. The ORR appeared slightly higher in patients with 3 or more prior therapies than in patients with 1-2 prior therapies. The response rate for patients that either received cabozantinib only, vandetanib only, or both therapies were similar in both data cutoffs. The DOR in all subgroups was not reached.

ORR by demography and baseline characteristics based on investigator assessment is provided in Table 14.3.8.2 (Original NDA Module 5.3.5.3 – SCE (MTC) Table 14.3.8.2 and 60-Day Update Table 14.3.8.2).

Table 8.30 Original NDA and 60-Day Update: ORR and DOR by Number and Type of Prior Therapy Based on IRC Assessment – *RET*-mutant MTC Primary Analysis Set

	Original NDA				60-Day Update			
	N	Responders	ORR, % (95% CI)	DOR, months (Range)	N	Responders	ORR, % (95% CI)	DOR, months (Range)
Overall	55	35	63.6% (49.6, 76.2)	NR (2.8+, 18.4+)	55	38	69.1 (55.2, 80.9)	NE (2.8+, 24.0+)
Number of Prior Therapies								
1–2	37	21	56 .8% (39.5, 72.9)	NR (2.8+, 18.4+)	37	24	64.9 (47.5, 79.8)	NR (2.8+, 24.0+)
3 or more	18	14	77.8 % (52.4, 93.6)	NR (3.7+, 17.6+)	18	14	77.8 (52.4, 93.6)	NR (2.8+, 23.1+)
Type of Prior Systemic Therapy								
Prior cabozantinib only	13	7	53.8 (25.1, 80.8)	NR (3.7+, 10.9+)	13	9	69.2 (38.6, 90.9)	NR (2.8+, 16.6+)
Prior vandetanib only	18	12	66.7 (41.0, 87.7)	NR (4.2, 18.4+)	18	12	66.7 (41.0, 86.7)	NR (2.8+, 24.0+)
Prior cabozantinib and vandetanib	24	16	66.7 (44.7, 84.4)	NR (2.8+, 17.6+)	24	17	70.8 (48.9, 87.4)	NR (2.8+, 23.1+)

NR: not reached
Source: Original NDA Module 2.7.3 Table 25 and Module 5.3.5.3 SCE (MTC) Tables 14.3.1.1, 14.3.3.1, 14.3.8.1; 60-Day Update Tables 14.3.1.1, 14.3.3.1, 14.3.8.1

The FDA's Assessment:

FDA agrees with Applicant's results provided above. however, results for the subgroups with small sample size, the estimated medians may not adequately characterize the DOR results.

8.1.2.3 Data Quality and Integrity

There were no data issues were identified.

The Applicant's Position:

This NDA submission contains all the required components of the electronic Common Technical Document (eCTD). Analysis-ready, efficacy and safety datasets, which support the efficacy and safety of selpercatinib for LOXO-RET-17001, are provided.

The FDA's Assessment:
FDA agrees that applicant has provided all the datasets and supporting metadata documentation required to validate the results. Note that the datasets for original NDA submission and the 60-Day update were submitted separately.

Dose/Dose Response

Not applicable

The FDA's Assessment:
The clinical pharmacology review included dose-response analyses. Refer to section 6.3.2.

Durability of Response

Please see the analysis of duration of response above.

The FDA's Assessment:
FDA has no additional comments.

Persistence of Effect

Not applicable

The FDA's Assessment:

The data available do not allow meaningful analysis of persistence of effect after drug discontinuation.

8.1.2.4 Efficacy Results – Secondary or exploratory COA (PRO) endpoints

European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and bowel diary assessments were administered according to the Schedule of Assessments. [CSR LOXO-RET-17001 Synopsis]

Among the 97 patients with RET fusion-positive NSCLC, 36.1% experienced definite improvement (defined as an improvement from baseline ≥ 10 points without any further deterioration in score ≥ 10 points) the in physical function subscale,, with an average time to definite improvement of 2.25 months; 22.1% of the 122 patients with *RET*-mutant MTC experienced definite improvement in physical function with an average time to definite improvement of 1.95 months. [CSR LOXO-RET-17001 Synopsis; CSR LOXO-RET-17001 Table 14.2.6.2]

Increase or reduction of symptom severity were defined as a change of ≥ 10 points from baseline for the QLQ C30. Patients with *RET* fusion-positive NSCLC (n = 97) and *RET*-mutant MTC (n = 122) experienced reduction in pain (53.6% and 54.9% of patients, respectively) and reduction in fatigue (60.8% and 62.3%, respectively). The average time to reduction in pain was less than 2 months for both groups, and the average time to reduction in fatigue was 2.13 months for NSCLC and 2.41 for MTC. Among the 97 patients with *RET* fusion-positive NSCLC, 47.4% (n = 46) experienced reduction in dyspnea. Among the 122 patients with *RET*-mutant MTC, 47.5% experienced improvement in insomnia whereas 23.0% experienced worsening, and 55.7% (n = 68) experienced a reduction in diarrhea with an average 1.98 months to first reduction. [CSR LOXO-RET-17001 Synopsis; CSR LOXO-RET-17001 Table 14.2.6.2]

For the 82 patients with MTC who had bowel diaries assessed, 55 (67.1%) reported urgency at baseline. This was reduced to 36.1% at the start of Cycle 2, to 31.7% at the start of Cycle 3, and was reported less and less frequently throughout the study period. This pattern of decline at subsequent study visits was similar for abdominal discomfort and fecal incontinence. More than 80% of the 64 MTC patients who reported diarrhea reported a reduction in diarrhea (n = 53, 82.8%) during the study. The average time to improvement was 0.60 months. Only 12 (18.8%) patients experienced worsening of diarrhea during the study. [CSR LOXO-RET-17001 Section 11.1.3.3; Tables 14.2.7.1.1 through 14.2.7.2.4]

The Applicant's Position:

The LOXO-RET-17001 interim CSR SAP pre-specified analysis of clinical outcomes assessment (COA) data to support the efficacy of selpercatinib. Quality of life was evaluated in Study LOXO-RET-17001 as an exploratory objective. [CSR LOXO-RET-17001 Synopsis]

The FDA's Assessment:

FDA did not conduct in-depth analyses of clinical outcomes assessments in this single-

arm study. FDA is supportive of clinical outcomes assessments conducted in the prospective, randomized study of selpercatinib in patients with medullary thyroid cancer (See Section 13). However, a threshold of 10 points for improvement or deterioration has not been sufficiently justified. FDA considers these analyses to be exploratory.

8.1.2.5 Additional Analyses Conducted on the Individual Trial

The LOXO-RET-17001 interim CSR summarized efficacy by Phase 2 cohorts. Below is a summary of the key efficacy results.

- Cohort 1 (*RET* fusion-positive solid tumors with received standard therapy): ORR was 62.4% (68/109; 95% CI = 52.6, 71.5); median DOR was 23.9 months (95% CI = 13.80, 23.98) with 79.4% of patients censored and median follow-up of 7.95 months.

- Cohort 2 (*RET* fusion-positive solid tumors without prior standard therapy): ORR was 76.5% (13/17; 95% CI = 50.1, 93.2); median DOR has not yet been reached with 84.6% of patients censored and median follow-up of 9.30 months.

- Cohort 3 (*RET*-mutant MTC with standard cabozantinib and/or vandetanib): ORR was 46.8% (36/77; 95% CI = 35.3, 58.5); median DOR has not yet been reached with 86.1% of patients censored and median follow-up of 9.17 months.

- Cohort 4 (*RET*-mutant MTC without prior standard cabozantinib and/or vandetanib or other kinase inhibitor): ORR was 70.6% (24/34; 95% CI = 52.5, 84.9); median DOR has not yet been reached with 100% of patients censored and median follow-up of 7.47 months.

- Cohort 5 (patients who had an advanced *RET*-altered solid tumor who did not otherwise qualify for Cohorts 1 through 4): ORR was 47.8% (32/67; 95% CI = 35.4, 60.3); median DOR was 20.3 months with 71.9% patients censored and median follow-up of 7.49 months. [CSR LOXO-RET-17001 Section 11.3]

The FDA's Assessment:
Analyses based on cohorts within LIBRETTO-001 were not analyzed by FDA as they did not align with the defined efficacy populations.

8.1.3 Integrated Review of Effectiveness

The FDA's Assessment:

The clinical and statistical review teams conclude that the Applicant has provided substantial evidence of the effectiveness of selpercatinib in the following populations:

- Adult patients with metastatic *RET* fusion-positive NSCLC
- Patients ≥ 12 years of age with advanced or metastatic *RET* mutation-positive MTC who require systemic therapy
- Patients ≥ 12 years of age with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

8.1.4 Assessment of Efficacy Across Trials

This section is not applicable to this review as the efficacy is supported by a single clinical trial in this application.

Subpopulations

Analysis by subpopulations is described above.

The FDA's Assessment:
FDA has no additional comments.

Additional Efficacy Considerations

The FDA's Assessment:
See discussion under Section 8.1.5.

8.1.5 Assessment of Effectiveness

***RET* Fusion-Positive NSCLC - Assessment of Efficacy**
[60-Day Update SCE NSCLC Tables 14.3.1.1, 14.3.1.3, 14.3.3.1, 14.3.3.3]

In this 60-Day Update, for patients in the PAS with advanced *RET* fusion-positive NSCLC who had received 1 or more lines of prior platinum-based chemotherapy, treatment with selpercatinib resulted in an independently-confirmed ORR of 63.8%, and a median DOR of 17.5 months with median DOR follow-up of 12.1 months and 23/67 (34.3%) events observed. The majority, 44 (65.7%) of the 67 responding patients in the NSCLC PAS, were alive without documented disease progression at the time of the data cutoff (16 December 2020).

In the first-line *RET* fusion-positive NSCLC setting, the activity of selpercatinib was also compelling. With the 60-Day Update, all of the 39 treatment-naïve *RET* fusion-positive NSCLC patients that had been treated with selpercatinib had the opportunity to be followed for at least 6 months from first dose and the ORR in these patients was 84.6% by IRC; median DOR was not reached with median DOR follow-up of 7.4 months and 7/33 (21.2%) events observed.

There are no RET-directed therapies approved for patients with *RET* fusion-positive NSCLC. Patients with *RET*-fusion NSCLC are typically treated with the standards of care utilized for NSCLC without a known oncogenic driver alteration. These regimens have limited efficacy and are associated with significant toxicity. The LOXO-RET-17001 data demonstrate a favorable benefit-risk profile for the use of selpercatinib in patients with *RET* fusion-positive NSCLC who require systemic therapy and have been previously treated with platinum-based chemotherapy. The data provided in this NDA and 60-Day Update also suggest a favorable benefit-risk profile for the use of selpercatinib in patients with treatment-naïve *RET* fusion-positive NSCLC who require systemic therapy. Approval for selpercatinib in a line agnostic setting would not only provide an important treatment option for patients with *RET* fusion-positive NSCLC, it would also reinforce the public health message that tumor genomic profiling is an important behavior in the newly diagnosed setting.

RET Fusion-Positive Thyroid Cancer - Assessment of Efficacy
[Module 2.5.6 (NSCLC)]
[60-Day Update SCE NSCLC Tables 14.3.1.1, 14.3.1.3, 14.3.3.1, 14.3.3.3]

In this 60-Day Update, for patients with previously-treated *RET* fusion-positive thyroid cancer also showed response rates with meaningful duration. Per IRC, the ORR in these 19 patients was 78.9%, and a median DOR of 18.4 months with median DOR follow-up of 17.5 months and 6/15 (40.0%) events observed.

For the 8 patients with treatment-naïve *RET* fusion-positive thyroid cancer, the ORR was 100.0%, and a median DOR of not reached with median DOR follow-up of 8.8 months and 0/8 (0%) events observed.

There are no RET-directed therapies approved for patients with *RET* fusion-positive thyroid cancer. The data provided in this NDA and 60-Day Update suggest a favorable benefit-risk profile for the use of selpercatinib in patients with *RET* fusion-positive thyroid cancer who require systemic therapy. Approval for selpercatinib in a line agnostic setting would not only provide an important treatment option for patients with *RET* fusion-positive thyroid cancer, it would also reinforce the public health message that tumor genomic profiling is an important behavior in the newly diagnosed setting.

RET-Mutant MTC - Assessment of Efficacy
[Module 2.5.6 (MTC)]
[60-Day Update SCE MTC Tables 14.3.1.1, 14.3.1.3, 14.3.3.1, 14.3.3.3]
In this 60-Day Update, for patients with advanced *RET*-mutant MTC who had received prior cabozantinib and/or vandetanib therapy, treatment with selpercatinib resulted in an independently-confirmed ORR of 69.1%, and a median DOR not reached with median DOR follow-up of 14.1 months and 6/38 (15.8%) events observed.

In cabozantinib and vandetanib-naïve *RET*-mutant MTC patients, the activity of selpercatinib was also compelling. As of the 60-Day Update, all 88 cabozantinib/vandetanib-naïve *RET*-mutant MTC patients who had been treated with selpercatinib had the opportunity to be followed for at least 6 months from first dose. The ORR in these patients was 72.7% by IRC, and a median DOR of 22.0 months with median DOR follow-up of 7.8 months and 4/64 (6.3%) events observed. It is important to note that median DOR may be statistically unstable due to a low number of events and the large number of patients still on treatment and in response (Table 8.27 and Figure 8.21).

There are no RET-directed therapies approved for patients with *RET*-mutant MTC. Patients with *RET*-mutant MTC are typically treated with cabozantinib or vandetanib. These regimens have limited efficacy and may be associated with significant toxicity. The LOXO-RET-17001 data demonstrate a favorable benefit-risk profile for the use of selpercatinib in patients with *RET*-mutant MTC who require systemic therapy and have been previously treated with cabozantinib and/or vandetanib. The data provided in this NDA and 60-Day Update also suggest a favorable benefit-risk profile for the use of selpercatinib in patients with cabozantinib/vandetanib-naïve *RET*-mutant MTC who require systemic therapy. Approval for selpercatinib in a line agnostic setting would not only provide an important treatment option for patients with *RET*-mutant MTC, it would also reinforce the public health message that tumor genomic profiling is an important behavior in the newly diagnosed setting.

The FDA's Assessment:

The clinical and statistical review teams conclude that the Applicant has provided substantial evidence of effectiveness of selpercatinib in the following populations:

- Adult patients with metastatic *RET* fusion-positive NSCLC
- Patients ≥ 12 years of age with advanced or metastatic *RET* mutation-positive MTC who require systemic therapy
- Patients ≥ 12 years of age with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

The application is supported by evidence of large, durable and clinically meaningful ORRs in each of these populations based on the experience in the first-in-human, single arm study LIBRETTO-001. FDA considers ORR of a sufficient magnitude with a meaningful duration of response as an intermediate endpoint likely to predict clinical benefit in these rare molecularly-defined populations of patients with advanced cancers.

For patients with metastatic *RET* fusion-positive NSCLC who have not received prior systemic therapy, the overall response rate represents an improvement over that provided by available, non-targeted therapy. Though the efficacy population of treatment-naïve metastatic NSCLC in LIBRETTO-001 is relatively small, the significant ORR and durability of these responses in this

molecularly-defined population demonstrates sufficient evidence of clinical benefit to warrant accelerated approval in the opinion of the review team. The durable ORR observed in patients with *RET* fusion-positive NSCLC who have received platinum therapy similarly represents an improvement over available therapy.

For patients with advanced or metastatic *RET* mutant MTC who have not received prior treatment with an approved TKI and require systemic therapy, the overall response rate observed in study LIBRETTO-001 demonstrates an improvement over available therapies for MTC. Patients with *RET* mutant MTC who have progressed following cabozantinib or vandetanib do not have approved treatment options. The durable ORR observed in this population provides evidence of clinical benefit in this population with an unmet medical need. Although patients with MTC with advanced or metastatic disease were eligible to enroll, only one patient in the efficacy populations did not have metastatic disease on enrollment. Patients with locally advanced MTC not amenable to local therapy are treated similarly to patients with metastatic disease and have an unmet medical need. The indication statement will reflect that selpercatinib should be used in patients with locally advanced or metastatic disease who require systemic therapy.

For patients with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are RAI-refractory, the response rates observed in response to selpercatinib exceed those provided by available therapy. No approved therapies are available for patients with *RET* fusion-positive thyroid cancer who are RAI-refractory and have progressed following subsequent therapy. Given the observation of partial responses in all histologic subtypes of *RET* fusion-positive thyroid cancer studied, the review team considered that an indication which encompassed multiple histologic subtypes of thyroid cancer with *RET* fusions was appropriate.

There are no therapies approved specifically for patients with *RET*-driven cancers. The durable response rate to selpercatinib observed across tumor types therefore meets an unmet medical need.

Due to small sample sizes and limited follow-up for some patients, there is uncertainty regarding the magnitude and durability of the treatment effect of selpercatinib in each population. The review team therefore recommends that the findings from LIBRETTO-001 in all disease types be confirmed in subsequent studies (see Section 13 for details).

8.2 Review of Safety

The safety analysis for the original NDA was based on 531 patients who received at least one dose of selpercatinib as of the data cutoff for the Original NDA (17 June 2019), also known as the Overall Safety Analysis Set (OSAS). The OSAS for this 60-Day Update is based on 702 patients who received at least one dose of selpercatinib as of the data cutoff (16 December 2019) and are inclusive of the 531 patients evaluated in the Original NDA. The data cutoff for this 60-Day Update provides 6 months of additional follow-up information for patients who were included in the Original NDA.

In addition to OSAS, separate analyses for the *RET* fusion-positive NSCLC and *RET*-mutant MTC patient populations as was presented for the Original NDA, and is also presented here for the 60-Day Update. Selpercatinib safety remained generally consistent across NSCLC and MTC patients.

While the frequency of occurrence for the most common AEs of any grade in the OSAS increased slightly in the 60-Day Update, the nature of these events remained consistent (original NDA frequency, 60-Day Update frequency): dry mouth (32.2%, 38.7%), diarrhea (31.3%, 36.2%), hypertension (28.8%, 35.0%), AST increase (27.5%, 29.9%), ALT increase (25.6%, 28.6%), fatigue (24.3%, 28.1%), and constipation (21.8%, 25.4%). Three additional AEs occurred at a frequency greater than 20% in the 60-Day Update: edema peripheral (23.5%), headache (22.9%), and nausea (22.6%). The frequency of the most common Grade 3-4 events illustrated the same trend (original NDA frequency, 60-Day Update frequency): hypertension (13.9%, 17.5%), ALT increase (8.5%, 9.1%), AST increase (6.4%, 7.4%), and hyponatremia (5.1%, 5.1%).

In the 60-Day Update, the AEs leading to dose reductions remained consistent (original NDA frequency, 60-Day Update frequency): ALT increase (5.8%, 6.4%), AST increase (4.3%, 5.6%), electrocardiogram QT prolonged (2.6%, 2.3%), fatigue (1.7%, 2.1%), drug hypersensitivity (1.1%, 1.7%), hypertension (1.1%, 1.3%), and thrombocytopenia (1.1%, 1.4%). In the 60-Day Update, 4 additional AEs were noted to cause dose reductions ≥ 1%: diarrhea (1.3%), rash (1.3%), hypersensitivity (1.1%), and pyrexia (1.0%).

The three AEs of special interest identified for focused analysis in the Original NDA remain unchanged for the 60-Day Update: ALT/AST increase, drug hypersensitivity reaction, and hypertension. All of these AEs are monitorable and reversible.

The Sponsor continues to believe the overall tolerability of selpercatinib is characterized by recognizable toxicities, which are either monitorable, reversible with dose interruption or addressable through dose reduction or concomitant medication when necessary. [Original NDA Module 2.7.4.2 and 60-Day Update Assessment Aid Addendum Section 8.2.11]

The FDA's Assessment:

FDA refers to the detailed description and summary below.

8.2.1 Safety Review Approach

The Applicants Position: [Module 2.7.4.2; 2.7.4.3]

The clinical assessment of safety of selpercatinib described in the Summary of Clinical Safety (SCS) is based on the interim clinical study report for LOXO-RET-17001 with a data cutoff of 17 June 2019. The primary analysis set in the SCS describes the safety of all 531 patients who received at least one dose of selpercatinib as of the data cutoff, also known as the OSAS. Separate analyses for the *RET* fusion-positive non-small cell lung cancer (NSCLC; n = 253) and *RET*-mutant MTC (n = 226) patient populations were also prepared, and descriptive safety summaries for 22 patients who received selpercatinib through single patient protocols, where data collection was more limited, are included. No unexpected safety findings were described for these 22 patients. In addition to studies in cancer patients, a comprehensive clinical pharmacology program was conducted in healthy subjects across 8 studies. The overall safety findings from these ancillary studies are consistent with those in the main SCS analysis.

Based on the finding described in the SCS, the overall tolerability of selpercatinib in adult cancer patients is characterized by recognizable toxicities, which are either monitorable, reversible with dose interruption or addressable through dose reduction or concomitant medication when necessary. In the context of the durable response rates reported, the Sponsor believes that the safety data supports a favorable risk-benefit determination for selpercatinib.

In addition to the safety data provided in the initial NDA submission, an update in the form of an addendum to the SCS is planned for submission with the Day 60 Safety Update Report. A data cutoff of 16 December 2019 will be utilized for this update and will provide 6 months of additional follow-up information for patients enrolled as of the initial data cutoff of 17 June 2019.

In this 60-day update, per ICH E3, patient safety narratives will be written for selpercatinib-treated patients meeting the following criteria post the 17 June 2019 data cutoff:

- Deaths on treatment or within 28 days of the last dose
- Treatment-emergent SAEs
- Adverse events leading to discontinuation

CRFs will be provided for all patients meeting the above criteria. Data captured in eCRFs will be presented in the NDA as bookmarked and hyperlinked PDFs. Audit trail changes will be part of the bookmarked exported PDFs. There will be one file per patient.

The FDA's Assessment:
This reviewer agrees with the description of the safety analysis population and the contents of the SCS and 60-day update.

8.2.2 Safety Review Approach for the 60-Day Update

The Applicants Position: [Original NDA Module 2.7.4.2; 2.7.4.3; 60-Day Update Assessment Aid Addendum Section 8.2.4]

The clinical assessment of safety of selpercatinib is based patients enrolled in LOXO-RET-17001 as of the data cutoff of 17 June 2019 for the Original NDA and 16 December 2019 for the 60-Day Update. The overall safety analysis set (OSAS) described the safety of 531 patients who received at least one dose of selpercatinib in the Original NDA, and with this 60-Day Update, describes the safety of all 702 patients who received at least one dose of selpercatinib. Separate analyses for the *RET* fusion-positive non-small cell lung cancer (NSCLC; Original NDA n = 253, 60-Day Update n = 329) and *RET*-mutant MTC (Original NDA n = 226, 60-Day Update n = 299) patient populations were again prepared.

In this 60-day update, per ICH E3, patient safety narratives have been written and/or updated for selpercatinib-treated patients meeting the following criteria post the 16 December 2019 data cutoff:

- Deaths on treatment or within 28 days of the last dose
- Treatment-emergent SAEs
- Adverse events leading to discontinuation

CRFs will be provided for all patients meeting the above criteria. Data captured in eCRFs will be presented in the NDA as bookmarked and hyperlinked PDFs. Audit trail changes will be part of the bookmarked exported PDFs. There will be one file per patient.

8.2.3 Review of the Safety Database

Overall Exposure
[Original NDA Module 2.7.4.4; 60-Day Update SCS Tables 14.1.2, 14.3.1, 14.3.2]

The Applicants Position:

At the time of the data cutoff for both the Original NDA and the 60-Day Update, the LOXO-RET-17001 trial was ongoing with patients still being treated and new patients being enrolled. All patients treated by the data cutoff were eligible for inclusion in the safety analysis. In the Original NDA, 441 of 531 treated patients (83.1%) were continuing to receive selpercatinib and 90 (16.9%) had discontinued therapy. In the 60-Day Update, 548 of 702 treated patients

(78.1%) were continuing to receive selpercatinib and 154 (21.9%) had discontinued therapy. For further details regarding patient disposition please see Table 8.31.

A summary of drug exposure is provided in Table 8.32. Daily starting doses ranged from 20 mg (given QD) to 480 mg (given 240 mg BID). Across all treated patients, the median time on treatment in the Original NDA was 5.9 months, ranging up to 25.1 months (and ongoing as of the data cutoff for the Original NDA); the median time on treatment in the 60-Day Update was 8.7 months, ranging up to 31.0 months (and ongoing as of the data cutoff for the 60-Day Update). The median time on treatment are affected by administrative censoring resulting from the data cutoff for the analysis and will grow longer with subsequent data cuts.

Median dose intensity of the overall population in the Original NDA was 97.7% and in the 60-Day Update was 96.7%. In the Original NDA, only 5.8% of patients received a selpercatinib dose intensity less than 50% of that intended (Table 8.33); for the OSAS, 52.4% of patients had dose interruptions, 47.3% were due to an AE, and any dose reductions occurred in 27.3% of patients with 25.6% due to an AE (Table 8.34). In the 60-Day Update, only 7.1% of patients received a selpercatinib dose intensity less than 50% of that intended (Table 8.33); for the OSAS, 58.7% of patients had any dose interruptions, 51.7% were due to an AE, and dose reductions occurred in 32.8% of patients with 30.9% due to an AE (Table 8.34).

Table 8.31 Original NDA and 60-Day Update: Patient Disposition for Overall Safety Population

	Original NDA			60-Day Update		
	***RET*-mutant MTC**	***RET* Fusion-positive NSCLC**	**Overall**	***RET*-mutant MTC**	***RET* Fusion-positive NSCLC**	**Overall**
Patients treated	226	253	531	299	329	702
On treatment, n (%)	200 (88.5)	202 (79.8)	441 (83.1)	256 (85.6)	240 (72.9)	548 (78.1)
Off treatment, n (%)	26 (11.5)	51 (20.2)	90 (16.9)	43 (14.4)	89 (27.1)	154 (21.9)
Disease progression	12 (5.3)	26 (10.3)	46 (8.7)	20 (6.7)	53 (16.1)	90 (12.8)
Adverse event	6 (2.7)	10 (4.0)	19 (3.6)	12 (4.0)	18 (5.5)	33 (4.7)
Intercurrent illness compromising ability to fulfill protocol requirements	–	–	–	1 (0.3)	0	1 (0.1)
Requirement for alternative treatment per investigator	–	–	–	2 (0.7)	0	2 (0.3)
Significant Noncompliance to Protocol	–	–	–	0	0	1 (0.1)

	Original NDA			60-Day Update		
	***RET*-mutant MTC**	***RET* Fusion-positive NSCLC**	**Overall**	***RET*-mutant MTC**	***RET* Fusion-positive NSCLC**	**Overall**
Withdrawal of consent	3 (1.3)	5 (2.0)	9 (1.7)	3 (1.0)	8 (2.4)	12 (1.7)
Death	2 (0.9)	5 (2.0)	7 (1.3)[a]	3 (1.0)	6 (1.8)	9 (1.3)
Other	3 (1.3)	5 (2.0)	9 (1.7)	2 (0.7)	4 (1.2)	6 (0.9)
Treated post-progression, n (%)	16 (7.1)	30 (11.9)	54 (10.2)	31 (10.4)	57 (17.3)	101 (14.4)
Time on treatment, months						
Mean (SD)	7.4 (5.4)	6.5 (5.5)	7.1 (5.5)	10.2	9.2	9.7
Median	6.2	5.3	5.9	9.4	7.7	8.7
Range	0.1, 23.9	0.0, 25.1	0.0, 25.1	0.1, 29.9	0.1, 31.0	0.1, 31.0

[a] Count includes Patient (b) (6) whose death occurred after the cutoff date.
Source: Original NDA Module 2.7.4 Table 6 and Module 5.3.5.3 – SCS Table 14.1.2; 60-Day Update SCS Table 14.1.2

Table 8.32 Original NDA and 60-Day Update: Study Drug Dosing for Overall Safety Population

	Original NDA			60-Day Update		
	***RET*-mutant MTC**	***RET* Fusion-positive NSCLC**	**Overall**	***RET*-mutant MTC**	***RET* Fusion-positive NSCLC**	**Overall**
N	226	253	531	299	329	702
Starting dose, n (%)						
20 mg QD	1 (0.4)	4 (1.6)	6 (1.1)	1 (0.3)	4 (1.2)	6 (0.9)
20 mg BID	3 (1.3)	6 (2.4)	10 (1.9)	3 (1.0)	6 (1.8)	10 (1.4)
40 mg BID	5 (2.2)	9 (3.6)	16 (3.0)	5 (1.7)	9 (2.7)	16 (2.3)
60 mg BID	3 (1.3)	5 (2.0)	12 (2.3)	3 (1.0)	5 (1.5)	12 (1.7)
80 mg BID	11 (4.9)	5 (2.0)	20 (3.8)	11 (3.7)	5 (1.5)	20 (2.8)
120 mg BID	3 (1.3)	13 (5.1)	19 (3.6)	3 (1.0)	13 (4.0)	19 (2.7)
160 mg QD[#]	0	0	0	1 (0.3)	0	1 (0.1)
160 mg BID (RP2D)	195 (86.3)	208 (82.2)	439 (82.7)	267 (89.3)	284 (86.3)	609 (86.8)
200 mg BID	3 (1.3)	0	3 (0.6)	3 (1.0)	0	3 (0.4)
240 mg BID	2 (0.9)	3 (1.2)	6 (1.1)	2 (0.7)	3 (0.9)	6 (0.9)

Received 160 mg BID (RP2D)	214 (94.7)	236 (93.3)	496 (93.4)	287 (96.0)	312 (94.8)	667 (95.0)
Starting dose	195 (86.3)	208 (82.2)	439 (82.7)	267 (89.3)	284 (86.3)	609 (86.8)
Intra-patient escalation	18 (8.0)	25 (9.9)	52 (9.8)	19 (6.4)	25 (7.6)	53 (7.5)
Dose reduction	1 (0.4)	3 (1.2)	5 (0.9)	1 (0.3)	3 (0.9)	5 (0.7)
Time on treatment, months						
Mean (SD)	7.4 (5.4)	6.5 (5.5)	7.1 (5.5)	10.15	9.18	9.66
Median	6.2	5.3	5.9	9.40	7.72	8.67
Range	0.1, 23.9	0.0, 25.1	0.0, 25.1	0.1, 29.9	0.1, 31.0	0.1, 31.0

Source: Original NDA Module 2.7.4 Table 9 and Module 5.3.5.3 – SCS Table 14.1.2; 60-Day Update SCS Tables 14.1.2, 14.3.1

[#] Patient (b) (6) started at 160 mg QD by mistake

Table 8.33 Original NDA and 60-Day Update: Selpercatinib Relative Dose Intensity for Overall Safety Population

	Original NDA			60-Day Update		
	***RET*-mutant MTC**	***RET* Fusion-positive NSCLC**	**Overall**	***RET*-mutant MTC**	***RET* Fusion-positive NSCLC**	**Overall**
N	226	253	531	299	329	702
Relative dose intensity (%)						
Mean (SD)	87.3 (18.9)	87.5 (18.2)	87.6 (18.3)	86.9	85.5	86.5
Median	97.8	97.7	97.7	97.0	96.3	96.7
Range	13.0, 100.0	21.3, 100.0	13.0, 100.0	21.4, 100.0	15.8, 100.1	15.8, 100.1
Category, n (%)						
≥ 90%	154 (68.1)	168 (66.4)	357 (67.2)	201 (67.2)	202 (61.4)	457 (65.1)
75–90%	20 (8.8)	29 (11.5)	56 (10.5)	28 (9.4)	50 (15.2)	85 (12.1)
50–75%	37 (16.4)	43 (17.0)	87 (16.4)	50 (16.7)	52 (15.8)	110 (15.7)
< 50%	15 (6.6)	13 (5.1)	31 (5.8)	20 (6.7)	25 (7.6)	50 (7.1)

Source: Original NDA Module 2.7.4 Table 10 and Module 5.3.5.3 – SCS Table 14.3.1; 60-Day Update SCS Table 14.3.1

Table 8.34 Original NDA and 60-Day Update: Selpercatinib Dose Modifications

	Original NDA			60-Day Update		
	***RET*-mutant MTC**	***RET* Fusion-positive NSCLC**	**Overall**	***RET*-mutant MTC**	***RET* Fusion-positive NSCLC**	**Overall**
N	226	253	531	299	329	702
Dose reduction, n (%)						
Any	60 (26.5)	73 (28.9)	145 (27.3)	89 (29.8)	123 (37.4)	230 (32.8)
For AE	56 (24.8)	68 (26.9)	136 (25.6)	82 (27.4)	117 (35.6)	217 (30.9)
Intra-Patient Dose Escalation	0	0	0	1 (0.3)	0	1 (0.1)
For other reason	8 (3.5)	7 (2.8)	17 (3.2)	12 (4.0)	12 (3.6)	26 (3.7)
Dose interruption, n (%)						
Any	110 (48.7)	136 (53.8)	278 (52.4)	163 (54.5)	208 (63.2)	412 (58.7)
For AE	101 (44.7)	122 (48.2)	251 (47.3)	147 (49.2)	181 (55.0)	363 (51.7)
For other reason	20 (8.8)	27 (10.7)	54 (10.2)	40 (13.4)	58 (17.6)	108 (15.4)
Dose increase, n (%)						
Any	32 (14.2)	54 (21.3)	100 (18.8)	49 (16.4)	73 (22.2)	138 (19.7)
Intra-patient escalation[1]	23 (10.2)	34 (13.4)	69 (13.0)	22 (7.4)	31 (9.4)	64 (9.1)
Reescalation[2]	5 (2.2)	15 (5.9)	21 (4.0)	19 (6.4)	37 (11.2)	60 (8.5)
Other reason	10 (4.4)	6 (2.4)	17 (3.2)	15 (5.0)	11 (3.3)	27 (3.8)

Source: Original NDA Module 2.7.4 Table 11 and Module 5.3.5.3 – SCS Table 14.3.2; 60-Day Update SCS Table 14.3.2

[1] Started at a lower dose during dose escalation that was subsequently increased

[2] Reescalation after a dose reduction

The FDA's Assessment:

Overall, 95% of the population received at least one dose of selpercatinib of 160 mg BID, the RP2D and dose proposed for approval. Eighty-seven percent (87%) of the OSAS received the RP2D as the starting dose, with 7.5% receiving the RP2D as a result of intra-patient dose escalation. Given that very small number of patients who did not receive the RP2D would be unlikely to dilute relevant safety signals given the size of the OSAS, the reviewer considered the entire OSAS as the relevant population for analyses.

Relevant Characteristics of the Safety Population

The Applicants Position: [Original NDA Module 2.7.4.4.2; 60-Day Update SCS Tables 14.2.1, 14.2.2, 14.2.3, 14.2.4]

The OSAS included a total of 531 patients in the Original NDA, and 702 patients in the 60-Day Update (Table 8.35). In the Original NDA, this population was primarily comprised of two tumor types: 256 (48.2%) NSCLC patients (253 with *RET* fusion-positive NSCLC and 3 patients who did not harbor a *RET* fusion) and 232 (43.7%) MTC patients (226 with *RET*-mutant MTC and 6 patients who did not harbor a known activating *RET* alteration or whose *RET* alteration status was unknown); additionally, there were 43 patients also included in the OSAS with other tumor types, including: 28 patients (5.3%) with thyroid cancer (none carry a diagnosis of MTC), 4 patients (0.8%) with *RET* fusion-positive pancreatic cancer and 11 patients (2.0% with other tumor types (some with activating *RET* alterations and some without) (Table 8.36). The 60-Day Update included 702 total patients, distributed similarly: 332 (47.3%) NSCLC patients (329 with *RET* fusion-positive NSCLC and 3 patients who did not harbor a *RET* fusion) and 306 (43.6%) MTC patients (299 with *RET*-mutant-positive MTC and 7 patients who did not harbor a known activating *RET* alteration or whose *RET* alteration status was unknown); additionally, there were 64 patients also included in the OSAS with other tumor types, including 38 patients (5.4%) with thyroid cancer (none carry a diagnosis of MTC), 7 patients (1.0%) with *RET* fusion-positive pancreatic cancer, and 19 patients (2.7%) with other tumor types (some with activating *RET* alterations and some without) (Table 8.36).

In the OSAS, the percentage of patients who were Stage IV at diagnosis was consistent across the Original NDA and the 60-Day Update (92.7% Original NDA, 92.2% 60-Day Update); likewise, the percentage of patients who had metastatic disease remained consistent (98.5% Original NDA, 97.9% 60-Day Update) (Table 8.36). In the same group in the Original NDA, 66.3% of patients underwent surgery for their primary cancer, 49.3% had received radiotherapy, and 77.6% had received some type of systemic therapy. The percentages were similar for the 60-Day Update: 65.7% of patients underwent surgery for their primary cancer, 46.9% had received radiotherapy, and 74.8% had received some type of systemic therapy.

It was more common for the MTC patients to have prior surgery than the NSCLC patients in the Original NDA (86.7% vs 44.7%, respectively) and in the 60-Day Update (87.0% vs 42.6%, respectively) (Table 8.36). This difference continues to reflect the natural history of each disease, with most patients with MTC diagnosed at an early stage and treated initially with surgery. The median duration of metastatic disease prior to treatment with selpercatinib was similar in the Original NDA and the 60-Day Update for *RET*-mutant MTC (48.1 months Original NDA, 48.6 months 60-Day Update); and was also similar for *RET* fusion-positive NSCLC (12.5 months Original NDA, 11.8 months 60-Day Update). At the time of study enrollment, most patients in the Original NDA and the 60-Day Update had an ECOG score of either 0 (35.6% Original NDA, 36.5% 60-Day Update) or 1 (60.3% Original NDA, 58.8% 60-Day Update).

Subgroup safety analyses were performed to evaluate the potential impact of age, sex and race on the frequency and nature of AEs; few trends were identified in both the original NDA and the 60-Day-Update.

Please reference Table 8.35 and Table 8.36 for a summary of demographics and baseline characteristics for *RET* fusion-positive NSCLC, *RET*-mutant MTC and the OSAS populations, respectively, for the Original NDA and 60-Day Update.

Table 8.35 Original NDA and 60-Day Update: Patient Demographics

	Original NDA			60-Day Update		
	***RET*-mutant MTC**	***RET* Fusion-positive NSCLC**	**Overall**	***RET*-mutant MTC**	***RET* Fusion-positive NSCLC**	**Overall**
N	226	253	531	299	329	702
Sex, n (%)						
Male	148 (65.5)	108 (42.7)	286 (53.9)	184 (61.5)	144 (43.8)	368 (52.4)
Female	78 (34.5)	145 (57.3)	245 (46.1)	115 (38.7)	185 (56.2)	334 (47.6)
Race, n (%)						
White	200 (88.5)	130 (51.4)	372 (70.1)	262 (87.6)	165 (50.2)	485 (69.1)
Asian	6 (2.7)	103 (40.7)	112 (21.1)	12 (4.0)	136 (41.3)	154 (21.9)
Black	2 (0.9)	12 (4.7)	16 (3.0)	4 (1.3)	16 (4.9)	24 (3.4)
American Indian or Alaska Native	–	–	–	1 (0.3)	1 (0.3)	2 (0.3)
Native Hawaiian or Other Pacific Islander	–	–	–	1 (0.3)	0	2 (0.3)
Other/ Unknown	18 (8.0)	8 (3.1)	31 (5.8)	19 (6.4)	11 (3.3)	35 (5.0)
Age group, n (%)						
< 18 years	3 (1.3)	0	3 (0.6)	3 (1.0)	0	3 (0.4)
18–44	46 (20.4)	31 (12.3)	89 (16.8)	67 (22.4)	39 (11.9)	123 (17.5)
45–64	108 (47.8)	126 (49.8)	258 (48.6)	136 (45.5)	169 (51.4)	337 (48.0)
65–74	49 (21.7)	76 (30.0)	135 (25.4)	61 (20.4)	96 (29.2)	172 (24.5)
≥ 75 years	20 (8.8)	20 (7.9)	46 (8.7)	32 (10.7)	25 (7.6)	67 (9.5)
Age, years						
Mean (SD)	56.1 (14.6)	59.5 (11.7)	57.7 (13.5)	55.9	59.4	57.5
Median	58	61	59	58.0	61.0	59.0
Range	15, 90	23, 86	15, 90	15, 90	23, 92	15, 92

Source: Original NDA Module 2.7.4 Table 7 and Module 5.3.5.3 – SCS Table 14.3.2; 60-Day Update SCS Table 14.2.1

Table 8.36 Original NDA and 60-Day Update: History and Characteristics of Primary Cancer

	Original NDA			60-Day Update		
	***RET*-mutant MTC**	***RET* Fusion-positive NSCLC**	**Overall**	***RET*-mutant MTC**	***RET* Fusion-positive NSCLC**	**Overall**
N	226	253	531	299	329	702
Tumor type, n (%)						
NSCLC	0	253 (100)	256 (48.2)	0	329 (100)	332 (47.3)
MTC	226 (100)	0	232 (43.7)	299 (100)	0	306 (43.6)
Other thyroid	0	0	28 (5.3)	0	0	38 (5.4)
Pancreas	0	0	4 (0.8)	0	0	7 (1.0)
Other	0	0	11 (2.0)	0	0	19 (2.7)
Stage at diagnosis, n (%)						
I	1 (0.4)	4 (1.6)	5 (0.9)	1 (0.3)	4 (1.2)	5 (0.7)
II	3 (1.3)	6 (2.4)	10 (1.9)	4 (1.3)	7 (2.1)	12 (1.7)
III	3 (1.3)	10 (3.9)	14 (2.6)	9 (2.9)	15 (4.6)	27 (3.8)
IV	213 (94.2)	232 (91.7)	492 (92.7)	278 (93.0)	302 (91.8)	647 (92.2)
Unknown stage	6 (2.7)	1 (0.4)	10 (1.9)	7 (2.4)	1 (0.3)	11 (1.6)
Metastatic disease at enrollment, n (%)	223 (98.7)	248 (98.0)	523 (98.5)	293 (98.7)	322 (97.9)	687 (97.9)
Duration, months						
Mean (SD)	67.5 (70.8)	20.7 (22.1)	45.0 (60.3)	72.32	20.16	46.64
Median	48.1	12.5	23.3	48.60	11.80	22.35
Range	0.5, 522.8	0.0, 108.1	0.0, 522.8	0.5, 593.1	0.0, 127.4	0.0, 593.1
Prior cancer treatment, n (%)						
Surgery	196 (86.7)	113 (44.7)	352 (66.3)	260 (87.0)	140 (42.6)	461 (65.7)
Radiotherapy	104 (46.0)	132 (52.2)	262 (49.3)	133 (44.5)	166 (50.5)	329 (46.9)
Systemic regimen(s)	148 (65.5)	214 (84.6)	412 (77.6)	186 (62.2)	269 (81.8)	525 (74.8)
1–2	111 (49.1)	124 (49.0)	263 (49.5)	142 (47.5)	157 (47.7)	339 (48.3)
≥ 3	37 (16.4)	90 (35.6)	149 (28.1)	44 (14.7)	112 (34.0)	185 (26.4)
RET alteration, n (%)						
Fusion	0	253 (100)	291 (54.8)	0	329 (100)	387 (55.1)
Mutation	226 (100)	0	233 (43.9)	299 (100.0)	0	307 (43.7)
Other	0	0	1 (0.2)	0	0	2 (0.3)
None	0	0	6 (1.1)	0	0	0
ECOG status, n (%)						
0	82 (36.3)	94 (37.2)	189 (35.6)	111 (37.1)	121 (36.8)	256 (36.5)
1	132 (58.4)	154 (60.9)	320 (60.3)	172 (57.5)	197 (59.9)	413 (58.8)
2	12 (5.3)	5 (2.0)	22 (4.1)	16 (5.4)	11 (3.3)	33 (4.7)
3	0	0	0	0	0	1 (0.1)

Source: Original NDA Module 2.7.4 Table 8 and Module 5.3.5.3 – SCS Tables 14.2.1, 14.2.2, 14.2.3, 14.2.4; 60-Day Update SCS
Tables 14.2.1, 14.2.2, 14.2.3, 14.2.4

The FDA's Assessment:
FDA agrees with the Applicant's description of the safety population including Tables 8.32 and 8.33 above. Regarding prior therapy in the safety population, 93.2% of patients with MTC in the OSAS had been treated with a prior multi-kinase inhibitor (MKI). Among patients with NSCLC in the OSAS, 78.7% had received prior chemotherapy, and 77.9% had received prior platinum chemotherapy. 45.8% of patients with NSCLC in the OSAS had received prior anti-PD1or PD-L1 therapy and 42.9% had received both a prior PD1 and platinum chemotherapy.

Adequacy of the safety database:

The Applicant's Position: [Original NDA Module 2.7.4.2; 60-Day Update Assessment Aid Addendum Table 8.31]

The safety database contains an adequate number of patients treated with selpercatinib (n = 531 in the Original NDA, n = 702 in the 60-Day Update) to provide a reasonable estimate of adverse reactions that may be observed with selpercatinib. *RET* fusion-positive NSCLC (n = 253 in the Original NDA, n = 329 in the 60-Day Update) and *RET*-mutant-positive MTC (n = 226 in the Original NDA, n = 299 in the 60-Day Update) were well-represented. Across all treated patients, the median time on treatment in the Original NDA was 5.9 months, ranging up to 25.1 months (and ongoing as of the data cutoff for the Original NDA); in the 60-Day Update, the median time on treatment was 8.7 months, ranging up to 31.0 months (and ongoing as of the data cutoff for the 60-Day Update). The median time on treatment are affected by administrative censoring resulting from the data cutoff for the analysis and will grow longer with subsequent data cuts.

This 60-Day Update, with a cutoff date of 16 December 2019, provides an additional 6 months of follow up relative to the 17 June 2019 data cutoff date used in the Original NDA submission.

The FDA's Assessment:
FDA agrees with the Applicant's assessment of the adequacy of the safety database. The safety narratives were also adequate to allow further assessment of relevant safety signals.

8.2.4 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

There were no data issues identified.

This NDA submission and 60-Day Update contains all the required components of the electronic Common Technical Document (eCTD). Analysis-ready, efficacy and safety datasets, which support the efficacy and safety of selpercatinib for LOXO-RET-17001, are provided.

The FDA's Assessment:
FDA agrees that the submission, including safety datasets and summary documents, was adequate to support the safety analysis.

Categorization of Adverse Event

The Applicant's Position: [Module 2.7.4.3.4]

The reported verbatim AE term was assigned a preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 and categorized by System Organ Class. Treatment-emergent adverse events (TEAEs) were defined as those with onset (or worsening) after administration of the first dose of study drug (more simply referred to as "AEs").

The severity of each AE was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. If a patient experienced repeat episode of the same AE (as defined by the MedDRA System Organ Class and preferred term), then the event with the highest reported severity grade and the strongest causal relationship to study drug was used for purposes of the incidence tabulations. In the event multiple actions taken with study drug are reported for the same AE, the most significant action taken with study drug will be used for purposes of the incidence tabulations. The significance order of the action taken with drug is withdrawn, reduced, interrupted.

AEs deemed to be of special interest for selpercatinib are hepatic effects/potential liver toxicity (inclusive of AST/ALT [transaminase] elevations and the analysis of potential Hy's Law cases), hypertension and drug hypersensitivity. AST/ALT elevations were frequent observations, with a high degree of relatedness to the study drug. The analysis of hepatic effects included procedures for identifying potential Hy's Law cases (none were identified). Hepatic effects were also evaluated using conventional summary statistics and toxicity shift analysis. Hypertension was also a frequent observation, with a high degree of relatedness to the study drug. This AE was evaluated using conventional summary statistics and toxicity shift analysis. Drug hypersensitivity was defined as a constellation of symptoms inclusive of maculopapular rash that was often preceded by fever and associated with arthralgias or myalgias, and followed commonly by decreased platelet count and/or increased transaminases, or less commonly by a decrease in blood pressure, tachycardia and/or increased creatinine. Drug hypersensitivity was rare and occurred during the first cycle of therapy. The reaction was recognized and defined early during clinical development, and termed hypersensitivity reaction or drug hypersensitivity reaction to allow for uniform safety reporting of these events by Investigators and overall frequency interpretation across the study.

Hematology, liver function tests, thyroid function tests and serum chemistry values were summarized in a descriptive manner by calculating the mean, standard deviation, median, and

range of values at baseline, the post-baseline minimum, the post-baseline maximum, and the last available post-baseline value. Using CTCAE toxicity grades when available, conventional shift tables were constructed showing baseline vs "worst" post-baseline value. For analytes without toxicity grades, similar tables displayed shifts relative to the normal range (above or below).

The FDA's Assessment:
FDA agrees with the Applicant's description of AE categorization.

Routine Clinical Tests

The Applicant's Position:

Laboratory assessments were performed at baseline prior to selpercatinib dosing, at regularly scheduled intervals and when medically necessary during drug administration. Additionally, vital sign measurements, physical exams, performance status, ECG tracings and pregnancy testing were also collected to allow for adequate safety monitoring. Please reference the LOXO-RET-17001 Assessment Table (Table 8.1) for a list of routine clinical tests. [CSR LOXO-RET-17001 Section 9.5.1.1]

The FDA's Assessment:
FDA has no additional comments regarding routine clinical testing.

8.2.5 Safety Results

Deaths

The Applicant's Position: [Original NDA Module 2.7.4.5.9.2; 60-Day Update Assessment Aid Addendum Table 8.37]

In the Original NDA, 43 of the 531 treated patients died by the data cutoff date and 19 (3.6%) of them died either while receiving selpercatinib or within 28 days of their last dose; 11 of these 19 deaths were attributed to an AE, 7 to disease progression, and 1 patient died of unknown causes. In the 60-Day Update, 75 of the 702 treated patients died by the data cutoff date, and 27 (3.8%) of the 75 patients died either while receiving selpercatinib or within 28 days of their last dose (60-Day Update SCS Table 14.4.18); of these 27 deaths, 13 were attributed to an AE, 13 to disease progression, and 1 patient died of unknown causes.

In the Original NDA, the 11 deaths that were due to an AE included cardiac arrest (2 patients), respiratory failure (2 patients), sepsis, cardiorespiratory arrest, cerebrovascular accident, postprocedural hemorrhage, hemoptysis, cerebral hemorrhage, and multiorgan dysfunction

syndrome (1 each) (Table 8.37). In the 60-Day Update, there were a total of 13 deaths that were due to an AE, this included:

- 10 patient deaths presented in the Original NDA
- 1 patient death presented in the Original NDA as AE cardiorespiratory arrest (b) (6) was updated to disease progression for the 60-Day Update
- 3 additional patient deaths due to the AE of cardiac failure, obstruction gastric, and brain herniation.

In the Original NDA, a fatal (Grade 5) AE was reported in a total of 15 patients. At the time of the data cutoff for the 60-Day Update, a fatal AE was reported in a total of 21 patients; 6 additional deaths since the Original NDA. There were no fatal AEs attributed to selpercatinib. Of the 21 patients with a fatal AE:

- 13 occurred on study (see above and Table 8.37).
- 3 deaths were reported as Grade 5 (fatal) AE that occurred concurrent with disease progression, thus cause of death was listed as disease progression (patient (b) (6) (neoplasm progression), patient (b) (6) (cardiac arrest) and patient (b) (6) (general physical health deterioration)).
- 5 patients died > 28 days after last study dose (2 events of sepsis [1 of whom was (b) (6) whose cause of death was presented in the Original NDA as Disease Progression and updated as AE sepsis] and 1 each: hypoxia, pneumonia and respiratory failure) (60-Day Update SCS Listing 16.2.3.3).

All 27 patients (19 patients in the Original NDA and 8 additional patients at the data cutoff for the 60-Day Update) who died either while receiving selpercatinib or within 28 days of their last dose and have CSR narratives summaries included for review (CSR LOXO-RET-17001 Section 14.3.3).

Table 8.37 Original NDA and 60-Day Update: Deaths Within 28 Days of Last Selpercatinib Dose

	Selpercatinib starting dose	Total days of treatment	Death on treatment	Study day of death	Days from last dose to death	Primary cause of death	Original NDA or 60-Day Update
(b) (6)	20 mg QD	8	no	24	16	Disease progression	Original NDA
	20 mg BID	3	no	8	5	Adverse event (Sepsis)	Original NDA
	60 mg BID	65	yes	70	5	Other (unknown)	Original NDA
	160 mg BID	406	no	410	4	Adverse event (Cardiac arrest)	Original NDA
	160 mg BID	130	yes	137	7	Adverse event (Cerebrovascular accident)	Original NDA
	160 mg BID	110	yes	112	2	Adverse event (Respiratory failure)	Original NDA
	160 mg BID	73	no	96	23	Disease progression[b]	Original NDA
	120 mg BID	312	no	337	25	Disease progression	Original NDA
	160 mg BID	27	yes	34	7	Adverse event (Postprocedural hemorrhage)	Original NDA
	160 mg BID	116	yes	118	2	Adverse event (Hemoptysis)	Original NDA
	160 mg BID	72	no	91	19	Disease progression	Original NDA
	160 mg BID	76	no	87	11	Adverse event (Respiratory failure)	Original NDA
	160 mg BID	53	no	67	14	Adverse event (Cerebral hemorrhage)	Original NDA
	160 mg BID	65	no	81	16	Adverse event (Cardiac arrest)	Original NDA
	160 mg BID	6	no	13	7	Adverse event (Multiple organ dysfunction)	Original NDA
	160 mg BID	274	no	276	2	Disease progression	Original NDA
	160 mg BID	57	no	75	18	Disease progression	Original NDA
	160 mg BID	84	no	88	4	Disease progression	Original NDA
	160 mg BID	56	no	66	10	Disease progression	Original NDA

	Selpercatinib starting dose	Total days of treatment	Death on treatment	Study day of death	Days from last dose to death	Primary cause of death	Original NDA or 60-Day Update
(b) (6)	160 mg BID	443	no	471	28	Disease progression	60-Day Update
	160 mg BID	113	no	120	7	Disease progression	60-Day Update
	60 mg BID	698	no	717	19	Adverse event (Cardiac failure)	60-Day Update
	160 mg BID	78	no	103	25	Disease progression	60-Day Update
	160 mg BID	111	no	129	18	Disease progression	60-Day Update
	160 mg BID	211	no	236	25	Disease progression	60-Day Update
	160 mg BID	89	no	96	7	Adverse event (Obstruction gastric)	60-Day Update
	160 mg BID	37	no	61	24	Adverse event (Brain herniation)	60-Day Update

[a] Patient had delayed dosing due to radiotherapy but died before drug was restarted
[b] Primary cause of death reported as AE cardiorespiratory arrest at Original NDA
Source: Original NDA Module 2.7.4 Table 26 and Module 5.3.5.3 – SCS Listings 16.2.1.2, 16.2.3.1.1, 16.2.3.3; 60-Day Update SCS Listings 16.2.1.2, 16.2.3.1.1, 16.2.3.3

The FDA's Assessment:
FDA confirmed the information and reviewed all narratives for deaths summarized in the table above. Selected narratives are summarized below, including several events of severe hemorrhage.

- Patient (b) (6) This is a 54-year-old female with metastatic MTC who developed Grade 5 post-procedural hemorrhage (tracheostomy site hemorrhage) 27 days after initiating treatment with selpercatinib. Prior treatment included total thyroidectomy with central neck dissection and multiple subsequent surgeries including tracheal resection, tracheal reconstructions and right neck dissections, as well as liver ablations. She also received intensity modulated radiation therapy. The patient presented via EMS with significant bleeding from her tracheostomy site, which had stopped by the time of arrival to the hospital; coagulation studies and platelet count were normal. Chest x-ray demonstrated ill-defined interstitial opacities and the lung bases (mild pulmonary edema vs. subsegmental atelectasis). She was admitted to the ICU for monitoring. The next day, bleeding resumed and the patient went into cardiopulmonary arrest; intubation could not be performed due to large distal hemorrhage in the trachea, and the patient died. An autopsy was not performed. The adverse event was reported as post-procedural hemorrhage which was unrelated to selpercatinib.

  Reviewer note: The patient experienced bleeding at the tracheostomy site after multiple surgeries and radiation for tumor control and tracheal reconstruction in the same area; however, the event occurred years after these local control measures. It is possible that selpercatinib contributed to bleeding in this event, but interpretation of an assessment of relatedness is confounded by the patient's prior history.

- Patient (b) (6) This is a 56-year-old male with metastatic MTC who developed Grade 5 hemoptysis 4 months after beginning therapy with selpercatinib. The patient had previously undergone bilateral complicated neck, mediastinal and paratracheal dissection, subtotal thymectomy, and total thyroidectomy and received intensity modulated radiation therapy; he also received treatment with vandetanib. One week prior to the event, the patient was hospitalized for acute hypoxemic respiratory failure and treated for bronchitis; CT angiogram excluded pulmonary embolism at that time, though the narrative states that there was suboptimal opacification of the pulmonary arteries. After discharge, the patient began to experience hemoptysis. The patient then experienced cardiac arrest during a CT scan and was resuscitated; the narrative notes that intubation was difficult. During this time he experienced severe hemoptysis. A chest X-ray was consistent with aspiration pneumonia. The patient became comatose; the patients' family elected to withdraw care and the patient died. The cause of death was attributed to hemoptysis, and assessed as not related to selpercatinib. The investigator felt that the most likely etiology for this event was considered to be acute

pulmonary pathology and respiratory arrest, originally diagnosed as acute bronchitis but potentially representing an undiagnosed pulmonary embolism.

Reviewer note: Additional information was requested during the course of the review regarding this case. The patient had multiple prior surgeries in the neck and mediastinum and had a history of receiving radiation, though these are relatively remote events. The event may represent an undiagnosed pulmonary embolism but given the lack of imaging findings at the time of initial hypoxemia could represent a case of pneumonitis (see below discussion of serious adverse events). As in the prior narrative, it is possible that selpercatinib contributed to bleeding in this event. Interpretation of an assessment of relatedness is limited by the lack of a known etiology of hemoptysis.

- Patient (b) (6) This is a 54-year-old male with metastatic NSCLC who developed Grade 5 cerebral hemorrhage. The patient had brain metastases at study entry, and presented with right frontal hemorrhage at the site of prior brain metastases in the setting of pancytopenia (values not provided). The patient died after clinically declining following an external ventricular drain placement, supraorbital and frontal craniotomy. The cause of death was listed as intracerebral hemorrhage and was assessed as unrelated to selpercatinib.

  Reviewer note: The event of cerebral hemorrhage is confounded by the presence of brain metastases.

  A broad analysis of events of hemorrhage is provided in Section 8.2.5.

- Patient (b) (6) This is a 70-year-old with NSCLC with history of pleural effusions and a recent diagnosis of a pulmonary embolus hospitalized for hypoxia with increase in the size of malignant pleural effusions. A pleural catheter was placed and anticoagulation was held. During this hospitalization, the patient's code status was updated to "do not resuscitate" (DNR). Thirteen days after this event (five days after discharge) the investigator was notified that the patient had died and that the death was likely from a blood clot. However, as additional details were not available the reported cause in the table above was "other (unknown)."

- Patient (b) (6) This is an 84-year-old male with metastatic MTC who experienced cardiac arrest during a hospitalization for sepsis following a transition to comfort care measures.

- Patient (b) (6): This is a 61-year-old female with non-small cell lung cancer who experienced cardiac arrest within 30 days after stopping therapy with selpercatinib due to disease progression. The event was considered related to metabolic acidosis secondary to metastatic lung cancer.

- Patient (b) (6) This is a 46-year-old female with metastatic non-small cell lung cancer died due to cardio-respiratory arrest secondary to underlying cancer. Notably, the patient had interrupted selpercatinib 23 days prior to the event in order to undergo palliative radiation therapy.

- Patient (b) (6) This is a 67-year-old male with NSCLC previously treated with nivolumab, ipilimumab and cabozantinib who experienced a cerebrovascular accident in the setting of severe illness with worsening peritoneal carcinomatosis and ascites, pleural effusion and cardiac tamponade.

- Patient (b) (6) This is an 80 year-old male with MTC who had received no prior systemic therapy who developed Grade 4 left ventricular dysfunction nearly 2 years after initiation of selpercatinib. The patient had a history of hypertension and hypercholesterolemia. The patient presented with weakness, ascites and abdominal distension; ECG suggested myocardial infarction 24 - 48 hours prior to presentation and the patient was diagnosed with acute systolic heart failure. The patient was discharged to hospice and died approximately 10 days after the initial diagnosis of heart failure.

In addition to the narratives listed in the table, FDA reviewed narratives for three patients who had treatment-emergent Grade 5 events in the 60-day update safety database:

- Patient (b) (6) This is a 67-year-old female with NSCLC previously treated with platinum based chemotherapy, pembrolizumab, bevacizumab/docetaxel, gemcitabine, vinorelbine and external beam radiation therapy (EBRT) who developed Grade 5 hypoxia 5 weeks after starting selpercatinib. Two weeks prior to presentation for the fatal event, the patient was evaluated and hospitalized for Grade 3 hypoxia and was discharged on trimethoprim sulfamethoxazole for treatment of PCP. Four days later, the patient presented again with hypoxia, was admitted to the ICU and intubated. She was treated with antibiotics, steroids, and ventilatory support and died two weeks later. The investigator considered the event unrelated to selpercatinib.

- Patient (b) (6) This is a 54-year-old with NSCLC previously treated with platinum based chemotherapy, nivolumab, alectinib, and EBRT who experienced Grade 5 pneumonia approximately 14 months after initiating selpercatinib. She was hospitalized for *Enterobacter* hospital acquired pneumonia with left lung collapse and right lung consolidation. The patient ultimately died after prolonged hospitalization.

- This is a 71-year-old male with NSCLC previously treated with EBRT who died of respiratory failure less than one month after initiating treatment with selpercatinib. The patient experienced respiratory failure while hospitalized for cancer pain; treatment included prednisone and furosemide. The patient also experienced Grade 4 thrombocytopenia and Grade 2 hematochezia. While receiving 10 liters per minute

supplemental oxygen, the patient's condition declined rapidly. The narrative states that the worsening respiratory status was suspicious for disease progression or infection.

FDA agrees that based on the information provided, the deaths were not likely to be related to selpercatinib.

Serious Adverse Events

The Applicant's Position:

The analysis of SAEs presented are based on the adverse event dataset and include the overall analysis safety population using the data submitted to support the Original NDA for patients who reported an AE that met any of the serious criteria, whether or not the event was judged to be related to study drug. SAEs were defined as any AE that met one of the following criteria: [CSR LOXO-RET-17001, Appendix 16.1.1]

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in disability/ incapacity.
- Is a congenital anomaly/ birth defect.
- Is an important medical event.

One or more SAEs occurred in 162 patients (30.3%) in the Original NDA, and in 234 patients (33.3%) in the 60-Day Update. SAEs considered related to selpercatinib occurred in only 6.2% of patients in the Original NDA, and in 7.7% in the 60-Day Update (Table 8.38). In the Original NDA, the most common SAEs were ALT increase, AST increase, pneumonia (each 2.1%), dyspnea (1.7%), and hyponatremia (1.5%); the SAEs most frequently considered related to selpercatinib were AST and ALT increase (both 1.5% of patients), followed by Drug hypersensitivity (1.1%). In the 60-Day Update, the most common SAEs were similar: pneumonia (3.0%), ALT increase, AST increase, dyspnea, and hyponatremia (each 1.7%), and abdominal pain (1.4%); the SAEs most frequently considered related to selpercatinib were also similar in the 60-Day Update: AST and ALT increase (both 1.3% of patients), followed by drug hypersensitivity (1.1%). [Original NDA Module 2.7.4.5.9.1; 60-Day Update SCS Tables 14.4.14, 14.4.15]

In the Original NDA, the incidences of the SAEs (NSCLC vs MTC) of dyspnea (3.2% vs 0.4%), drug hypersensitivity (2.4% vs 0%), and ALT and AST (both 3.2% vs 0.9%) were higher in NSCLC than MTC patients. The trend was similar in the 60-Day Update: dyspnea (2.4% vs 0.7%), drug hypersensitivity (2.4% vs 0%), and ALT and AST (both 2.7% vs 0.7%) were higher in NSCLC than MTC patients. [Original NDA Module 2.7.4.5.9.1; 60-Day Update SCS Tables 14.4.14, 14.4.15]

Table 8.38 Original NDA and 60-Day Update: Serious Adverse Events in 1% or More Patients

Preferred term	Incidence, n (%)							
	Original NDA				60-Day Update			
	RET-mutant MTC (N = 226)	*RET* Fusion-positive NSCLC (N = 253)	Overall (N = 531)	Overall Related (N = 531)	*RET*-mutant MTC (N = 299)	*RET* Fusion-positive NSCLC (N = 329)	Overall (N = 702)	Overall Related (N = 702)
1 or more SAEs	59 (26.1)	80 (31.6)	161 (30.3)	33 (6.2)	89 (29.8)	118 (35.9)	234 (33.3)	54 (7.7)
Pneumonia	3 (1.3)	7 (2.8)	11 (2.1)	0	7 (2.3)	13 (4.0)	21 (3.0)	0
ALT increased	2 (0.9)	8 (3.2)	11 (2.1)	8 (1.5)	2 (0.7)	9 (2.7)	12 (1.7)	9 (1.3)
AST increased	2 (0.9)	8 (3.2)	11 (2.1)	8 (1.5)	2 (0.7)	9 (2.7)	12 (1.7)	9 (1.3)
Dyspnea	1 (0.4)	8 (3.2)	9 (1.7)	0	2 (0.7)	8 (2.4)	12 (1.7)	0
Hyponatremia	3 (1.3)	3 (1.2)	8 (1.5)	0	3 (1.0)	7 (2.1)	12 (1.7)	0
Abdominal pain	1 (0.4)	1 (0.4)	5 (0.9)	1 (0.2)	4 (1.3)	1 (0.3)	10 (1.4)	2 (0.3)
Acute kidney injury	2 (0.9)	4 (1.6)	7 (1.3)	0	4 (1.3)	4 (1.2)	8 (1.1)	0
Diarrhea	3 (1.3)	1 (0.4)	4 (0.8)	1 (0.2)	5 (1.7)	3 (0.9)	8 (1.1)	3 (0.4)
Drug hypersensitivity	0	6 (2.4)	6 (1.1)	6 (1.1)	0	8 (2.4)	8 (1.1)	8 (1.1)
Dysphagia	1 (0.4)	3 (1.2)	6 (1.1)	0	1 (0.3)	4 (1.2)	7 (1.0)	1 (0.1)
Pleural effusion	0	4 (1.6)	4 (0.8)	0	1 (0.3)	6 (1.8)	7 (1.0)	0
Pyrexia	3 (1.3)	3 (1.2)	7 (1.3)	2 (0.4)	3 (1.0)	3 (0.9)	7 (1.0)	2 (0.3)
Sepsis	2 (0.9)	2 (0.8)	5 (0.9)	0	3 (1.0)	3 (0.9)	7 (1.0)	0

Source: Original NDA Module 2.7.4 Table 25 and Module 5.3.5.3 – SCS Tables 14.4.14, 14.4.15; 60-Day Update SCS Tables 14.4.14, 14.4.15

The FDA's Assessment:

FDA confirmed **Error! Reference source not found.**, though FDA does not necessarily agree with the column indicating the number of events assessed as related to selpercatinib. Of note, while this table provides all SAEs which occurred in ≥1% of all patients in the OSAS, there were certain SAEs which occurred in ≥1% of either the MTC or NSCLC safety population but not the overall population. Table 8.39provides the FDA analysis which includes these additional SAEs. Some SAEs which occurred at greater frequency in patients with MTC or NSCLC may be related to underlying disease, such as hypocalcemia in patients with MTC (who frequently have a history of parathyroidectomy) and respiratory SAEs such as pleural effusion, pneumothorax, and respiratory failure in patients with NSCLC.

Table 8.39: Serious Adverse Events in > 1% of patients with MTC or NSCLC

SAE	RET-mutant MTC (N=226) n (%)	RET Fusion-positive NSCLC (N=253) n (%)	Overall (N=531) n (%)
Hypertension	3 (1.3)	2 (0.8)	5 (0.9)
Squamous cell carcinoma of skin	1 (0.4)	3 (1.2)	5 (0.9)
Diarrhoea	3 (1.3)	1 (0.4)	4 (0.8)
Hypocalcaemia	4 (1.8)	0 (0.0)	4 (0.8)
Pleural effusion	0 (0.0)	4 (1.6)	4 (0.8)
Respiratory failure	0 (0.0)	4 (1.6)	4 (0.8)
Back pain	0 (0.0)	3 (1.2)	3 (0.6)
Hypersensitivity	0 (0.0)	3 (1.2)	3 (0.6)
Pneumothorax	0 (0.0)	3 (1.2)	3 (0.6)
Pulmonary embolism	0 (0.0)	3 (1.2)	3 (0.6)

In addition, FDA requested analyses of the incidence of SAEs in patients with RET fusion positive thyroid cancer. The table below provides the incidence of treatment emergent SAEs in at least 1% of the overall safety population (n=702). No other SAEs occurred in > 1 patient with RET fusion-positive thyroid cancer. A similar percentage of patients with each tumor type experienced SAEs.

Table 8.40: Serious Treatment-emergent Adverse Events by Preferred Term based on 60-day Update (Applicant Analysis)

Preferred Term	RET-mutant MTC (N=299) n (%)	RET Fusion-positive NSCLC (N=329) n (%)	RET Fusion-positive Thyroid Cancer (N= 37) n (%)	Overall Safety (N=702) n (%)
Patients with TESAEs	89 (29.8)	118 (35.9)	13 (35.1)	234 (33.3)
Pneumonia	7 (2.3)	13 (4.0)	1 (2.7)	21 (3.0)
Alanine aminotransferase increased	2 (0.7)	9 (2.7)	1 (2.7)	12 (1.7)
Aspartate aminotransferase increased	2 (0.7)	9 (2.7)	1 (2.7)	12 (1.7)
Dyspnoea	2 (0.7)	8 (2.4)	2 (5.4)	12 (1.7)
Hyponatraemia	3 (1.0)	7 (2.1)	1 (2.7)	12 (1.7)

Preferred Term	RET-mutant MTC (N=299) n (%)	RET Fusion-positive NSCLC (N=329) n (%)	RET Fusion-positive Thyroid Cancer (N= 37) n (%)	Overall Safety (N=702) n (%)
Abdominal pain	4 (1.3)	1 (0.3)	2 (5.4)	10 (1.4)
Acute kidney injury	4 (1.3)	4 (1.2)	0 (0.0)	8 (1.1)
Diarrhoea	5 (1.7)	3 (0.9)	0 (0.0)	8 (1.1)
Drug hypersensitivity	0 (0.0)	8 (2.4)	0 (0.0)	8 (1.1)
Dysphagia	1 (0.3)	4 (1.2)	2 (5.4)	7 (1.0)
Pleural effusion	1 (0.3)	6 (1.8)	0 (0.0)	7 (1.0)
Sepsis	3 (1.0)	3 (0.9)	1 (2.7)	7 (1.0)
Hypertension	3 (1.0)	3 (0.9)	0 (0.0)	6 (0.9)
Hypocalcaemia	6 (2.0)	0 (0.0)	0 (0.0)	6 (0.9)
Pyrexia	2 (0.7)	3 (0.9)	1 (2.7)	6 (0.9)
Respiratory failure	1 (0.3)	5 (1.5)	0 (0.0)	6 (0.9)
Dehydration	2 (0.7)	3 (0.9)	0 (0.0)	5 (0.7)
Lung infection	2 (0.7)	1 (0.3)	1 (2.7)	5 (0.7)

Source: Table 14.4.14

FDA reviewed trends in SAEs and selected narratives for review. Liver injury, bleeding events, acute kidney injury, pneumonia/pneumonitis, pleural and pericardial effusions, and tumor lysis syndrome were among those selected for further review. Liver injury, hypertension, and hypersensitivity events will be reviewed in Section 8.2.6.1.

Events of acute kidney injury were reported in seven patients (1.3%) in the OSAS. All narratives were reviewed and were assessed by the reviewer as unlikely related to the study drug. Some cases were confounded by recent or concomitant medications (such as concomitant NSAID use), concomitant hypertension, or acute illness with dehydration. All cases except one were noted to have resolved; in the remaining case the patient withdrew consent to the study prior to the event, and follow-up beyond one month was not available.

Serious bleeding events occurred in 12 (1.7 %) patients in the OSAS. These included three events resulting in death (hemoptysis, post-procedural hemorrhage, and cerebral hemorrhage) reviewed previously. The other serious events included upper gastrointestinal hemorrhage, lower gastrointestinal hemorrhage, anal hemorrhage, intracranial hemorrhage (n=2), hemoptysis, gastric hemorrhage, retroperitoneal hematoma and diverticulosis bleed. Five of the nine non-fatal events were confounded by concomitant anticoagulant medications

(acetylsalicylic acid, enoxaparin, or warfarin).

An analysis of serious pulmonary events was performed to evaluate the potential for pneumonitis using the terms pneumonia, lung infection, pneumonia aspiration, pulmonary edema, dyspnea , acute respiratory failure, and respiratory failure. There were no serious adverse events with the preferred term interstitial lung disease. Pleural effusions were evaluated separately (see below). Overall, 29 patients (5.4% of the OSAS based on the original DCO) experienced at least one of these events that was considered serious. Severe pulmonary events were more common in patients with NSCLC compared to patients with MTC or in the OSAS, which may be related to the potential for obstructive pathophysiology due to the location of the tumor.

Review of the narratives revealed that most of these cases were suspicious for bacterial pneumonia, disease progression, or malignant effusions and were not suggestive of pneumonitis. However, two patients who presented with respiratory failure who lacked definitive areas of consolidation on imaging were treated with steroids and represent potential cases of pneumonitis. The narratives for these patients are presented below:

- (b) (6): This is a 35-year-old female with metastatic NSCLC hospitalized for respiratory failure approximately 3 months after initiating selpercatinib. She presented to the emergency department following several days of worsening shortness of breath, and was afebrile with oxygen saturation in the 70s. Imaging demonstrated diffuse airspace opacities throughout both lung fields with left lower lobe dominance. Treatment included broad spectrum antibiotics, BiPAP, and corticosteroids. The differential diagnosis included sepsis or interstitial pneumonitis in the setting of tyrosine kinase inhibitor treatment, versus possible acute pulmonary edema related to systolic heart failure. The patient was discharged with a prednisone taper (recorded in ADCM.xpt as 1 month in duration), and subsequently restarted Loxo-292 at a reduced dose. Approximately 4 weeks later, the patient discontinued Loxo-292 related to progressive disease ("brain tumor" presumed to be brain metastases).

  Reviewer note: The diffuse findings on imaging and apparent response to corticosteroids could be consistent with pneumonitis related to selpercatinib. The patient's prior therapy included platinum-based chemotherapy and pembrolizumab in combination with pemetrexed; pembrolizumab was initiated five months prior to study entry completed two months prior to study entry. Although checkpoint-inhibitor-related pneumonitis usually occurs within several months of initiation of therapy, it can have a delayed onset; autoimmune phenomenon can occur even after discontinuation of immune checkpoint therapy. (Couey, 2019) The patient's underlying malignancy is also a confounder. Though the case is confounded, the role of selpercatinib cannot be excluded.

- (b) (6): This is a 56-year-old male with metastatic MTC who developed Grade 4 acute respiratory failure 4 months after beginning therapy with selpercatinib. The patient had previously undergone bilateral complicated neck, mediastinal and paratracheal dissection, subtotal thymectomy, and total thyroidectomy and received intensity modulated radiation therapy; he also received treatment with vandetanib. After presenting to the emergency department with shortness of breath, cough and congestion, patient was hospitalized for acute hypoxemic respiratory failure and treated for bronchitis with antibiotics and corticosteroids; CT angiogram excluded pulmonary embolism at that time though the narrative notes that the quality of the study was suboptimal. The patient was discharged home and subsequently began to experience hemoptysis; he did not initially present to medical attention. During a CT scan, he experienced cardiorespiratory arrest. Hemoptysis complicated resuscitation efforts and the patient died (See narrative in "Deaths" section above).
  Reviewer note: As discussed previously, the investigator felt that this case represented an undiagnosed case of pulmonary embolus. The etiology of these events is not clear based on objective findings. However, the case could represent an undiagnosed case of pneumonitis based on the presentation with hypoxia, lack of consolidation on chest x-ray and treatment with corticosteroids. Given the subsequent course and the clinical judgement of the investigator, pneumonitis is less likely in the opinion of this reviewer.

Though the event described above for patient (b) (6) could represent a potential case of pneumonitis that is related to selpercatinib, confounding factors (lung cancer, prior exposure to checkpoint inhibitor therapy) are present. Based on the data cutoff in the 60-day update, there were a total of 7 non-serious cases and no serious cases reported with a preferred term of pneumonitis (0.1%, Grade 1 – 2), one of which required dose interruption and was treated with steroids. The sponsor performed an analysis serious pulmonary events with the terms specified by FDA (pneumonia, lung infection, pneumonia aspiration, pulmonary edema, dyspnea , acute respiratory failure, and respiratory failure) including concomitant use of steroids. Sixty events in 46 patients met these criteria; 45 events were serious. Only one additional patient with a prolonged course (> 10 days) of steroids was identified, which represented an increase in chronic dosing of dexamethasone.
Reviewer note: This reviewer concludes that the safety database does not suggest a significant risk of pneumonitis in patients treated with selpercatinib.

In the OSAS (original data cut-off), 8 patients (1.5%) experienced serious adverse events of hyponatremia reported as adverse events; all were assessed as unrelated by the Applicant. Narratives were reviewed by FDA. In two cases, patients had baseline serum sodium < 125 mEq/L prior to starting treatment with selpercatinib; this reviewer agrees with assessing these events as unlikely related to selpercatinib. Five cases were confounded by the use of concomitant medications known to be associated with hyponatremia (thiazides, loop diuretics, and ACE inhibitors) for the treatment of hypertension or edema. Excluding these confounded cases, there was one SAE of Grade 3 hyponatremia in a patient with NSCLC who developed

hyponatremia after approximately two months of taking selpercatinib. It is possible that selpercatinib has contributed to these events of hyponatremia, but based on the narratives reviewed, it seems likely that these events are primarily iatrogenic due to concomitant medications administered to manage hypertension and edema.

In the OSAS based on the original DCO, 10 patients (1.9%) developed a serious event of hypersensitivity (preferred terms drug hypersensitivity, drug eruption and hypersensitivity) to selpercatinib. Events generally occurred 1 – 2 weeks (range 7 – 48 days, median 12 days) after initiating selpercatinib and involved fever and rash. In some cases, additional features included transaminase elevation, decrease in platelet count, or arthralgias. One patient was diagnosed with drug rash with eosinophilia and systemic symptoms (DRESS) after a skin biopsy. Standard treatment was with acetaminophen, antihistamines, and corticosteroids, along with holding selpercatinib. Drug rechallenge generally occurred with continued corticosteroid administration at a lower dose (40 mg BID according to guidance in the Investigator's Brochure and referenced in the protocol) with the potential to re-escalate. Three patients with serious events of hypersensitivity discontinued from the study due to the adverse event, including two who failed rechallenge; notably these patients re-initiated selpercatinib at 120 mg BID, consistent with the general dose modification guidance for all AEs, rather than the specific guidance for management of hypersensitivity.

Two patients had events consistent with tumor lysis syndrome (TLS) reported as SAEs; one was reported as hyperphosphatemia. Both events occurred in patients with systemic treatment-naïve MTC. The events occurred after 7 and 8 days of treatment. One patient required treatment with rasburicase and discontinued selpercatinib after recurrent TLS despite resuming drug at a lower dose. The other patient was treated with allopurinol.

Reviewer note: an analysis of potential additional events of TLS was performed through review of TEAEs (preferred terms of hyperuricemia, hyperphosphatemia and tumor lysis syndrome) and concomitant medications (medications indicated for tumor lysis syndrome, allopurinol, and rasburicase). This search revealed two patients for whom allopurinol was administered as prophylaxis. Additional events of hyperuricemia and hyperphosphatemia were identified, with a maximum Grade of 2; only two of these events resulted in interruption of study drug.

Dropouts and/or Discontinuations Due to Adverse Effects

<u>The Applicants Position:</u>

Nineteen patients (3.6%) in the Original NDA and 37 patients (5.3%) in the 60-Day Update experienced an AE that led to permanent treatment discontinuation (Table 8.41 and Table 8.42). In the Original NDA, only 4 of these AEs occurred in more than 1 patient each:

ALT increase, drug hypersensitivity, hypoxia, and sepsis (2 patients each, 0.4%). In the 60-Day Update, 6 of these AEs occurred in more than 1 patient each: ALT increase, sepsis (3 patients each, 0.4%), AST increase, drug hypersensitivity, fatigue, and thrombocytopenia (2 patients each, 0.3%). More AEs leading to treatment discontinuation occurred in NSCLC patients (11 in the Original NDA, 21 in the 60-Day Update) than MTC patients (5 in the Original NDA, 11 patients in the 60-Day Update), and more NSCLC patients experienced multiple AEs leading to treatment discontinuation (17 events among 11 patients in the Original NDA, 31 events among 21 patients in the 60-Day Update). In the Original NDA, only 9 of 19 patients (1.7% of the total) had treatment permanently discontinued for a treatment-related AE; in the 60-Day Update, 14 of 37 patients (2.0% of the total) had treatment permanently discontinued for a treatment-related AE (Table 8.41 and Table 8.42). [Original NDA Module 2.7.4.5.7; 60-Day Update Tables SCS 14.4.12, 14.4.13]

Table 8.41 Original NDA: Adverse Events Leading to Treatment Discontinuation

	Patient incidence, n (%)					
	***RET*-mutant MTC (N = 226)**		***RET* Fusion-positive NSCLC (N = 253)**		**Overall (N = 531)**	
Preferred term[1]	**All**	**Related**	**All**	**Related**	**All**	**Related**
Patients with AEs leading to drug discontinuation	5 (2.2)	4 (1.8)	11 (4.3)	4 (1.6)	19 (3.6)	9 (1.7)
ALT increased	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.4)	2 (0.4)
Drug hypersensitivity	0	0	2 (0.8)	2 (0.8)	2 (0.4)	2 (0.4)
Hypoxia	0	0	2 (0.8)	0	2 (0.4)	0
Sepsis	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
Abdominal pain	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
AST increased	0	0	1 (0.4)	0	1 (0.2)	0
Blood bilirubin increased	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
Cardiac dysfunction	0	0	0	0	1 (0.2)	0
Cerebral haemorrhage	0	0	1 (0.4)	0	1 (0.2)	0
Chills	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
Dysphagia	0	0	1 (0.4)	0	1 (0.2)	0
Erythema[1]	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
Hemiparesis	0	0	1 (0.4)	0	1 (0.2)	0
Hepatitis acute	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Jaundice cholestatic	0	0	0	0	1 (0.2)	0
Multiple organ dysfunction syndrome	0	0	1 (0.4)	0	1 (0.2)	0
Neutropenia	0	0	0	0	1 (0.2)	1 (0.2)
Rash	0	0	1 (0.4)	0	1 (0.2)	0
Tachycardia[1]	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
Tumour lysis syndrome	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Urinary retention	0	0	1 (0.4)	0	1 (0.2)	0

[1] Patient (b) (6) discontinued therapy due to tachycardia and erythema which occurred during drug re-exposure following a drug hypersensitivity reaction. These listed events are considered by the Sponsor to be a recurrence.

Source: Original NDA Module 2.7.4 Table 22 and Module 5.3.5.3 – SCS Table 14.4.12, Table 14.4.13

Table 8.42 60-Day Update: Adverse Events Leading to Treatment Discontinuation

	Patient incidence, n (%)					
	***RET*-mutant MTC (N = 299)**		***RET* Fusion-positive NSCLC (N = 329)**		**Overall (N = 702)**	
Preferred term[1]	**All**	**Related**	**All**	**Related**	**All**	**Related**
Patients with AEs leading to drug discontinuation	11 (3.7)	6 (2.0)	21 (6.4)	8 (2.4)	37 (5.3)	14 (2.0)
ALT increased	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)	3 (0.4)	3 (0.4)
Sepsis	1 (0.3)	0	1 (0.3)	0	3 (0.4)	0
AST increased	0	0	2 (0.6)	2 (0.6)	2 (0.3)	2 (0.3)
Drug hypersensitivity	0	0	2 (0.6)	2 (0.6)	2 (0.3)	2 (0.3)
Fatigue	0	0	2 (0.6)	1 (0.3)	2 (0.3)	1 (0.1)
Thrombocytopenia	0	0	2 (0.6)	1 (0.3)	2 (0.3)	1 (0.1)
Abdominal pain	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)
Bacteraemia	0	0	1 (0.3)	0	1 (0.1)	0
Blood bilirubin increased	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)
Cardiac dysfunction	0	0	0	0	1 (0.1)	0
Cardiac failure	1 (0.3)	0	0	0	1 (0.1)	0
Cerebral haemorrhage	0	0	1 (0.3)	0	1 (0.1)	0
Cerebral infarction	0	0	1 (0.3)	0	1 (0.1)	0
Drug eruption	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)
Dysphagia	0	0	1 (0.3)	0	1 (0.1)	0
Erythema[1]	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)
Febrile neutropenia	0	0	0	0	1 (0.1)	0
Gastric cancer	1 (0.3)	0	0	0	1 (0.1)	0
Hepatitis acute	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)
Hypersensitivity	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)
Hypoxia	0	0	1 (0.3)	0	1 (0.1)	0
Jaundice cholestatic	0	0	0	0	1 (0.1)	0
Multiple organ dysfunction syndrome	0	0	1 (0.3)	0	1 (0.1)	0
Muscular weakness	0	0	1 (0.3)	0	1 (0.1)	0
Obstruction gastric	0	0	0	0	1 (0.1)	0
Pericardial effusion	0	0	1 (0.3)	0	1 (0.1)	0
Pleurocutaneous fistula	0	0	1 (0.3)	0	1 (0.1)	0
Pneumatosis intestinalis	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)
Pneumonia	1 (0.3)	0	0	0	1 (0.1)	0
Pulmonary embolism	0	0	1 (0.3)	0	1 (0.1)	0
Rash	0	0	1 (0.3)	0	1 (0.1)	0
Retroperitoneal haematoma	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)
Sensation of foreign body	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)
Skin ulcer	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)
Squamous cell carcinoma	1 (0.3)	0	0	0	1 (0.1)	0
Tachycardia	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)
Transient ischemic attack	0	0	1 (0.3)	0	1 (0.1)	0
Tumour lysis syndrome	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)

	Patient incidence, n (%)					
	RET-mutant MTC (N = 299)		*RET* Fusion-positive NSCLC (N = 329)		Overall (N = 702)	
Preferred term[1]	**All**	**Related**	**All**	**Related**	**All**	**Related**
Urinary retention	0	0	1 (0.3)	0	1 (0.1)	0

1 Patient (b) (6) discontinued therapy due to tachycardia and erythema which occurred during drug re-exposure following a drug hypersensitivity reaction. These listed events are considered by the Sponsor to be a recurrence.

Source: 60-Day Update SCS Tables 14.4.12, 14.4.13

The FDA's Assessment:

FDA confirmed the information presented in the table above and agrees with the exception of the information regarding relatedness; the reviewer analyzed selected narratives. FDA notes that several individual terms (hepatitis acute, ALT increased and AST increased) refer to liver dysfunction which has been identified as an adverse effect of selpercatinib during clinical development.

Dose Interruption/Reduction Due to Adverse Effects

The Applicants Position:

Treatment modifications consisted of dose interruptions and dose reductions. In the OSAS, AEs leading to dose reduction occurred in 26.7% of patients in the Original NDA and in 31.2% of patients in the 60-Day Update. These AEs were considered related to study drug in 22.8% in the Original NDA and in 28.3% of patients in the 60-Day Update (Table 8.43 and Table 8.44). In the Original NDA, the most common AEs leading to dose reduction were ALT increase (5.8%; 5.3% related), AST increase (4.3%; 3.6% related), and QT prolongation (2.6%, all related). In the 60-Day Update, the most common AEs leading dose reduction were the same: ALT increase (6.4%; 6.0% related), AST increase (5.6%; 5.0% related), and QT prolongation (2.3%, all related).

AEs leading to dose interruptions occurred in 38.4% of patients in the Original NDA and in 41.9% of patients in the 60-Day Update. These AEs were considered related to study drug in 19.2% of patients in the Original NDA and 21.2% of patients in the 60-Day Update (Table 8.45 and Table 8.46). In the Original NDA, the most common AEs leading to dose interruption were ALT increase (5.6%; 4.7% related), AST increase (4.9%; 4.0% related), and hypertension (3.8%; 2.6% related); all other AEs occurred at a frequency less than 2%. In the 60-Day Update, the most common AEs leading to dose interruption were the same: ALT increase (5.1%; 4.1% related), AST increase (4.8%; 4.0% related), and hypertension (4.6%, 3.7% related). Three additional AEs occurred at a frequency greater than 2% including diarrhea (2.6%, 1.3% related), pyrexia (2.4%, 0.9% related), and electrocardiogram QT prolonged (2.1%, 1.7% related). [Original NDA Module 2.7.4.5.7; 60-Day Update SCS Tables 14.4.8, 14.4.9, 14.4.10, 14.4.11]

Table 8.43 Original NDA: Adverse Events Leading to Dose Reduction (occurring in ≥ 1%)

	Patient incidence, n (%)					
	RET-mutant MTC (N = 226)		*RET* Fusion-positive NSCLC (N = 253)		Overall (N = 531)	
Preferred term	**All**	**Related**	**All**	**Related**	**All**	**Related**
Patients with AEs leading to dose reduction	**55 (24.3)**	**46 (20.4)**	**74 (29.2)**	**67 (26.5)**	**142 (26.7)**	**121 (22.8)**
Alanine aminotransferase increased	13 (5.8)	13 (5.8)	15 (5.9)	14 (5.5)	31 (5.8)	28 (5.3)
Aspartate aminotransferase increased	9 (4.0)	8 (3.5)	11 (4.3)	10 (4.0)	23 (4.3)	19 (3.6)
Electrocardiogram QT prolonged	4 (1.8)	4 (1.8)	9 (3.6)	9 (3.6)	14 (2.6)	14 (2.6)
Fatigue	3 (1.3)	3 (1.3)	4 (1.6)	4 (1.6)	9 (1.7)	8 (1.5)
Drug hypersensitivity	0	0	6 (2.4)	6 (2.4)	6 (1.1)	6 (1.1)
Hypertension	3 (1.3)	2 (0.9)	3 (1.2)	2 (0.8)	6 (1.1)	4 (0.8)
Thrombocytopenia	1 (0.4)	1 (0.4)	5 (2.0)	4 (1.6)	6 (1.1)	5 (0.9)

Source: Original NDA Module 2.7.4 Table 20; Module 5.3.5.3 – SCS Tables 14.4.9, 14.4.11

Table 8.44 60-Day Update: Adverse Events Leading to Dose Reduction (occurring in ≥ 1%)

	Patient incidence, n (%)					
	RET-mutant MTC (N = 299)		*RET* Fusion-positive NSCLC (N = 329)		Overall (N = 702)	
Preferred term	**All**	**Related**	**All**	**Related**	**All**	**Related**
Patients with AEs leading to dose reduction	**83 (27.8)**	**74 (24.7)**	**117 (35.6)**	**109 (33.1)**	**219 (31.2)**	**199 (28.3)**
Alanine aminotransferase increased	16 (5.4)	16 (5.4)	25 (7.6)	24 (7.3)	45 (6.4)	42 (6.0)
Aspartate aminotransferase increased	13 (4.3)	12 (4.0)	20 (6.1)	19 (5.8)	39 (5.6)	35 (5.0)
Electrocardiogram QT prolonged	5 (1.7)	5 (1.7)	10 (3.0)	10 (3.0)	16 (2.3)	16 (2.3)
Fatigue	7 (2.3)	7 (2.3)	5 (1.5)	5 (1.5)	15 (2.1)	14 (2.0)
Drug hypersensitivity	1 (0.3)	1 (0.3)	11 (3.3)	11 (3.3)	12 (1.7)	12 (1.7)
Thrombocytopenia	1 (0.3)	1 (0.3)	8 (2.4)	7 (2.1)	10 (1.4)	9 (1.3)
Diarrhoea	3 (1.0)	2 (0.7)	6 (1.8)	6 (1.8)	9 (1.3)	8 (1.1)
Hypertension	4 (1.3)	3 (1.0)	5 (1.5)	5 (1.5)	9 (1.3)	8 (1.1)
Rash	3 (1.0)	3 (1.0)	6 (1.8)	6 (1.8)	9 (1.3)	9 (1.3)
Hypersensitivity	0	0	7 (2.1)	7 (2.1)	8 (1.1)	8 (1.1)

	Patient incidence, n (%)					
	***RET*-mutant MTC (N = 299)**		***RET* Fusion-positive NSCLC (N = 329)**		**Overall (N = 702)**	
Preferred term	**All**	**Related**	**All**	**Related**	**All**	**Related**
Pyrexia	0	0	7 (2.1)	7 (2.1)	7 (1.0)	7 (1.0)

Source: 60-Day Update SCS Tables 14.4.9, 14.4.11

Table 8.45 Original NDA: Adverse Events Leading to Dose Interruption (occurring in ≥ 1%)

	Patient incidence, n (%)					
	***RET*-mutant MTC (N = 226)**		***RET* Fusion-positive NSCLC (N = 253)**		**Overall (N = 531)**	
	All	**Related**	**All**	**Related**	**All**	**Related**
Patients with AEs leading to dose interruption	**85 (37.6)**	**43 (19.0)**	**93 (36.8)**	**50 (19.8)**	**204 (38.4)**	**102 (19.2)**
Alanine aminotransferase increased	11 (4.9)	10 (4)	16 (6.3)	13 (5.1)	30 (5.6)	25 (4.7)
Aspartate aminotransferase increased	10 (4.4)	9 (4.0)	13 (5.1)	12 (4.7)	26 (4.9)	21 (4.0)
Hypertension	9 (4.0)	5 (2.2)	10 (4.0)	9 (3.6)	20 (3.8)	14 (2.6)
Electrocardiogram QT prolonged	6 (2.7)	4 (1.8)	3 (1.2)	3 (1.2)	10 (1.9)	7 (1.3)
Fatigue	5 (2.2)	3 (1.3)	3 (1.2)	2 (0.8)	10 (1.9)	6 (1.1)
Pyrexia	4 (1.8)	2 (0.9)	4 (1.6)	3 (1.2)	10 (1.9)	6 (1.1)
Thrombocytopenia	1 (0.4)	1 (0.4)	9 (3.6)	7 (2.8)	10 (1.9)	8 (1.5)
Diarrhoea	5 (2.2)	4 (1.8)	3 (1.2)	0	9 (1.7)	4 (0.8)
Acute kidney injury	3 (1.3)	0	3 (1.2)	0	8 (1.5)	1 (0.2)
Pneumonia	3 (1.3)	0	3 (1.2)	0	8 (1.5)	0
Blood bilirubin increased	5 (2.2)	4 (1.8)	0	0	7 (1.3)	5 (0.9)
Nausea	1 (0.4)	0	4 (1.6)	0	7 (1.3)	1 (0.2)
Hyponatraemia	2 (0.9)	0	2 (0.8)	0	6 (1.1)	1 (0.2)

Source: Original NDA Module 2.7.4 Table 21

Table 8.46 60-Day Update: Adverse Events Leading to Dose Interruption (occurring in ≥ 1%)

	Patient incidence, n (%)					
	***RET*-mutant MTC (N = 299)**		***RET* Fusion-positive NSCLC (N = 329)**		**Overall (N = 702)**	
	All	**Related**	**All**	**Related**	**All**	**Related**
Patients with AEs leading to dose interruption	**117 (39.1)**	**61 (20.4)**	**143 (43.5)**	**74 (22.5)**	**294 (41.9)**	**149 (21.2)**
Alanine aminotransferase increased	12 (4.0)	11 (3.7)	19 (5.8)	14 (4.3)	36 (5.1)	29 (4.1)
Aspartate aminotransferase increased	12 (4.0)	11 (3.7)	17 (5.2)	15 (4.6)	34 (4.8)	28 (4.0)

	Patient incidence, n (%)					
	***RET*-mutant MTC (N = 299)**		***RET* Fusion-positive NSCLC (N = 329)**		**Overall (N = 702)**	
	All	**Related**	**All**	**Related**	**All**	**Related**
Patients with AEs leading to dose interruption	**117 (39.1)**	**61 (20.4)**	**143 (43.5)**	**74 (22.5)**	**294 (41.9)**	**149 (21.2)**
Hypertension	13 (4.3)	10 (3.3)	16 (4.9)	15 (4.6)	32 (4.6)	26 (3.7)
Diarrhoea	10 (3.3)	6 (2.0)	7 (2.1)	3 (0.9)	18 (2.6)	9 (1.3)
Pyrexia	5 (1.7)	2 (0.7)	9 (2.7)	3 (0.9)	17 (2.4)	3 (0.9)
Electrocardiogram QT prolonged	7 (2.3)	5 (1.7)	7 (2.1)	6 (1.8)	15 (2.1)	12 (1.7)
Abdominal pain	7 (2.3)	3 (1.0)	2 (0.6)	0	12 (1.7)	3 (0.4)
Fatigue	6 (2.0)	4 (1.3)	4 (1.2)	1 (0.3)	12 (1.7)	6 (0.9)
Pneumonia	4 (1.3)	0	5 (1.5)	0	11 (1.6)	0
Acute kidney injury	6 (2.0)	0	2 (0.6)	0	9 (1.3)	0
Blood bilirubin increased	5 (1.7)	4 (1.3)	2 (0.6)	1 (0.3)	9 (1.3)	6 (0.9)
Hyponatraemia	2 (0.7)	0	5 (1.5)	2 (0.6)	9 (1.3)	2 (0.3)
Rash	3 (1.0)	2 (0.7)	6 (1.8)	3 (0.9)	9 (1.3)	5 (0.7)
Thrombocytopenia	0	0	9 (2.7)	6 (1.8)	9 (1.3)	6 (0.9)
Nausea	2 (0.7)	0	3 (0.9)	1 (0.3)	8 (1.1)	2 (0.3)
Dehydration	3 (1.0)	1 (0.3)	3 (0.9)	2 (0.6)	7 (1.0)	3 (0.4)

Source: 60-Day Update SCS Tables 14.4.8, 14.4.10

The FDA's Assessment:

FDA confirmed the Applicant's analyses of dose interruption and dose reduction; FDA did not confirm the assessment of relatedness included in the sponsor's assessment and does not necessarily agree with the assessment of the percent of adverse events deemed related to selpercatinib. Overall, though a substantial number of patients required temporary interruption or dose reduction (38.4% in the original NDA) of selpercatinib, few patients (3.6%) required permanent discontinuation due to adverse events.

Significant Adverse Events

Refer to Dropouts and/or Discontinuations Due to Adverse Effects and Dose Interruption/Reduction Due to Adverse Effects for discussion of TEAEs leading discontinuation of study treatment and TEAEs leading to any dose adjustments of study treatment, respectively.

Three AEs of special interest were identified for focused analysis: ALT/AST increase, drug hypersensitivity reaction, and hypertension. These are described in Section 8.2.5.1.

Grade 3-4 AEs

Fifty-one percent of all 531 selpercatinib-treated patients in the Original NDA and 56.1% of 702 treated patients in the 60-Day Update had at least 1 Grade 3 or Grade 4 AE (Table 8.47). In the

Original NDA 44.1% of patients had an AE with worst severity of Grade 3 and 7.0% had an AE with worst severity of Grade 4; in the 60-Day Update, 48.7% of patients had an AE with worst severity of Grade 3 and 7.4% had an AE with worst severity of Grade 4 (Original NDA Module 5.3.5.3 SCS Table 14.4.4; 60-Day Update SCS Table 14.4.4). In the Original NDA, the most common Grade 3-4 events were hypertension (13.9%; 8.1% related), ALT increase (8.5%; 7% related), AST increase (6.4%; 4.5% related), and hyponatremia (5.1%; 0.4% related); in the 60-Day Update, the most common Grade 3-4 events were the same: hypertension (17.5%; 11.3% related), ALT increase (9.1%; 7.4% related), AST increase (7.4%; 5.7% related), and hyponatremia (5.1%; 0.4% related). At least 1 Grade 3 or 4 AE considered related to selpercatinib occurred in 132 patients (24.9%) overall in the Original NDA, and in 206 patients (29.3%) in the 60-Day Update. [Original NDA Module 2.7.4.5.5; 60-Day Update SCS Tables 14.4.6, 14.4.7]

Table 8.47 Original NDA and 60-Day Update: Grades 3–4 Adverse Events in 2% or More Patients

	Incidence, n (%)							
	Original NDA				60-Day Update			
Preferred term	*RET*-mutant MTC (N = 226)	*RET* Fusion-positive NSCLC (N = 253)	Overall (N = 531)	Overall Related (N = 531)	*RET*-mutant MTC (N = 299)	*RET* Fusion-positive NSCLC (N = 329)	Overall (N = 702)	Overall Related (N = 702)
1 or more Grade 3–4 AEs	114 (50.4)	127 (50.2)	271 (51.0)	132 (24.9)	168 (56.2)	183 (55.6)	394 (56.1)	206 (29.3)
Hypertension	37 (16.4)	31 (12.3)	74 (13.9)	43 (8.1)	55 (18.4)	55 (16.7)	123 (17.5)	79 (11.3)
ALT increased	16 (7.1)	24 (9.5)	45 (8.5)	37 (7.0)	21 (7.0)	37 (11.2)	64 (9.1)	52 (7.4)
AST increased	12 (5.3)	18 (7.1)	34 (6.4)	24 (4.5)	18 (6.0)	28 (8.5)	52 (7.4)	40 (5.7)
Hyponatremia	10 (4.4)	12 (4.7)	27 (5.1)	2 (0.4)	12 (4.0)	18 (5.5)	36 (5.1)	3 (0.4)
Lymphopenia	9 (4.0)	6 (2.4)	18 (3.4)	6 (1.1)	12 (4.0)	14 (4.3)	29 (4.1)	8 (1.1)
ECG QT prolonged	6 (2.7)	11 (4.3)	19 (3.6)	13 (2.4)	9 (3.0)	16 (4.9)	27 (3.8)	18 (2.6)
Diarrhea	7 (3.1)	4 (1.6)	11 (2.1)	4 (0.8)	12 (4.0)	9 (2.7)	24 (3.4)	10 (1.4)
Pneumonia	3 (1.3)	5 (2.0)	9 (1.7)	0	8 (2.7)	12 (3.6)	21 (3.0)	0
Thrombocytopenia	2 (0.9)	10 (4.0)	12 (2.3)	10 (1.9)	1 (0.3)	16 (4.9)	18 (2.6)	14 (2.0)
Dyspnoea	2 (0.9)	7 (2.8)	10 (1.9)	1 (0.2)	4 (1.3)	9 (2.7)	16 (2.3)	0
Neutropenia	1 (0.4)	9 (3.6)	12 (2.3)	8 (1.5)	2 (0.7)	11 (3.3)	15 (2.1)	9 (1.3)
Hypocalcaemia	6 (2.7)	1 (0.4)	8 (1.5)	1 (0.2)	11 (3.7)	2 (0.6)	14 (2.0)	2 (0.3)
Hypophosphataemia	2 (0.9)	4 (1.6)	8 (1.5)	0	3 (1.0)	9 (2.7)	14 (2.0)	2 (0.3)

	Incidence, n (%)							
	Original NDA				60-Day Update			
Preferred term	*RET*-mutant MTC (N = 226)	*RET* Fusion-positive NSCLC (N = 253)	Overall (N = 531)	Overall Related (N = 531)	*RET*-mutant MTC (N = 299)	*RET* Fusion-positive NSCLC (N = 329)	Overall (N = 702)	Overall Related (N = 702)

Source: Original NDA Module 2.7.4 Table 16 and Module 5.3.5.3 – SCS Tables 14.4.6, 14.4.7; 60-Day Update SCS Tables 14.4.6, 14.4.7

The FDA's Assessment:
FDA confirmed the analysis of Grade 3 – 4 AEs but cannot confirm the assessment of relatedness.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicants Position:

The following safety data are derived from the interim analysis of the ongoing LOXO-RET-17001 clinical study, using a data cutoff date of 17 June 2019 for the Original NDA and 16 December 2019 for the 60-Day Update. The tables in this section summarize the TEAEs for the respective data cutoff dates, defined as AEs with onset (or worsening) after administration of the first dose of study drug. [60-Day Update SCS Tables 14.4.1, 14.4.4]

Overall safety is summarized in Table 8.48. Most treated patients experienced at least 1 AE during the study in the Original NDA (97.7% of patients) and in the 60-Day Update (99.0% of patients). At least 1 AE that was attributed to selpercatinib by the investigator occurred in 84.9% of patients in the Original NDA and occurred in 91.2% in the 60-Day Update. In the Original NDA, approximately half the patients (51.0%) had Grade 3 or higher AEs, 24.9% considered related to selpercatinib; similarly, in the 60-Day Update, approximately half the patients (56.1%) had Grade 3 or higher AEs, 29.3% considered related to selpercatinib. [Original NDA Module 2.7.4.5.1; 60-Day Update SCS Table 14.4.1].

AEs reported in ≥ 15% of patients are presented in Table 8.49 and Table 8.50 by maximum severity (Grades 1-4) for each of the analysis sets. None of these AEs were Grade 5 in severity. Apart from hypertension, most reported AEs which occurred in ≥ 15% of patients were Grades 1 or 2 in severity. In the Original NDA, the most common AEs were dry mouth (32.2%), diarrhea (31.3%), hypertension (28.8%), AST increase (27.5%), ALT increase (25.6%), fatigue (24.3%), and constipation (21.8%). All others occurred at a frequency of less than 20%. In the 60-Day Update, the most common AEs were the same: dry mouth (38.7%), diarrhea (36.2%), hypertension (35.0%), AST increase (29.9%), ALT increase (28.6%), fatigue (28.1%), and constipation (25.4%). Three additional AEs occurred at a frequency greater than 20% in the 60-Day Update: edema

peripheral (23.5%), headache (22.9%), and nausea (22.6%). [Original NDA Module 2.7.4.5.3; 60-Day Update SCS Tables 14.4.1, 14.4.4]

Table 8.48 Original NDA and 60-Day Update: Summary of Safety Trends

	Incidence, n (%)					
	Original NDA			60-Day Update		
	***RET*-mutant MTC (N = 226)**	***RET* Fusion-positive NSCLC (N = 253)**	**Overall (N = 531)**	***RET*-mutant MTC (N = 299)**	***RET* Fusion-positive NSCLC (N = 329)**	**Overall (N = 702)**
Any AE						
All	224 (99.1)	244 (96.4)	519 (97.7)	297 (99.3)	325 (98.8)	695 (99.0)
Related to selpercatinib	193 (85.4)	219 (86.6)	451 (84.9)	276 (92.3)	301 (91.5)	640 (91.2)
Grade 3 or 4 AE						
All	114 (50.4)	127 (50.2)	271 (51.0)	168 (56.2)	183 (55.6)	395 (56.1)
Related to selpercatinib	53 (23.5)	70 (27.7)	132 (24.9)	82 (27.4)	106 (32.2)	206 (29.3)
AE leading to treatment discontinuation						
All	5 (2.2)	11 (4.3)	19 (3.6)	11 (3.7)	21 (6.4)	37 (5.3)
Related to selpercatinib	4 (1.8)	4 (1.6)	9 (1.7)	6 (2.0)	8 (2.4)	14 (2.0)
SAE						
All	59 (26.1)	80 (31.6)	161 (30.3)	89 (29.8)	118 (35.9)	234 (33.3)
Related to selpercatinib	11 (4.9)	21 (8.3)	33 (6.2)	16 (5.4)	36 (10.9)	54 (7.7)
Fatal AE (none related to selpercatinib)	4 (1.8)	9 (3.6)	15 (2.8)	6 (2.0)	12 (3.6)	21 (3.0)

Source: Original NDA Module 2.7.4 Table 12 and Module 5.3.5.3 SCS - 14.4.1; 60-Day Update SCS Table 14.4.1

Table 8.49 Original NDA: Common Adverse Events All Grades (15% or greater in any analysis set)

Preferred term	Maximum Severity Patient incidence, n (%)														
	RET-mutant MTC (N = 226)					*RET* Fusion-positive NSCLC (N = 253)					Overall (N = 531)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total
Dry mouth	63 (27.9)	6 (2.7)	0	0	69 (30.5)	72 (28.5)	13 (5.1)	0	0	85 (33.6)	152 (28.6)	19 (3.6)	0	0	171 (32.2)
Diarrhea	35 (15.5)	17 (7.5)	7 (3.1)	0	59 (26.1)	63 (24.9)	24 (9.5)	4 (1.6)	0	91 (36.0)	112 (21.1)	43 (8.1)	11 (2.1)	0	166 (31.3)
Hypertension	11 (4.9)	26 (11.5)	36 (15.9)	1 (0.4)	74 (32.7)	7 (2.8)	27 (10.7)	31 (12.3)	0	65 (25.7)	23 (4.3)	56 (10.5)	73 (13.7)	1 (0.2)	153 (28.8)
AST increased	43 (19.0)	8 (3.5)	11 (4.9)	1 (0.4)	63 (27.9)	40 (15.8)	13 (5.1)	14 (5.5)	4 (1.6)	71 (28.1)	88 (16.6)	24 (4.5)	29 (5.5)	5 (0.9)	146 (27.5)
ALT increased	37 (16.4)	6 (2.7)	14 (6.2)	2 (0.9)	59 (26.1)	31 (12.3)	10 (4.0)	20 (7.9)	4 (1.6)	65 (25.7)	70 (13.2)	21 (4.0)	39 (7.3)	6 (1.1)	136 (25.6)
Fatigue	35 (15.5)	25 (11.1)	0	0	60 (26.5)	34 (13.4)	14 (5.5)	2 (0.8)	0	50 (19.8)	80 (15.1)	45 (8.5)	4 (0.8)	0	129 (24.3)
Constipation	51 (22.6)	11 (4.9)	0	0	62 (27.4)	37 (14.6)	4 (1.6)	1 (0.4)	0	42 (16.6)	98 (18.5)	17 (3.2)	1 (0.2)	0	116 (21.8)
Headache	35 (15.5)	12 (5.3)	4 (1.8)	0	51 (22.6)	37 (14.6)	7 (2.8)	1 (0.4)	0	45 (17.8)	80 (15.1)	20 (3.8)	5 (0.9)	0	105 (19.8)
Nausea	31 (13.7)	14 (6.2)	0	0	45 (19.9)	36 (14.2)	5 (2.0)	2 (0.8)	0	43 (17.0)	80 (15.1)	21 (4.0)	2 (0.4)	0	103 (19.4)
Oedema peripheral	35 (15.5)	8 (3.5)	1 (0.4)	0	44 (19.5)	39 (15.4)	9 (3.6)	0	0	48 (19.0)	83 (15.6)	17 (3.2)	1 (0.2)	0	101 (19.0)
Blood creatinine increased	35 (15.5)	10 (4.4)	0	0	45 (19.9)	33 (13.0)	6 (2.4)	0	1 (0.4)	40 (15.8)	72 (13.6)	20 (3.8)	0	1 (0.2)	93 (17.5)

Source: Original NDA Module 2.7.4 Table 14 and Module 5.3.5.3 SCS - Table 14.4.4

Table 8.50 60-Day Update: Common Adverse Events All Grades (15% or greater in any analysis set)

	Maximum Severity Patient incidence, n (%)														
	RET-mutant MTC (N = 299)					*RET* Fusion-positive NSCLC (N = 329)					Overall (N = 702)				
Preferred term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Dry mouth	99 (33.1)	11 (3.7)	0	0	110 (36.8)	116 (35.3)	18 (5.5)	0	0	134 (40.7)	241 (34.3)	31 (4.4)	0	0	272 (38.7)
Diarrhoea	61 (20.4)	22 (7.4)	12 (4.0)	0	95 (31.8)	93 (28.3)	31 (9.4)	9 (2.7)	0	133 (40.4)	175 (24.9)	55 (7.8)	24 (3.4)	0	254 (36.2)
Hypertension	16 (5.4)	42 (14.0)	54 (18.1)	1 (0.3)	113 (37.8)	7 (2.1)	43 (13.1)	55 (16.7)	0	105 (31.9)	29 (4.1)	94 (13.4)	122 (17.4)	1 (0.1)	246 (35.0)
Aspartate aminotransferase increased	56 (18.7)	8 (2.7)	17 (5.7)	1 (0.3)	82 (27.4)	57 (17.3)	23 (7.0)	23 (7.0)	5 (1.5)	108 (32.8)	122 (17.4)	36 (5.1)	46 (6.6)	6 (0.9)	210 (29.9)
Alanine aminotransferase increased	46 (15.4)	11 (3.7)	19 (6.4)	2 (0.7)	78 (26.1)	51 (15.5)	14 (4.3)	32 (9.7)	5 (1.5)	102 (31.0)	103 (14.7)	34 (4.8)	57 (8.1)	7 (1.0)	201 (28.6)
Fatigue	50 (16.7)	41 (13.7)	2 (0.7)	0	93 (31.1)	52 (15.8)	22 (6.7)	4 (1.2)	0	78 (23.7)	118 (16.8)	71 (10.1)	8 (1.1)	0	197 (28.1)
Constipation	76 (25.4)	16 (5.4)	1 (0.3)	0	93 (31.1)	51 (15.5)	12 (3.6)	3 (0.9)	0	66 (20.1)	143 (20.4)	31 (4.4)	4 (0.6)	0	178 (25.4)
Oedema peripheral	61 (20.4)	10 (3.3)	1 (0.3)	0	72 (24.1)	68 (20.7)	13 (4.0)	0	0	81 (24.6)	140 (19.9)	24 (3.4)	1 (0.1)	0	165 (23.5)
Headache	58 (19.4)	17 (5.7)	6 (2.0)	0	81 (27.1)	53 (16.1)	9 (2.7)	3 (0.9)	0	65 (19.8)	124 (17.7)	27 (3.8)	10 (1.4)	0	161 (22.9)
Nausea	50 (16.7)	20 (6.7)	1 (0.3)	0	71 (23.7)	59 (17.9)	8 (2.4)	2 (0.6)	0	69 (21.0)	125 (17.8)	30 (4.3)	4 (0.6)	0	159 (22.6)
Blood creatinine increased	50 (16.7)	17 (5.7)	0	0	67 (22.4)	48 (14.6)	9 (2.7)	0	1 (0.3)	58 (17.6)	104 (14.8)	31 (4.4)	0	1 (0.1)	136 (19.4)
Abdominal pain	40 (13.4)	15 (5.0)	5 (1.7)	0	60 (20.1)	34 (10.3)	11 (3.3)	1 (0.3)	0	46 (14.0)	86 (12.3)	26 (3.7)	12 (1.7)	0	124 (17.7)

Preferred term	Maximum Severity Patient incidence, n (%)														
	***RET*-mutant MTC (N = 299)**					***RET* Fusion-positive NSCLC (N = 329)**					**Overall (N = 702)**				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Total**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Rash	36 (12.0)	5 (1.7)	1 (0.3)	0	42 (14.0)	50 (15.2)	19 (5.8)	2 (0.6)	0	71 (21.6)	94 (13.4)	26 (3.7)	3 (0.4)	0	123 (17.5)
Electrocardiogram QT prolonged	20 (6.7)	23 (7.7)	8 (2.7)	1 (0.3)	52 (17.4)	16 (4.9)	22 (6.7)	16 (4.9)	0	54 (16.4)	40 (5.7)	48 (6.8)	27 (3.8)	0	115 (16.4)
Vomiting	31 (10.4)	14 (4.7)	0	0	45 (15.1)	39 (11.9)	8 (2.4)	1 (0.3)	0	48 (14.6)	81 (11.5)	23 (3.3)	2 (0.3)	0	106 (15.1)
Arthralgia	41 (13.7)	10 (3.3)	0	0	51 (17.1)	19 (5.8)	8 (2.4)	0	0	27 (8.2)	69 (9.8)	23 (3.3)	0	0	92 (13.1)
Hypocalcaemia	21 (7.0)	14 (4.7)	9 (3.0)	2 (0.7)	46 (15.4)	6 (1.8)	1 (0.3)	1 (0.3)	1 (0.3)	9 (2.7)	30 (4.3)	21 (3.0)	11 (1.6)	3 (0.4)	65 (9.3)
Pyrexia	14 (4.7)	5 (1.7)	0	0	19 (6.4)	50 (15.2)	14 (4.3)	1 (0.3)	0	65 (19.8)	73 (10.4)	21 (3.0)	1 (0.1)	0	95 (13.5)
Thrombocytopenia	23 (7.7)	2 (0.7)	0	1 (0.3)	26 (8.7)	30 (9.1)	11 (3.3)	11 (3.3)	5 (1.5)	57 (17.3)	60 (8.5)	16 (2.3)	11 (1.6)	7 (1.0)	94 (13.4)
Cough	33 (11.0)	8 (2.7)	0	0	41 (13.7)	43 (13.1)	7 (2.1)	0	0	50 (15.2)	86 (12.3)	17 (2.4)	0	0	103 (14.7)

Source: 60-Day Update SCS Table 14.4.4

The FDA's Assessment:

FDA agrees with the Applicant's description of treatment-emergent adverse events. A table demonstrating the incidence of TEAE in patients with RET fusion-positive thyroid cancer is included below. AEs which occurred at a higher incidence (> 10% difference compared to either MTC or NSCLC subsets) in patients with RET fusion-positive thyroid cancer included hypertension (43%), fatigue (43.2%), and constipation (37.8%). Given the small number of patients in this subgroup, these differences may not be clinically meaningful. Table 8.52 provides an overview of TEAEs, Grade 3 – 4 AEs, SAEs, discontinuations and deaths by histologic subtype and did not reveal major differences between histologic groups.

Table 8.51: Treatment-emergent Adverse Events (TEAEs) by Primary Diagnosis and RET Alteration Status (LIBRETTO-001 Analysis Sets)- Applicant's Analysis

	RET-mutant		RET-fusion		RET-fusion		RET-fusion Other Solid			
	MTC		NSCLC		Thyroid		Tumor		Other	
	(N=299)		(N=329)		(N= 37)		(N= 21)		(N= 16)	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with TEAEs	297	(99.3)	325	(98.8)	37	(100.0)	20	(95.2)	16	(100.0)
Dry mouth	110	(36.8)	134	(40.7)	17	(45.9)	7	(33.3)	4	(25.0)
Diarrhoea	95	(31.8)	133	(40.4)	14	(37.8)	5	(23.8)	7	(43.8)
Hypertension	113	(37.8)	105	(31.9)	16	(43.2)	4	(19.0)	8	(50.0)
Aspartate aminotransferase	82	(27.4)	108	(32.8)	9	(24.3)	8	(38.1)	3	(18.8)
Alanine aminotransferase	78	(26.1)	102	(31.0)	8	(21.6)	10	(47.6)	3	(18.8)
Fatigue	93	(31.1)	78	(23.7)	16	(43.2)	4	(19.0)	6	(37.5)
Constipation	93	(31.1)	66	(20.1)	14	(37.8)	2	(9.5)	3	(18.8)
Oedema peripheral	72	(24.1)	81	(24.6)	5	(13.5)	4	(19.0)	3	(18.8)
Headache	81	(27.1)	65	(19.8)	9	(24.3)	4	(19.0)	2	(12.5)
Nausea	71	(23.7)	69	(21.0)	10	(27.0)	5	(23.8)	4	(25.0)
Blood creatinine increased	67	(22.4)	58	(17.6)	5	(13.5)	3	(14.3)	3	(18.8)
Abdominal pain	60	(20.1)	46	(14.0)	7	(18.9)	6	(28.6)	5	(31.3)
Rash	42	(14.0)	71	(21.6)	8	(21.6)	2	(9.5)	0	(0.0)
Electrocardiogram QT	52	(17.4)	54	(16.4)	4	(10.8)	4	(19.0)	1	(6.3)
Vomiting	45	(15.1)	48	(14.6)	9	(24.3)	2	(9.5)	2	(12.5)
Cough	41	(13.7)	50	(15.2)	7	(18.9)	3	(14.3)	2	(12.5)
Dyspnoea	42	(14.0)	45	(13.7)	5	(13.5)	2	(9.5)	3	(18.8)
Pyrexia	19	(6.4)	65	(19.8)	7	(18.9)	1	(4.8)	3	(18.8)

Source: ISS Table 13.4.33.4 based on DCO 12/16/19.

Table 8.52: Adverse Event Trends in LIBRETTO-001 Analysis Sets- Applicant's Analysis

	RET-mutant MTC (N=299) n (%)	RET Fusion-positive NSCLC (N=329) n (%)	RET Fusion-positive Thyroid Cancer (N= 37) n (%)	Overall Safety (N=702) n (%)
Patients with TEAEs	297 (99.3)	325 (98.8)	37 (100.0)	695 (99.0)
Patients with TEAEs and Related to LOXO-292	276 (92.3)	301 (91.5)	34 (91.9)	640 (91.2)
Patients with TEAEs Maximum Severity 3 or 4	168 (56.2)	183 (55.6)	23 (62.2)	394 (56.1)
Patients with TEAEs Maximum Severity 3 or 4 and Related to LOXO-292	82 (27.4)	106 (32.2)	12 (32.4)	206 (29.3)
Patients with Serious TEAEs	89 (29.8)	118 (35.9)	13 (35.1)	234 (33.3)
Patients with Serious TEAEs and Related to LOXO-292	16 (5.4)	36 (10.9)	1 (2.7)	54 (7.7)
Patients with Fatal TEAEs	6 (2.0)	12 (3.6)	1 (2.7)	21 (3.0)
Patients with Fatal TEAEs and Related to LOXO-292	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with TEAEs and Action Taken of LOXO-292 Permanently Discontinued	11 (3.7)	21 (6.4)	2 (5.4)	37 (5.3)
Patients with TEAEs and Action Taken of LOXO-292 Permanently Discontinued and Related to LOXO-292	6 (2.0)	8 (2.4)	0 (0.0)	14 (2.0)

Based on Data Cut-off 12/1/2019

Laboratory Findings

The Applicants Position: [Original NDA Module 2.7.4.6; 60-Day Update Assessment Aid Addendum: Hematologic Abnormalities; Serum Chemistries and Liver Abnormalities; Thyroid Function Tests; Vital Signs; ECGs]

Analysis of laboratory values were graded utilizing CTCAE v4.03 guidance. Per FDA request, CTCAE v5.0 was used for creatinine increase.

Hematology analytes, serum chemistries, and thyroid function were assessed by means of summary statistics and shift analysis, provided in the SCS. The analysis of liver abnormalities was summarized in Section 8.2.5.1.

The values for treatment-emergent laboratory abnormalities are assessed using the laboratory dataset, and not as a PT using the AE dataset, as the AE listed only lab abnormalities that the investigator considered to be clinically important. If an abnormal laboratory value is not considered clinically significant by the investigator, it is still captured in the laboratory dataset. Therefore, analyses of laboratory and adverse event datasets typically yield different results, because the latter requires the investigator to make a determination of clinical significance.

Hematologic Abnormalities
[Original NDA Module 2.7.4.6.1; 60-Day Update SCS Table 14.4.25.2]

Based on laboratory reports,

- In the Original NDA, 39.7% patients had a decrease of lymphocytes of any grade and 13.0% of Grade 3 or 4 (Table 8.53); lymphopenia was only reported as an AE in 50 patients (9.4% overall; 4.9% related to selpercatinib); 18 (3.4%) cases of Grade 3-4 lymphopenia were reported as an AE of which 6 (1.1%) were considered related to selpercatinib (Table 8.47). In the 60-Day Update, 44.3% patients had a decrease of lymphocytes of any grade and 14.8% of Grade 3 or 4 (Table 8.54); lymphopenia was only reported as an AE in 71 patients (10.1% overall; 4.6% related to selpercatinib) (60-Day Update SCS Tables 14.4.3, 14.4.5); 29 (4.1%) cases of Grade 3-4 lymphopenia were reported as an AE of which 8 (1.1%) were considered related to selpercatinib (Table 8.47).

- In the Original NDA, 17.2% patients had a treatment-emergent decreased neutrophil count of any grade and 2.7% of Grade 3 or 4 (Table 8.53); neutropenia was only reported as an AE in 42 patients (7.9% overall; 5.8% related to selpercatinib); 12 (2.3%) cases of Grade 3-4 neutropenia were reported as an AE of which 8 (1.5%) were considered related to selpercatinib (Table 8.47). In the 60-Day Update, 19.4% patients had a treatment-emergent decreased neutrophil count of any grade and 2.5% of Grade 3 or 4 (Table 8.54); neutropenia was only reported as an AE in 54 patients (7.7% overall; 5.8% related to selpercatinib) (60-Day Update SCS Tables 14.4.3, 14.4.5); 15 (2.1%) cases of Grade 3-4 neutropenia were reported as an AE of which 9 (1.3%) were considered related to selpercatinib (Table 8.47).

- In the Original NDA, 31.5% patients had a decrease in platelets across all grades of which 2.3% were Grade 3 or 4; thrombocytopenia was only reported as an AE in 67 patients (12.6% overall; 10.0% considered related to selpercatinib) (Original NDA Module 5.3.5.3 SCS - Tables 14.4.4 and 14.4.4.1). In the 60-Day Update, 33.2% patients had a decrease in platelets across all grades of which 2.7% were Grade 3 or 4 (Table 8.54); thrombocytopenia was only reported as an AE in 94 patients (13.4% overall; 10.1%

considered related to selpercatinib) (60-Day Update SCS Tables 14.4.3, 14.4.5).

Table 8.53 Original NDA: Summary of Abnormal Hematologic Laboratory Tests (Patients with 2% or More Grade 3 or 4 Abnormalities in Overall Analysis Set)

	Overall (N = 531)						
	N*	All Grade n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3-4 n (%)
Lymphocyte count decreased	509	202 (39.7)	49 (9.6)	87 (17.1)	57 (11.2)	9 (1.8)	66 (13.0)
Neutrophil count decreased	511	88 (17.2)	43 (8.4)	31 (6.1)	12 (2.3)	2 (0.4)	14 (2.7)
Platelets decreased	524	165 (31.5)	136 (26.0)	16 (3.1)	6 (1.1)	7 (1.3)	13 (2.5)

Source: Original NDA Module 2.7.4 Table 37 and Module 5.3.5.3 – SCS Table 14.4.25.2 for Patients with 2% or More Grade 3 or 4 Abnormalities
Percentage is calculated based on the number of patients with baseline assessment and at least one post-baseline assessment as the denominator (N*).
Treatment-emergent post baseline grade is a grade that is worse than baseline grade for a given parameter in decrease direction.

Table 8.54 60-Day Update: Summary of Abnormal Hematologic Laboratory Tests (Patients with 2% or More Grade 3 or 4 Abnormalities in Overall Analysis Set)

	Overall (N = 702)						
	N*	**All Grade n (%)**	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 3-4 n (%)**
Lymphocyte count decreased	670	297 (44.3)	70 (10.4)	128 (19.1)	90 (13.4)	9 (1.3)	99 (14.8)
Platelets Decreased	692	230 (33.2)	189 (27.3)	22 (3.2)	10 (1.4)	9 (1.3)	19 (2.7)
Neutrophil Count Decreased	675	131 (19.4)	63 (9.3)	51 (7.6)	15 (2.2)	2 (0.3)	17 (2.5)

Source: 60-Day Update SCS Table 14.4.25.2
Percentage is calculated based on the number of patients with baseline assessment and at least one post-baseline assessment as the denominator (N*).
Treatment-emergent post baseline grade is a grade that is worse than baseline grade for a given parameter in decrease direction.

Serum Chemistry and Liver Abnormalities:
[Original NDA Module 2.7.4.6.2; 60-Day Update SCS Table 14.4.25.1]

Treatment-emergent increases were observed in ALT and AST. These are addressed in Section 8.2.5.1. Other common abnormalities consisted of abnormalities in other LFTs and electrolyte decreases and are discussed below.

- Calcium decreases of any grade were reported as the AE "Hypocalcemia" (7.7% of patients in the Original NDA, 9.3% in the 60-Day Update) and "Blood calcium decreased" (0.2% in the Original NDA, 0.4% in the 60-Day Update) (60-Day Update SCS Table 14.4.3). Based on laboratory analysis, in the Original NDA, 3.6% had treatment-emergent Grade 3 or 4 toxicity, and in the 60-Day Update, 3.8% had treatment-emergent Grade 3 or 4 toxicity (Table 8.55 and Table 8.56). In the Original NDA, fewer patients in the MTC population started treatment with a normal calcium value relative to NSCLC (82.7% vs 90.3%, respectively) and more patients had treatment-emergent Grade 3–4 (6.2% vs 0.8%); this trend was also seen in the 60-Day Update: fewer patients in the MTC population started treatment with a normal calcium value relative to NSCLC (82.5% vs 91.0%, respectively) and more patients had treatment-emergent Grade 3–4 (6.7% vs 0.9%) (60-Day Update SCS Table 14.4.20.7). Previous thyroidectomy with removal of or damage to the parathyroid glands could have contributed to this difference.
- Sodium decreases of any grade during the study were reported as the AEs "Hyponatremia" (6.6% of patients in the Original NDA, 8.5% in the 60-Day Update) and "Blood sodium decreased" (0.2% in the Original NDA, 0% in the 60-Day Update) (60-Day Update SCS Table 14.4.3). Based on laboratory analysis, in the Original NDA, 6.3% of patients had treatment-emergent Grade 3 or 4 toxicity, and in the 60-Day Update, 7.2% had treatment-emergent Grade 3 or 4 toxicity (Table 8.55 and Table 8.56) (Grade 2 hyponatremia is not defined in the CTCAE v4.03 toxicity grading scale).
- In the Original NDA, alkaline phosphatase showed a similar trend as AST and ALT but of lesser magnitude, with 31.1% of patients having a treatment-emergent increase of at least 1 grade and only 2.3% patients reported Grade 3 or 4 increases; in the 60-Day Update, this trend was also observed with 35.8% of patients having a treatment-emergent increase of alkaline phosphatase of at least 1 grade and only 2.3% patients reported Grade 3 or 4 increases (Table 8.55 and Table 8.56).
- Treatment-emergent elevations in total bilirubin were observed in 19.8% of patients in the Original NDA, 22.8% in the 60-Day Update (Table 8.55 and Table 8.56). Most elevations were from Grade 0 to Grade 1 (Original NDA Module 5.3.5.3 SCS Table 14.4.20.5; 60-Day Update SCS Table 14.4.20.5); only 2.3% of patients in the Original NDA, and 2.0% of patients in the 60-Day Update had Grade 3 as their worst toxicity and none had Grade 4 (Table 8.55 and Table 8.56).

Table 8.55 Original NDA: Summary of Abnormal Serum Chemistry Laboratory Tests (Patients with 2% or More Grade 3 or 4 Abnormalities in Overall Analysis Set)

	Overall (N = 531)						
	N*	All Grade n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3-4 n (%)
Alanine aminotransferase increased	524	206 (39.3)	133 (25.4)	26 (5.0)	42 (8.0)	5 (1.0)	47 (9.0)

Aspartate aminotransferase increased	524	240 (45.8)	177 (33.8)	27 (5.2)	31 (5.9)	5 (1.0)	36 (6.9)
Sodium decreased	524	114 (21.8)	81 (15.5)	0	28 (5.3)	5 (1.0)	33 (6.3)
Calcium decreased	524	182 (34.7)	100 (19.1)	63 (12.0)	15 (2.9)	4 (0.8)	19 (3.6)
Alkaline phosphatase increased	524	163 (31.1)	119 (22.7)	32 (6.1)	11 (2.1)	1 (0.2)	12 (2.3)
Total bilirubin increased	524	104 (19.8)	60 (11.5)	32 (6.1)	12 (2.3)	0	12 (2.3)

Source: Original NDA Module 2.7.4 Table 41 and Module 5.3.5.3 SCS Table 14.4.25.1 for Patients with 2% or More Grade 3 or 4 Abnormalities

[1]Toxicity grade assignment based on CTCAE (v5.0).

Percentage is calculated based on the number of patients with baseline assessment and at least one post-baseline assessment as the denominator (N*).

Treatment-emergent post baseline grade is a grade that is worse than baseline grade for a given parameter in decrease direction.

Table 8.56 60-Day Update: Summary of Abnormal Serum Chemistry Laboratory Tests (Patients with 2% or More Grade 3 or 4 Abnormalities in Overall Analysis Set)

	Overall (N = 531)						
	N*	All Grade n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3-4 n (%)
Alanine aminotransferase increased	692	309 (44.7)	204 (29.5)	42 (6.1)	56 (8.1)	7 (1.0)	63 (9.1)
Aspartate aminotransferase increased	692	352 (50.9)	257 (37.1)	43 (6.2)	47 (6.8)	5 (0.7)	52 (7.5)
Sodium decreased	692	187 (27.0)	137 (19.8)	0	45 (6.5)	5 (0.7)	50 (7.2)
Calcium decreased	692	285 (41.2)	174 (25.1)	85 (12.3)	21 (3.0)	5 (0.7)	26 (3.8)
Alkaline phosphatase increased	692	248 (35.8)	180 (26.0)	52 (7.5)	15 (2.2)	1 (0.1)	16 (2.3)
Glucose increased	691	305 (44.1)	209 (30.2)	81 (11.7)	12 (1.7)	3 (0.4)	15 (2.2)
Total bilirubin increased	692	158 (22.8)	96 (13.9)	48 (6.9)	14 (2.0)	0	14 (2.0)

Source: 60-Day Update SCS Table 14.4.25.1

[1]Toxicity grade assignment based on CTCAE (v5.0).

Percentage is calculated based on the number of patients with baseline assessment and at least one post-baseline assessment as the denominator (N*).

Treatment-emergent post baseline grade is a grade that is worse than baseline grade for a given parameter in decrease direction.

Thyroid Function Tests:

[Original NDA Module 2.7.4.6.4; 60-Day Update SCS Table 14.4.26.1]

Thyroid-stimulating hormone (TSH) is the most sensitive and accurate test for assessing thyroid function and was therefore analyzed in detail. Overall, there appeared to be a general trend towards increase in the TSH value with selpercatinib treatment, higher for MTC patients than

for NSCLC patients. This disparity is not unexpected as most MTC patients have undergone thyroidectomy and require chronic oral thyroid hormone supplementation (Table 8.57).

Importantly, in the Original NDA, the median last post-baseline values were 2.585, 2.075 and 2.770 mIU/L for all, MTC and NSCLC patients, respectively, indicating that effects on TSH levels of selpercatinib treatment are mostly transient and/or easily corrected (e.g., by adjusting the dose of oral thyroid hormone). The last post-baseline values were consistent in the 60-Day Update: 2.536, 2.400 and 2.810 mIU/L for all, MTC and NSCLC patients, respectively (60-Day Update SCS Table 14.4.26.1).

In the Original NDA, hypothyroidism was reported as an AE in 41 patients (7.7% overall; more common with MTC [10.2%] than NSCLC [6.3%]); and, remained consistent in the 60-Day Update, hypothyroidism was reported as an AE in 62 patients (8.8% overall; more common with MTC [10.7%] than NSCLC [8.2%]) (60-Day Update SCS Table 14.4.3) and there were no cases of Grade 3-4 AEs of hypothyroidism (60-Day Update SCS Table 14.4.6). This provides further evidence that potential effects of selpercatinib treatment on thyroid function were clinically mild, easily monitored and reversible.

Table 8.57 Original NDA and 60-Day Update: Thyroid Stimulating Hormone Values

	Original NDA			60-Day Update		
	***RET*-mutant MTC (N = 226)**	***RET* Fusion-positive NSCLC (N = 253)**	**Overall (N = 531)**	***RET*-mutant MTC (N = 299)**	***RET* Fusion-positive NSCLC (N = 329)**	**Overall (N = 702)**
Baseline value						
n	224	251	526	294	327	694
Median	0.940	1.710	1.400	0.970	1.740	1.380
Range	0.00, 88.00	0.01,68.60	0.00, 88.00	0.0-88.00	0.01-103.00	0.0-103.00
Maximum post baseline value						
n[1]	214	234	498	287	316	672
Median	8.540	4.250	5.375	8.730	4.380	5.440
Range	0.01, 339.00	0.35, 67.90	0.01, 339.00	0.02-339.00	0.35-117.00	0.02-1140.00
Maximum increase from baseline						
n[1]	214	234	498	287	316	672
Median	6.245	2.210	3.068	6.390	2.125	3.255
Range	-43.70, 291.40	-21.30, 62.14	-43.70, 291.40	-36.0, 291.30	-10.5, 62.14	-36.0, 1139.88

Source: Original NDA Module 2.7.4 Table 41 and Module 5.3.5.3 SCS Table 14.4.26.1; 60-Day Update Table SCS 14.4.26.1

Baseline is defined as the last measurement available prior to the first dose of LOXO-292.

[1] n is the number of subjects with a baseline value and at least one post baseline value during the study.

The FDA's Assessment:

FDA agrees with the analysis of serum laboratory tests presented above and notes the following additional points (data based on original data cut-off):

- Sodium decreases based on laboratory testing occurred in 21.8% of patients, with Grade 3 – 4 decreases occurring in 6.3% of patients. Grade 3 – 4 sodium decreases were observed more frequently in patients with NSCLC than with MTC (6.5% vs. 4.9%), as were sodium decreases overall (25.4% vs. 16%).

- 33.8% of patients had a worsening in creatinine; the majority of these were Grade 1 – 2 (33.2%) with 0.6% of patients experiencing Grade 3 – 4 creatinine elevation based on laboratory analysis.

- As indicated above, Grade 3 – 4 events of hypocalcemia occurred in 3.7% of patients. Nearly all of the Grade 3 - 4 events occurred in patients with MTC who often have hypoparathyroidism related to prior surgeries and require calcium supplementation.

- FDA agrees with the above analysis of TSH. Regarding the reported incidence of hypothyroidism, FDA notes that per CTCAE v 4.03, hypothyroidism is graded based on symptoms and intervention indicated. Grades 3 and 4 hypothyroidism are defined by severe symptoms, limiting self-care activities of daily living, or hospitalization; and life-threatening consequences, respectively. A shift analysis performed for TSH (using the categories of below lower limit of normal [LLN], normal, or above the upper limit of normal[ULN]) demonstrated that 44.1% had a shift from either below the LLN or normal ranges to above the ULN at some point during the study. At the time of last post-baseline measurement, the percentage who had shifted to above the ULN was 19.5%.

Vital Signs

The Applicant's Position: [Original NDA Module 2.7.4.7.1; 60-Day Update SCS Tables 14.4.28.1, 14.4.28.2]

In Study LOXO-RET-17001 vital sign measurements included temperature, pulse rate, respiration rate, and blood pressure. Measurements were obtained at baseline, weekly for the first three weeks then prior to each cycle, at the end of therapy, and 28 days post-therapy per protocol.

As with the Original NDA, in the 60-Day Update, summary statistics for weight, pulse, respiration, and temperature showed no meaningful trends (60 Day-Update SCS Tables 14.4.28.4, 14.4.28.5, 14.4.28.6 and 14.4.29).

Summary statistics and shift analyses across all patients based on the overall analysis vital sign datasheet included in the NDA for blood pressure were analyzed. In the Original NDA, median baseline systolic blood pressure for the overall population was 119 mm Hg (range: 82, 166) (Table 8.58), and median maximum systolic blood pressure was 147 mm Hg (range: 95, 210), reflecting a median difference of 27 mm Hg (range: -14, +96); median difference from baseline was +5 mm Hg (range: –52, +64). In the 60-Day Update, median baseline systolic blood pressure for the overall population was the same as the Original NDA (119 mm Hg, but had a wider range (range: 72, 170) (Table 8.58), and median maximum systolic blood pressure was 149 mm Hg (range: 95, 210), reflecting a median difference of 28 mm Hg (range: -27, +96); median difference from baseline was +7 mm Hg (range: –51, +76). Summary statistics for diastolic blood pressure demonstrated similar trends (Table 8.58).

In the Original NDA, at the last available measurement, 65.1% of patients had returned to the baseline systolic grade level or better, while 34.9% still had a residual elevation. In the 60-Day

Update 60.7% of patients had returned to the baseline systolic grade level or better, while 39.3% still had a residual elevation. Diastolic blood pressure results were similar, although the increases were of lower magnitude (Original NDA Module 5.3.5.3 – SCS Table 14.4.28.3; 60-Day Update SCS Table 14.4.28.3).

Hypertension was identified as an AE of special interest and further information is provided in Section 8.2.5.1.

Table 8.58 Original NDA and 60-Day Update: Systolic and Diastolic Blood Pressure Changes

	Original NDA (Overall, N = 531)		60-Day Update (Overall, N = 702)	
	Systolic	Diastolic	Systolic	Diastolic
Baseline, mm Hg				
n	531	531	702	702
Mean (SD)	120.2 (15.0)	72.8 (10.0)	120.4 (15.5)	73.0 (10.3)
Median	119.0	73.0	119.0	73.0
Range	82, 166	45, 105	72, 170	45, 118
Maximum value, mm Hg				
n	530	530	698	698
Mean (SD)	148.4 (18.8)	91.5 (10.8)	150.1 (18.8)	92.9 (10.8)
Median	147.0	92.0	149.0	93.0
Range	95, 210	55, 148	95, 210	58, 148
Maximum increase from baseline, mm Hg				
n	530	530	698	698
Mean (SD)	28.2 (17.1)	18.7 (10.8)	29.7 (16.9)	19.9 (10.5)
Median	27.0	18.0	28.0	19.0
Range	-14, +96	–13, +70	-27, 96	-13, 70
95% CI for mean	26.7, 29.7	17.8, 19.6	28.4, 30.9	19.2, 20.7
Last value, mm Hg				
n	530	530	698	698
Mean (SD)	125.8 (16.1)	78.0 (10.6)	127.2 (16.8)	78.8 (11.0)
Median	125.0	78.0	126.0	79.0
Range	83, 177	46, 114	78, 186	49, 123
Change from baseline, mm Hg				
n	530	530	698	698
Mean (SD)	5.6 (17.2)	5.3 (11.5)	6.7 (17.9)	5.9 (11.7)
Median	5.0	5.0	7.0	6.0

	Original NDA (Overall, N = 531)		60-Day Update (Overall, N = 702)	
	Systolic	**Diastolic**	**Systolic**	**Diastolic**
Range	–52, +64	–35, +42	-51, 76	-35, 58
95% CI for mean	4.2, 7.1	4.3, 6.3	5.4, 8.1	5.0, 6.7

Source: Original NDA Module 2.7.4 Table 34 and Module 5.3.5.3 – SCS Tables 14.4.28.1, 14.4.28.2; 60-Day Update SCS Tables 14.4.28.1, 14.4.28.2

The FDA's Assessment:
The analysis of vital signs was confirmed. See section 8.2.6 for a discussion of hypertension in patients treated with selpercatinib.

Electrocardiograms (ECGs)

The Applicant's Position: [Module 2.7.4.7.3; Module 2.7.2.1]
[Original NDA Module 2.7.4.7.3; 60-Day Update Tables 14.4.3, 14.4.4, 14.4.4.1, 14.4.5, 14.4.31.1, 14.4.31.2, 14.4.31.3, 14.4.31.4, 14.4.31.5, 14.4.31.6, 14.4.32.1, 14.4.32.2; Listing 16.2.3.1.1]

In Study LOXO-RET-17001, 12 lead ECGs were performed at baseline, weekly for the first 2 weeks then at the start of each cycle through cycle 6 and then every 12 weeks thereafter, at the end of treatment and 28 days (+7 days) after the final selpercatinib dose.

During the clinical trial, the QT interval was corrected using the Fridericia method (QTcF) by protocol. If the QTcF was not provided, the value was derived using the heartrate (HR), QT interval and RR interval values provided, as outlined in the SAP. Summary statistics for ECG parameters are provided in Original NDA Module 5.3.5.3 – SCS Table 14.4.31.1 through Table 14.4.31.6 and in 60-Day Update Tables 14.4.31.1 through Table 14.4.31.6.

In the Original NDA, electrocardiogram QT prolonged was reported as an AE in 13.4% of patients; 9.6% were considered related to selpercatinib (Original NDA Module 5.3.5.3 – SCS Tables 14.4.3 and 14.4.5). Most patients had AEs which were Grade 1 (5.3%) or Grade 2 (4.5%); 3.6% of patients had a Grade 3 event and there were no Grade 4 events reports (Original NDA Module 5.3.5.3 – SCS Table 14.4.4); only 1 patient had the AE of QTcF prolongation deemed serious (Original NDA Module 5.3.5.3 – SCS Table 14.4.14). In the 60-Day Update electrocardiogram QT prolonged was reported as an AE in 16.4% of patients; 12.7% were considered related to selpercatinib (60-Day Update Tables 14.4.3 and 14.4.5). As seen in the Original NDA, most patients had AEs which were Grade 1 (5.7%) or Grade 2 (6.8%); 3.8% of patients had a Grade 3 event, and there were no Grade 4 events (60-Day Update Table 14.4.4); only 1 patient had the AE of QTcF prolongation deemed serious (this is the same patient as noted in the original NDA; 60-Day Update Table 14.4.14).

QTcF prolongation was manageable by selpercatinib dose interruptions (10 patients in the Original NDA, 15 patients in the 60-Day Update; 60-Day Update SCS Table 14.4.8) or reductions (14 patients in the Original NDA, 16 patients in the 60-Day Update; 60-Day Update SCS Table 14.4.9), while no action with drug was taken in 47 (8.9%) patients in the Original NDA and 84 (12.0%) patients in the 60-Day Update. Importantly, no patient discontinued treatment due to QT prolongation in either the Original NDA or the 60-Day Update (60-Day Update SCS Table 14.4.12; Original NDA Module 5.3.5.3 – SCS Table 14.4.12; 60-Day Update Listing 16.2.3.1.1).

Based on ECG values entered into the electronic data capture system by the treating physician, for the population as a whole in the Original NDA, the median baseline QTcF value was 417 msec, the median maximum value on treatment was 453.3 msec, representing an increase in the median of 36.3 msec; at the time of the last measurement, the median QTcF value was still elevated above baseline at 435 msec (Original NDA Module 5.3.5.3 – SCS Table 14.4.31.6). In the 60-Day Update, the median baseline QTcF value was 416.33 msec, the median maximum post-baseline value on treatment was 455.0 msec, representing an increase in the median of 37.67 msec; at the time of the last measurement, the median QTcF value was still elevated above baseline at 433.00 msec (60-Day Update SCS Table 14.4.31.6).

Shift analysis of QTcF in the Original NDA (Original NDA Module 5.3.5.3 – SCS Table 14.4.32.1) showed the majority of the population (93.6%) with a baseline of 450 msec or less.; less than half (44.8%) retained that level; 37.7% increased to between 450 and 480 msec, 6.8% increased to between 480 and 500 msec, and 4.3% increased to greater than 500 msec; at the time of the last measurement, 21.5% were still demonstrating an elevated QTcF relative to their baseline; overall, 60.5% of patients increased by at least 30 msec over their baseline during treatment and 13.6% increased by at least 60 msec (Original NDA Module 5.3.5.3 – SCS Table 14.4.32.2). Similarly, in the 60-Day Update, shift analysis of QTcF showed the majority of the population (93.8%) with a baseline of 450 msec or less.; less than half (42%) retained that level; 39.9% increased to between 450 and 480 msec, 7.9% increased to between 480 and 500 msec, and 4% increased to greater than 500 msec; at the time of the last measurement, 20.2% were still demonstrating an elevated QTcF relative to their baseline; overall, 64.7% of patients increased by at least 30 msec over their baseline during treatment and 15.4% increased by at least 60 msec (60-Day Update SCS Tables 14.4.32.1, 14.4.32.2).

A dedicated clinical pharmacology was conducted to evaluate the effects of selpercatinib on the heart rate corrected QT (QTc) interval by assessing concentration-QT (C-QT) relationship using exposure-response modelling and to assess the effect exposure of selpercatinib on other electrocardiogram (ECG) parameters. Following single doses of 320 mg (targeting the therapeutic exposure of approximately 3300 ng/mL) and 640 mg (targeting supratherapeutic exposure), selpercatinib caused prolongation of QTc less than that observed with moxifloxacin, and no other clinically relevant effects on studied ECG parameters. At the geometric mean concentrations, the predicted QT effect (ΔΔQTcF) was 7.10 ms (90% CI: 6.10 to 8.10) and

8.36 ms (90%CI: 7.21 to 9.51) for 320 and 640 mg selpercatinib, respectively. A concentration-QTc analysis showed that a QTcF effect above 10 ms and 20 ms can be excluded up to selpercatinib plasma concentration of approximately 2470 ng/mL and 4770 ng/mL, respectively [Original NDA Module 2.7.2 Table 13; Figure 15]. Additionally, a single patient in Study LOXO-RET-17003 had an unrelated reported event of Grade 3 QTc prolongation [Original NDA Module 2.7.4 Table 47].

No cases of torsades de pointes or sudden death were identified and guidance has been provided in the proposed warnings and precautions section for prescribers. This is a recognizable toxicity, which is either monitorable, reversible with dose interruption or addressable through dose reduction when necessary.

The FDA's Assessment:
FDA agrees with the Applicant's description of the incidence and severity of QT prolongation. A warning for QT prolongation will be included in the product label.

QT

Not applicable

The FDA's Assessment:

The FDA clinical pharmacology team provided an in-depth analysis regarding QT prolonging potential. The dedicated QT review found that concentration-dependent QTc prolongation was detected in the TQT study. Based on the model, the mean increase in the QTc interval at the proposed dosing regimen (160 mg BID) is 10.6 msec (90% CI: 9.1, 12.1) msec. At the time of the QT review, the maximum effect on selpercatinib exposure appeared to be by strong CYP3A4 inhibition (1.3-fold change in Cmax and 2.3-fold change in AUC); however, age, sex, race, food, P-gp/CYP3A4 inhibitor, proton-pump inhibitor and H2 antagonist do not result in substantial increases in selpercatinib exposure. The high exposure scenario in patients has not been determined because organ impairment studies were still ongoing at the time of this review.

Immunogenicity

The Applicants Position

No safety issues related to immunogenicity were identified for selpercatinib.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

8.2.6 Analysis of Submission-Specific Safety Issues

8.2.6.1 Adverse Events of Special Interest (AESI)

The Applicants Position [Module 2.7.4.5.10]

[Original NDA Module 2.7.4.5.10; 60-Day Update SCS Tables 14.4.2.1, 14.4.17.6, 14.4.17.7, 14.4.17.8]

Based upon theoretical considerations of RET biology, preclinical toxicology, and emerging safety data during the conduct of the LOXO-RET-17001 study, the following AEs were deemed AEs of special interest (AESI): ALT and AST increases, hypertension, and drug hypersensitivity. Detailed discussion and analysis of each has been provided in the SCS.

ALT and AST Increases

In Study LOXO-RET-17001, liver function tests were performed at baseline, bi-weekly for the first 3 cycles then at the start of each cycle, at the end of treatment and 28 days (+7 days) after the final selpercatinib dose.

Throughout the course of the selpercatinib clinical program, all hepatic effects were continually reviewed. Early in the program, AST and/or ALT (transaminases) illustrated the strongest trend of elevations and relatedness and were identified to represent the primary physiologic hepatic effect.

As outlined in Treatment Emergent Adverse Events and Adverse Reactions, in the OSAS in the Original NDA, investigators reported AEs of AST increases in 27.5% of patients (21.7% related), and ALT increases in 25.6% of patients (20.5% related), respectively; the majority were Grade 1 and 2; in the 60-Day Update, investigators reported AEs of AST increases in 29.9% of patients (24.4% related), and ALT increases in 28.6% of patients (23.8% related), respectively; the majority were Grade 1 and 2 (Table 8.59). Although ALT and AST increases were the most common reasons for dose interruption and reduction, they led to permanent discontinuation in only 2 (0.4%) and 1 (0.2%) patients, respectively, in the Original NDA. In the 60-Day Update, ALT and AST increases led to discontinuation in 3 (0.4%) and 2 (0.3%) patients, respectively (Table 8.59).

Listings for individual patients who required dose modifications (interruption or reduction) for an AE of AST and/or ALT are provided in 60-Day Update SCS Listing 16.2.3.1.3. Listings for individual patients who displayed elevations in AST and/or ALT based on laboratory values are provided 60-Day Update SCS Listing 16.2.3.2.1.

No patients met the criteria for Hy's Law drug induced liver injury. [60-Day Update SCS Table 14.4.17.5]

Table 8.59 Original NDA and 60-Day Update: AST and ALT Adverse Events

	Original NDA (Overall, N = 531)		60-Day Update (Overall, N = 702)	
	AST Increased	ALT Increased	AST Increased	ALT Increased
Number of patients with AE, n (%)				
Any grade	146 (27.5)	136 (25.6)	210 (29.9)	201 (28.6)
Grade 1	88 (16.6)	70 (13.2)	122 (17.4)	103 (14.7)
Grade 2	24 (4.5)	21 (4.0)	36 (5.1)	34 (4.8)
Grade 3	29 (5.5)	39 (7.3)	46 (6.6)	57 (8.1)
Grade 4	5 (0.9)	6 (1.1)	6 (0.9)	7 (1.0)
Drug-related AE	115 (21.7)	109 (20.5)	171 (24.4)	167 (23.8)
Serious AE	11 (2.1)	11 (2.1)	12 (1.7)	12 (1.7)
Drug-related SAE	8 (1.5)	8 (1.5)	9 (1.3)	9 (1.3)
Dose modification due to AE, n (%)				
Interruption	26 (4.9)	30 (5.6)	34 (4.8)	36 (5.1)
Reduction	23 (4.3)	31 (5.8)	39 (5.6)	45 (6.4)
Discontinuation	1 (0.2)	2 (0.4)	2 (0.3)	3 (0.4)
Time to first onset of increase (weeks)				
N	146	136	210	201
Mean (SD)	9.3 (13.2)	8.2 (11.9)	10.4 (15.1)	9.0 (12.4)
Median	4.1	4.1	4.1	4.1
Range	0.1, 68.1	0.1, 68.1	0.1, 111.1	0.1, 79.7

Source: Original NDA Module 2.7.4 Table 27 and Module 5.3.5.3 – SCS Table 14.4.17.7; 60-Day Update SCS Table 14.4.17.7

Hypertension:

In Study LOXO-RET-17001, blood pressure values were obtained at baseline, weekly for the first three weeks then prior to each cycle, at the end of therapy, and 28 days (+7 days) post-therapy per protocol.

Treatment-emergent elevations in blood pressure were extracted as the MedDRA terms “Hypertension” or “Blood pressure increased.” In the Original NDA, 29.8% of patients experienced one or the other of these AEs (Table 8.60); almost one half (14.1% of all patients) had a worst severity of Grade 3 or 4 (only 1 patient with Grade 4); for 5 patients (0.9% of all patients), hypertension was deemed serious. In the 60-Day Update, 35.9% of patients experienced one or the other of these AEs; almost one half (17.8% of all patients) had a worst severity of Grade 3 or 4 (only 1 patient with Grade 4) (Table 8.60); for 6 patients (0.9% of all patients) hypertension was deemed serious (60-Day Update SCS Table 14.4.14). The overall frequency of hypertension was similar between NSCLC and MTC patients. (Original NDA Module 2.7.4.5.10.3; 60-Day Update SCS Table 14.4.2.1)

Table 8.60 Original NDA and 60-Day Update: Hypertensive Adverse Events

	Incidence, n (%)			
	Original NDA (Overall, N = 531)		60-Day Update (Overall, N = 702)	
Preferred term	**All Grades**	**Grades 3–4**	**All Grades**	**Grades 3–4**
1 or more Hypertensive AE	158 (29.8)	75 (14.1)	252 (35.9)	125 (17.8)
Hypertension	153 (28.8)	74 (13.9)	246 (35.0)	123 (17.5)
Blood pressure increase	5 (0.9)	1 (0.2)	8 (1.1)	2 (0.3)

Source: Original NDA Module 2.7.4 Table 33 and Module 5.3.5.3 – SCS Table 14.4.2.1; 60-Day Update SCS Table 14.4.2.1

Treatment-emergent hypertension was also examined in relation to the patients' medical histories. A history of hypertension was documented in the medical history in 41.8% of patients in the Original NDA and in 41.2% of patients in the 60-Day Update (Table 8.61).

In the Original NDA, although the overall incidence of treatment-emergent hypertension was similar in patients with and without a medical history of hypertension, (32.0% vs 28.2%), patients with a preexisting history of hypertension displayed a higher frequency of treatment-emergent Grade 3 hypertension than patients without a documented history of hypertension (19.8% vs 9.7%, respectively).

A similar trend was seen in the 60-Day Update: The overall incidence of treatment-emergent hypertension was similar in patients with and without a medical history of hypertension, (39.4% vs 33.4%), patients with a preexisting history of hypertension displayed a higher frequency of treatment-emergent Grade 3 hypertension than patients without a documented history of hypertension (24.2% vs 13.1%, respectively) (Table 8.61).

Patients with a history of hypertension were also more likely to have had an antihypertensive medication added and a preexisting antihypertensive medication regimen adjusted during selpercatinib treatment, as well as a selpercatinib dose modification. The time to the first report of an AE of hypertension was similar between NSCLC and MTC patients. [Original NDA Module 2.7.4.5.10; 60-Day Update SCS Table 14.4.17.6]

Table 8.61 Original NDA and 60-Day Update: Incidence of Hypertension by Previous History

	Original NDA (Overall, N = 531)		60-Day Update (Overall, N = 702)	
	History of hypertension	No history of hypertension	History of hypertension	No history of hypertension
N	222	309	289	413
Grade, n (%)				
Any	71 (32.0)	87 (28.2)	114 (39.4)	138 (33.4)
Grade 1	3 (1.4)	22 (7.1)	4 (1.4)	27 (6.5)
Grade 2	24 (10.8)	34 (11.0)	40 (13.8)	56 (13.6)
Grade 3	44 (19.8)	30 (9.7)	70 (24.2)	54 (13.1)
Grade 4	0	1 (0.3)	0	1 (0.2)
Institution of antihypertensives, n (%)[1]	53 (23.9)	53 (17.2)	93 (32.2)	84 (20.3)
Time to first onset, weeks				
n	71	87	114	138
Mean (SD)	6.7 (8.63)	8.3 (13.65)	8.6 (13.6)	9.4 (14.4)
Median	2.4	2.1	2.5	2.2
Range	0.1, 52.1	0.1, 59.9	0.1, 83.0	0.1, 60.0
Dose modification due to hypertension, n (%)				
Interruption	13 (5.9)	8 (2.6)	17 (5.9)	16 (3.9)
Reduction	4 (1.8)	2 (0.6)	5 (1.7)	4 (1.0)

[2] Initiation of new medication or alteration of existing medication on or around time of hypertension

Source: Original NDA Module 2.7.4 Table 35 and Module 5.3.5.3 – SCS Table 14.4.17.6; 60-Day Update SCS Table 14.4.17.6

Listings for individual patients who displayed treatment-emergent hypertension are provided in 60-Day Update SCS Listing 16.2.3.2.2.

Drug Hypersensitivity:

Drug hypersensitivity reactions were identified as an AESI early in the clinical program. Rare patients developed a constellation of symptoms and findings characterized by a maculopapular rash, often preceded by fever, with associated arthralgias or myalgias during the patient's initial weeks of treatment, which were then followed by at least one of the following:

- more commonly: platelet decrease and AST/ALT increase
- less commonly: blood pressure decrease, tachycardia, and creatinine increase

Once this reaction was recognized, early cases were reviewed with a specialist in the field of oncodermatology and a dose modification strategy for selpercatinib was implemented in

conjunction with steroid therapy. Investigators were then educated regarding the definition, timing of onset and this information was also included in clinical study related documents. This allowed for the uniform recognition, management and safety reporting across the study using the terms of hypersensitivity reaction and drug hypersensitivity reaction.

This management strategy was ultimately successful; all but 3 patients were able to continue on study utilizing this plan. One of these 3 patients discontinued therapy prior to implementation of the dose modification strategy. All patients recovered without sequalae apart from 1 patient (b) (6) who is noted to be resolving and the status of this patient's event has not yet been updated.

In the Original NDA, a search using the MedDRA preferred terms "Hypersensitivity" and "Drug hypersensitivity" identified 14/531 patients (2.6%) who had 1 or more AE that mapped to these terms (

Table 8.62); 10 patients had a single event; 4 had multiple events (range 2, 5); the median time to first onset was 1.6 weeks (range: 1, 22) (

Table 8.62). In the 60-Day Update, 30/702 patients (4.3%; 3.4% related) had 1 or more AE that mapped to the terms "Hypersensitivity" and "Drug hypersensitivity' (

Table 8.62) (60-Day Update SCS Listing 16.2.3.1.1); the median time to first onset was 1.7 weeks (range: 0.9, 77.0) (

Table 8.62).

Of note, in the Original NDA, all 14 patients with treatment-emergent hypersensitivity were NSCLC patients, and all received the assigned dose of 160 mg BID (Original NDA Module 5.3.5.3 – SCS Listing 16.2.3.2.2; 60-Day Update SCS Table 14.4.17.8. In the 60-Day Update, 25/30 patients with treatment-emergent hypersensitivity were NSCLC patients, and 4/30 patients were MTC patients; all received the assigned dose of 160 mg BID. [Original NDA Module 2.7.4.5.10.2 60-Day Update SCS Table 14.4.17.8 and Listing 16.2.3.2.2]

Table 8.62 Original NDA and 60-Day Update: Hypersensitivity Adverse Events[1]

	Original NDA (Overall, N = 531)	60-Day Update (Overall, N = 702)
Number of patients with hypersensitivity, n (%)		
Any grade	14 (2.6)	30 (4.3)
Grade 1	2 (0.4)	5 (0.7)
Grade 2	6 (1.1)	14 (2.0)
Grade 3	6 (1.1)	11 (1.6)
Drug-related AE	12 (2.3)	24 (3.4)
Serious AE	9 (1.7)	12 (1.7)

	Original NDA (Overall, N = 531)	60-Day Update (Overall, N = 702)
Drug-related SAE	9 (1.7)	12 (1.7)
Dose modification due to hypersensitivity, n (%)		
Interruption	4 (0.8)	6 (0.9)
Reduction	9 (1.7)	20 (2.8)
Discontinuation	2 (0.4)	3 (0.4)
Time to first onset, weeks		
n	14	30
Mean (SD)	4.2 (6.4)	7.2 (15.4)
Median	1.6	1.7
Range	1.0, 22.1	0.9, 77.0

[1] The analysis is based on consolidated AE terms. The searching PT terms for 'Hypersensitivity' are 'Drug hypersensitivity' and 'Hypersensitivity'.
Source: Original NDA Module 2.7.4 Table 31; Module 5.3.5.3 – SCS Table 14.4.17.8; 60-Day Update SCS Table 14.4.17.8

All of the identified AESIs are monitorable and reversible with successful dose modification strategies which allow majority of patients who experience these events to continue safely on therapy. Unique dose modification strategies implemented during Study LOXO-RET-17001 have been provided as guidance for prescribers in the proposed safety label information. [Original NDA Module 2.7.4.5.10; 60-Day Update SCS Tables 14.4.17.1 through 14.4.17.8]

The FDA's Assessment:

FDA has the following additional comments regarding AESI:

- AST/ALT elevation: FDA confirmed the analyses in Table 8.59 and notes that this table is based on adverse event reports. Based on laboratory data, 50.9% of patients experienced AST increase of any Grade (7.5% Grade 3 – 4) and 44.7% experienced ALT increase of any Grade (9.1% Grade 3 – 4). The time to onset of first increase had similar medians for both AST and ALT (4.1 weeks).
  FDA confirmed that there were no cases that met Hy's law criteria in the original safety dataset or in the updated 60-day cutoff.
- Hypertension: FDA requested additional analysis of concomitant medications required to manage hypertension. The Applicant provided an analysis based on the data in the 60-day update (safety database of 702 patients). 177 patients had an AE of hypertension reported and had a concomitant medication added or adjusted.

  A review was conducted to determine whether patients who started an additional antihypertensive medication and subsequently discontinued selpercatinib (for any reason) were able to discontinue the added medication.

Twenty-three of 36 such patients were evaluable given available follow-up; four of these patients discontinued the antihypertensive medication started on study, and the remaining 19 patients had no change in antihypertensive medication recorded.

Reviewer note: Given the small number of patients available for analysis and number of patients with post-treatment follow-up, an assessment of the persistence of hypertension following treatment with selpercatinib is limited.

- Hypersensitivity: A summary of SAEs of hypersensitivity was provided in the discussion of serious adverse events. Based on the data in the 60-day update, the timing of onset and proportion of patients requiring drug interruptions, discontinuation, and withdrawal is relatively consistent with the data presented in Table 8.62. Based on the updated DCO, 4.3% of patients had an event of hypersensitivity or drug hypersensitivity; 1.6% of patients had a Grade 3 AE and there were no Grade 4 AEs.

  FDA requested an SMQ analysis of events of hypersensitivity. The sponsor performed this search, which generated 65 unique terms including terms related to dermatologic adverse events and edema. This reviewer considered terms generally specific to drug-induced hypersensitivity to be hypersensitivity, drug hypersensitivity, drug eruption, and anaphylactic reaction. Based on the updated DCO, there were two patients who experienced an event with the preferred term “anaphylactic reaction” including one Grade 3 event. However, this was attributed to a concomitant medication and not to selpercatinib.

Analysis of Potential Off-Target Effects

FDA performed several analyses to assess for potential off-target effects based on the mechanism of action of selpercatinib, namely class effects associated with inhibition of VEGF receptor and FGFR pathways. FDA requested that the Applicant perform analyses based on Standardized MedDRA queries (SMQs) for class effects associated with inhibition of these pathways and requested additional narrative summaries. An overview of these analyses is provided below.

<u>Effects associated with VEGF Pathway Inhibition</u>

FDA requested additional analysis of potential adverse reactions associated with VEGF pathway inhibition. Hypertension has been addressed in this review previously. Analyses of proteinuria, arterial and venous thromboembolic events, posterior reversible encephalopathy syndrome, gastrointestinal perforation, and hemorrhage were performed.

A search for events of wound healing problems, such as wound dehiscence, was performed given problems with wound healing observed other inhibitors of the VEGF pathway. A safety

signal was not identified.

Reviewer note: FDA has included Warnings in Section 5 of product labels for products which inhibit VEGF. Successful wound healing depends upon angiogenesis, a prominent feature of the repair process. Studies examining VEGFR have shown that it plays a key role in several facets of the wound healing. According to literature (see references cited at the end of this document), angiogenesis starts and peaks during the proliferative phase of healing (approximately 3-10 days), when new capillaries are being formed, and their appearance is synonymous with granulation, the creation of a provisional matrix comprised of blood vessels, migrating fibroblasts and new collagen. It is during this period that VEGF inhibition may have the most deleterious effect. Based on review of preclinical and clinical data for multiple drug products with VEGF pathway antagonism, FDA has determined that the labeling for drug products with VEGF inhibition will include consistent instructions to withhold such a drug product for at least 2 weeks following surgery and until adequate wound healing.

Proteinuria (based on SMQ analysis including the terms proteinuria and urine protein present) occurred in 4.8% of all patients and was Grade ≥ 3 in two patients (2/702, 0.3%). Posterior reversible encephalopathy syndrome was reported as an AE in one patients (0.1%); the SMQ query (noninfectious encephalopathy/delirium) generated 144 potential cases, though the terms encompass a broad range of events (dysphagia, muscular weakness, and tremor being the most commonly-reported). The results of the applicant's SMQ analysis for hemorrhage are demonstrated below.

Table 8.63 SMQ Analysis of Hemorrhagic Events based on 60-Day Update

	MTC Safety (N=299)		NSCLC Safety (N=329)		Overall Safety (N=702)	
AE Category Preferred Term	**All Grades**	**>= Grade 3**	**All Grades**	**>= Grade 3**	**All Grades**	**>= Grade 3**
Haemorrhage terms (excl laboratory terms) (SMQ)	52 (17.4%)	7 (2.3%)	44 (13.4%)	6 (1.8%)	105 (15%)	16 (2.3%)
Epistaxis	14 (4.7%)	0	14 (4.3%)	0	30 (4.3%)	0
Haematuria	13 (4.3%)	0	4 (1.2%)	0	19 (2.7%)	0
Haemoptysis	4 (1.3%)	1 (0.3%)	4 (1.2%)	0	10 (1.4%)	2 (0.3%)
Contusion	4 (1.3%)	0	4 (1.2%)	0	9 (1.3%)	0
Rectal haemorrhage	3 (1%)	0	3 (0.9%)	0	6 (0.9%)	0
Vaginal haemorrhage	2 (0.7%)	0	2 (0.6%)	0	4 (0.6%)	0
Ecchymosis	1 (0.3%)	0	2 (0.6%)	0	3 (0.4%)	0
Haematochezia	1 (0.3%)	0	2 (0.6%)	0	3 (0.4%)	0
Petechiae	1 (0.3%)	0	2 (0.6%)	0	3 (0.4%)	0
Traumatic haematoma	0	0	3 (0.9%)	1 (0.3%)	3 (0.4%)	1 (0.1%)
Anal haemorrhage	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	2 (0.3%)	1 (0.1%)
Blood blister	0	0	2 (0.6%)	0	2 (0.3%)	0
Blood urine present	1 (0.3%)	0	1 (0.3%)	0	2 (0.3%)	0
Cerebral haemorrhage	0	0	2 (0.6%)	2 (0.6%)	2 (0.3%)	2 (0.3%)
Gastric haemorrhage	1 (0.3%)	1 (0.3%)	0	0	2 (0.3%)	2 (0.3%)
Haemorrhage intracranial	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.1%)
Spontaneous haematoma	0	0	2 (0.6%)	0	2 (0.3%)	0
Abdominal wall haematoma	0	0	1 (0.3%)	1 (0.3%)	1 (0.1%)	1 (0.1%)
Angina bullosa haemorrhagica	0	0	1 (0.3%)	0	1 (0.1%)	0

Diverticulum intestinal haemorrhagic	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Eye haemorrhage	1 (0.3%)	0	0	0	1 (0.1%)	0
Gastrointestinal haemorrhage	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Gingival bleeding	0	0	1 (0.3%)	0	1 (0.1%)	0
Haematemesis	0	0	0	0	1 (0.1%)	1 (0.1%)
Haemorrhagic anaemia	0	0	1 (0.3%)	0	1 (0.1%)	0
Intra-abdominal haemorrhage	0	0	1 (0.3%)	1 (0.3%)	1 (0.1%)	1 (0.1%)
Lower gastrointestinal haemorrhage	1 (0.3%)	0	0	0	1 (0.1%)	0
Melaena	0	0	0	0	1 (0.1%)	0
Mouth haemorrhage	1 (0.3%)	0	0	0	1 (0.1%)	0
Occult blood positive	1 (0.3%)	0	0	0	1 (0.1%)	0
Pelvic haematoma	0	0	1 (0.3%)	1 (0.3%)	1 (0.1%)	1 (0.1%)
Periorbital haematoma	0	0	1 (0.3%)	0	1 (0.1%)	0
Pharyngeal haemorrhage	0	0	1 (0.3%)	0	1 (0.1%)	0
Post procedural haemorrhage	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Pulmonary contusion	0	0	1 (0.3%)	0	1 (0.1%)	0
Purpura	0	0	1 (0.3%)	0	1 (0.1%)	0
Retroperitoneal haematoma	0	0	1 (0.3%)	1 (0.3%)	1 (0.1%)	1 (0.1%)
Subarachnoid haemorrhage	0	0	1 (0.3%)	0	1 (0.1%)	0
Subdural haemorrhage	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Upper gastrointestinal haemorrhage	0	0	0	0	1 (0.1%)	1 (0.1%)
Vessel puncture site haematoma	1 (0.3%)	0	0	0	1 (0.1%)	0

The analysis performed by the Applicant was confirmed by FDA. Among 702 patients, there were 105 patients (15%) with at least one bleeding event with 2.3% (16/702) Grade ≥ 3 events including 3 (0.8%) fatal events. The Grade 5 events of bleeding are discussed in Section 8.2.4 (Deaths) and included an event of tracheostomy site hemorrhage, an event of cerebral hemorrhage in a patient with brain metastasis, and an event of hemoptysis (etiology unclear, but thought by the investigator to be due to an undiagnosed pulmonary embolus). Serious bleeding events occurred in 12 (1.7 %) patients in the OSAS; some of these events (5/9 non-fatal serious events) were confounded by concomitant anticoagulant or antiplatelet medications. The majority of patients who experienced bleeding (99/702, 12.7%) had mild bleeding events, most commonly epistaxis and hematuria. Narratives for selected serious bleeding events are provided below:

- Patient (b) (6) This is a 67-year-old female with NSCLC with no prior systemic therapy who experienced a retroperitoneal hematoma approximately 3 weeks after initiating treatment with selpercatinib. Vascular surgery was consulted and identified a pseudo-aneurysm arising from a branch of the inferior pancreaticoduodenal artery and noted an additional branch of the inferior pancreaticoduodenal arcade was enlarged with multiple tiny aneurysms. She was treated successfully with embolization. The event was assessed as related to selpercatinib. The patient was withdrawn from the study.

- Patient (b) (6) This is a 55-year-old female with MTC who experienced Grade 3 gastric hemorrhage 11 months after initiating treatment with selpercatinib. The patient had discontinued PPI treatment prior to study entry and had been experiencing an increase in heartburn; she was found to have a gastric ulcer and treated with a PPI. The event was assessed as not related to selpercatinib.

- Patient (b) (6) This is a 41-year-old male with MTC with no prior systemic therapy who experienced a Grade 2 gastrointestinal bleed. He was treated for *Campylobacter* diarrhea; he also had a history of ulcerative colitis. The event was assessed as not related to selpercatinib.

Additional events included diverticulosis bleed in a patient receiving aspirin, lower gastrointestinal hemorrhage in a patient receiving enoxaparin, upper gastrointestinal hemorrhage, anal hemorrhage in a patient with diverticulitis receiving aspirin, and hemoptysis in a patient receiving enoxaparin.

Reviewer note: Though confounding factors are present in many cases, there is a plausible mechanism of action (VEGF pathway inhibition) that could lead to bleeding in patients treated with selpercatinib, and serious and fatal events have occurred. In a single arm study, it is difficult to distinguish events attributable to drug from events which may occur in the population due to underlying risk factors, concomitant illnesses or the disease under study.

Information to describe this risk will be included in the product label under Warnings & Precautions.

SMQ analyses for cardiac failure and cardiomyopathy were performed by the Applicant at the request of FDA and is reproduced in the table below.

Table 8.64 SMQ Analysis of Cardiac Failure based on 60-Day Update

	MTC Safety (N=299)		**NSCLC Safety (N=329)**		**Overall Safety (N=702)**	
AE Category Preferred Term	**All Grades**	**>= Grade 3**	**All Grades**	**>= Grade 3**	**All Grades**	**>= Grade 3**
Cardiac failure (SMQ)	82 (27.4%)	5 (1.7%)	89 (27.1%)	0	186 (26.5%)	6 (0.9%)
Oedema peripheral	72 (24.1%)	1 (0.3%)	81 (24.6%)	0	165 (23.5%)	1 (0.1%)
Peripheral swelling	8 (2.7%)	0	6 (1.8%)	0	16 (2.3%)	0
Lower respiratory tract congestion	2 (0.7%)	0	3 (0.9%)	0	5 (0.7%)	0
Ejection fraction decreased	2 (0.7%)	2 (0.7%)	1 (0.3%)	0	3 (0.4%)	2 (0.3%)
Pulmonary oedema	0	0	2 (0.6%)	0	3 (0.4%)	1 (0.1%)
Cardiac failure	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	2 (0.3%)	1 (0.1%)
Acute left ventricular failure	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Cardiac dysfunction	0	0	0	0	1 (0.1%)	1 (0.1%)
Cardiac failure congestive	1 (0.3%)	0	0	0	1 (0.1%)	0
Left ventricular dysfunction	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Left ventricular failure	1 (0.3%)	0	0	0	1 (0.1%)	0
Oedema	1 (0.3%)	0	0	0	1 (0.1%)	0
Orthopnoea	0	0	1 (0.3%)	0	1 (0.1%)	0
Cardiomyopathy (SMQ)	69 (23.1%)	11 (3.7%)	63 (19.1%)	17 (5.2%)	146 (20.8%)	33 (4.7%)

Dyspnoea	42 (14%)	4 (1.3%)	45 (13.7%)	9 (2.7%)	97 (13.8%)	16 (2.3%)
Ascites	11 (3.7%)	1 (0.3%)	9 (2.7%)	1 (0.3%)	20 (2.8%)	2 (0.3%)
Chest pain	4 (1.3%)	0	6 (1.8%)	2 (0.6%)	11 (1.6%)	2 (0.3%)
Syncope	2 (0.7%)	2 (0.7%)	5 (1.5%)	3 (0.9%)	8 (1.1%)	6 (0.9%)
Palpitations	5 (1.7%)	0	2 (0.6%)	0	7 (1%)	0
Cardiac arrest	1 (0.3%)	1 (0.3%)	2 (0.6%)	2 (0.6%)	3 (0.4%)	3 (0.4%)
Computerised tomogram thorax abnormal	3 (1%)	0	0	0	3 (0.4%)	0
Ejection fraction decreased	2 (0.7%)	2 (0.7%)	1 (0.3%)	0	3 (0.4%)	2 (0.3%)
Cardiac failure	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	2 (0.3%)	1 (0.1%)
Nocturia	1 (0.3%)	0	1 (0.3%)	0	2 (0.3%)	0
Orthostatic hypotension	2 (0.7%)	0	0	0	2 (0.3%)	0
Acute left ventricular failure	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Cardiac dysfunction	0	0	0	0	1 (0.1%)	1 (0.1%)
Cardiac failure congestive	1 (0.3%)	0	0	0	1 (0.1%)	0
Electrocardiogram abnormal	0	0	0	0	1 (0.1%)	0
Left ventricular dysfunction	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Left ventricular failure	1 (0.3%)	0	0	0	1 (0.1%)	0
Mental status changes	1 (0.3%)	0	0	0	1 (0.1%)	0
Oedema	1 (0.3%)	0	0	0	1 (0.1%)	0
Restrictive cardiomyopathy	0	0	1 (0.3%)	1 (0.3%)	1 (0.1%)	1 (0.1%)
Stress cardiomyopathy	1 (0.3%)	0	0	0	1 (0.1%)	0
Ventricular arrhythmia	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	1 (0.1%)

The SMQ analysis for cardiac failure generated 6 events (0.9%) that were ≥ Grade 3 with the preferred terms peripheral edema, ejection fraction decreased, cardiac failure, cardiac dysfunction, acute left ventricular failure, and left ventricular dysfunction. Although the search generated any grade event in 26.5% of patients, the vast majority of these events were due to the preferred term peripheral edema, which appears to be a non-serious effect of selpercatinib.

Excluding only peripheral edema, events of any grade generated by the SMQ of cardiac failure occurred in 2.9% of patients. The SMQ for cardiomyopathy generated 33 events that were ≥ Grade 3, which included 16 events of dyspnea. This included one event of stress cardiomyopathy and one event of restrictive cardiomyopathy considered potentially relevant in addition to the terms generated from the cardiac failure SMQ. There was one Grade 5 event of cardiac failure (see "Deaths" and summary of patient (b) (6) below) and an event of Grade 4 left ventricular dysfunction in the same patient. A summary of serious and selected nonserious events are provided below:

- Patient (b) (6) This is a 78-year-old female who developed Grade 3 acute left ventricular failure on day 6 of treatment with selpercatinib in the setting of hospitalization for parainfluenza infection which required respiratory support with BiPap. The event resolved after holding selpercatinib during the illness.
- Patient (b) (6): This is a 38-year-old female with large cell neuroendocrine carcinoma previously treated with cisplatin, etoposide, carboplatin, paclitaxel, nivolumab, doxorubicin, external beam radiation therapy (twice) and gamma knife therapy who developed Grade 3 cardiac dysfunction (ejection fraction 25%). Heart failure was diagnosed in the wake of a hospitalization for abdominal abscess and drainage following re-initiation of selpercatinib. The patient was withdrawn from the study due to the event. Heart failure was thought to be due to prior treatment with doxorubicin, which was completed approximately 5 months prior to the event.
- Patient (b) (6) This is a 70 year old male with NSCLC, previously treated with EBRT, diagnosed with Grade 3 restrictive cardiomyopathy on day 9 of treatment with selpercatinib after presenting with ongoing dyspnea (present prior to starting selpercatinib) and tachycardia. Ejection fraction was 35% (baseline 60%). The patient was treated with supplemental oxygen, carvedilol, lisinoprin and enoxaparin; he was discharged two days later and the event was considered resolved with sequelae.
- Patient (b) (6) This is a 45-year-old female with MTC previously treated with cabozantinib, vandetanib and EBRT found to have decreased ejection fraction (Grade 3) after 6 days of treatment with selpercatinib during hospitalization for empyema. The lowest ejection fraction was not reported, but follow-up echo ~3 weeks later demonstrated an improved EF of 36% (baseline 44%) with no clinical signs of heart failure. The dose of selpercatinib was not changed in response to the event.
- Patient (b) (6) This is a 91-year-old male with MTC previously treated with vandetanib, EBRT, and transarterial chemoembolization who was diagnosed with Grade 2 non-ischemic stress cardiomyopathy during a hospitalization for gastroenteritis and pneumonia approximately one month after initiating selpercatinib. The event was noted as resolving when the patient withdrew from the study. Risk factors for cardiac disease include age and hypertension.
- Patient (b) (6) This is a 71-year-old female with NSCLC developed Grade 2 ejection fraction decreased after 2.5 months of treatment with selpercatinib. An

echo was performed due to an event of syncope demonstrated EF of 45% (Grade 2). There was no available baseline for comparison and follow-up 1 month later had "no important changes." No change was made to the study drug, and the patient continued selpercatinib for an additional 6 months until disease progression.

- Patient (b) (6) This is a 69 year-old female with MTC who experienced Grade 3 decreased ejection fraction (assessed as unrelated and non-serious). The patient's medical history is notable for hyperlipidemia and hypertension. During a hospitalization for a complex lung abscess, she underwent bronchoscopy and became hypotensive and bradycardic with multiple premature ventricular complexes (PVCs). Following the procedure, she was noted to be hemiparetic and CT revealed right cerebral artery and middle cerebral artery infarcts. Echocardiogram performed during this hospitalization demonstrated decreased EF of 30 – 35% felt to be secondary to the serious events described above.
- Patient (b) (6) This is an 80 year-old male with MTC who had received no prior systemic therapy who developed Grade 4 left ventricular dysfunction nearly 2 years after initiation of selpercatinib. The patient had a history of hypertension and hypercholesterolemia. The patient presented with weakness, ascites and abdominal distension; ECG suggested myocardial infarction 24 - 48 hours prior to presentation and the patient was diagnosed with acute systolic heart failure. The patient was discharged to hospice and died approximately 10 days after the initial diagnosis of heart failure.
- Patient (b) (6) This is a 70-year-old male with NSCLC who developed Grade 1 cardiac failure on day 114 of study. The patient presented with peripheral edema and mild dyspnea and was treated with furosemide; the event was presumed to be cardiac in nature. However, a subsequent echocardiogram demonstrated a normal EF (70%) and the investigator assessed the event was more accurately described as peripheral edema.

The serious events of cardiac failure and decreased ejection fraction occurred from 6 – 717 days after initiating treatment with selpercatinib. Many cases are confounded by prior therapy or intercurrent illnesses, and some are complicated by the lack of baseline or routine echocardiogram assessments in LIBRETTO-001. Combining the results of the SMQ of cardiac failure and selected terms from the cardiomyopathy SMQ, Grade ≥ 3 cardiac dysfunction occurred in 1% (7/ 702) of patients in the safety database, including a fatal event. Assessment of the potential impact of selpercatinib on cardiac function is limited by the single arm nature of the study, and by the lack of baseline and routine echocardiograms, but given the confounding factors demonstrated by the narratives above, a significant effect of selpercatinib on cardiac function appears uncertain.

The Applicant performed an analysis of arterial thromboembolic events as demonstrated in the table below.

Table 8.65: SMQ Analysis of Arterial Thromboembolic Events based on 60 Day Update

	MTC Safety (N=299)		NSCLC Safety (N=329)		Overall Safety (N=702)	
AE Category Preferred Term	**All Grades**	**>= Grade 3**	**All Grades**	**>= Grade 3**	**All Grades**	**>= Grade 3**
Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ)	4 (1.3%)	2 (0.7%)	14 (4.3%)	5 (1.5%)	20 (2.8%)	8 (1.1%)
Embolism	2 (0.7%)	1 (0.3%)	7 (2.1%)	0	11 (1.6%)	2 (0.3%)
Hemiparesis	0	0	3 (0.9%)	1 (0.3%)	3 (0.4%)	1 (0.1%)
Cerebrovascular accident	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.3%)
Cardiac ventricular thrombosis	1 (0.3%)	0	0	0	1 (0.1%)	0
Catheter site thrombosis	0	0	1 (0.3%)	0	1 (0.1%)	0
Cerebral infarction	0	0	1 (0.3%)	1 (0.3%)	1 (0.1%)	1 (0.1%)
Cerebrovascular disorder	0	0	1 (0.3%)	1 (0.3%)	1 (0.1%)	1 (0.1%)
Paraplegia	0	0	1 (0.3%)	1 (0.3%)	1 (0.1%)	1 (0.1%)
Renal infarct	0	0	1 (0.3%)	0	1 (0.1%)	0
Splenic infarction	0	0	1 (0.3%)	0	1 (0.1%)	0

Overall 2.8% of patients had events generated by the SMQ analysis for arterial thromboembolic events, and 1.1% had Grade ≥ 3 events. Narratives for serious events generated by the SMQ analysis were reviewed. Events of hemiparesis (n=3) were not concerning for stroke. Two serious events of embolism included a 71-year-old female with NSCLC diagnosed with a DVT and possible anterior myocardial infarct (risk factors for cardiac disease included age, diabetes, hyperlipidemia, and hypertension) and a 72-year-old male with anaplastic thyroid cancer with segmental pulmonary emboli (risk factors included age and underlying malignancy). One

patient with Grade 5 cerebrovascular accident (b) (6) was reviewed previously (see Deaths) and deemed unlikely related to selpercatinib. Overall, there were few serious events generated by the SMQ analysis. Narratives for Grade 3 – 5 events consistent with stroke are summarized below.

- Patient (b) (6) This is a 68-year-old female with MTC previously treated with cabozantinib who experienced Grade 3 cerebrovascular accident approximately 2 months after initiating selpercatinib. She had a history of hypertension and hyperlipidemia. She was hospitalized for pneumonia and became hypotensive and bradycardic during bronchoscopy. Following the procedure she was observed to be not moving her left upper and lower extremities and was diagnosed with right anterior cerebral and middle cerebral infarcts. The event was considered unrelated to selpercatinib.
- Patient (b) (6) This is a 54-year-old female with NSCLC previously treated with platinum chemotherapy, nivolumab and alectinib as well as whole brain radiation therapy who experienced Grade 3 cerebrovascular disorder 12 months after initiating treatment with selpercatinib. She was diagnosed with ischemic stroke. She subsequently developed Enterobacter pneumonia and died; the event of cerebrovascular disorder was considered unresolved at the time of death, and unrelated to selpercatinib. Whole brain radiation therapy is a significant risk factor.
- Patient (b) (6) This is a 50-year-old female with metastatic NSCLC with brain metastases and extensive prior systemic treatment (platinum, anti-PD1, multiple TKIs) and stereotactic radiosurgery, and a history of hypertension. The patient was diagnosed with cerebral infarction approximately one year after initiating treatment with selpercatinib. Selpercatinib was withdrawn in response to the event and the patient died approximately 3 weeks later of disease progression. The patient had multiple risk factors including brain metastases, prior SRS and hypertension. A role of selpercatinib cannot be excluded.
- Patient (b) (6) This is a 67-year-old male with NSCLC previously treated with ipilimumab, nivolumab, and cabozantinib who experienced Gr 5 cerebrovascular accident approximately 4 months after initiating treatment with selpercatinib. The patient had a history of coronary artery disease, hyperlipidemia, and hypertension. The patient was diagnosed with a cerebrovascular accident in the setting of severe illness. The patient experienced peritoneal carcinomatosis and ascites followed by hospitalization for pleural effusion and cardiac tamponade. After experiencing agitation, the patient was managed with dexmedetomidine and underwent right plural fluid drainage, pigtail catheter placement, and paracentesis. After discontinuation of dexmedetomidine, the patient did not awaken and cerebrovascular accident was diagnosed. The patient developed further hypoxia and hypotension and died two days later. Although cerebrovascular accident is listed as the cause of death, the severe illness described was ongoing at the time of death. The event was considered unrelated to selpercatinib.

Reviewer note: A role of selpercatinib in the events of cerebrovascular accident and cerebral infarction listed above cannot be excluded. However, it is notable that all patients had underlying risk factors, and two of the four events occurred in a periprocedural setting.

The Applicant performed an analysis of events of gastrointestinal perforation based on the SMQ (see Table 8.66). Overall there were very few events of fistula or perforation in LIBRETTO-001. Several cases were confounded in some way (such as by prior radiation or metastatic disease).

Table 8.66: SMQ Analysis of Gastrointestinal Perforation Based on 60-day Update

	MTC Safety (N=299)		**NSCLC Safety (N=329)**		**Overall Safety (N=702)**	
AE Category Preferred Term	**All Grades**	**>= Grade 3**	**All Grades**	**>= Grade 3**	**All Grades**	**>= Grade 3**
Gastrointestinal perforation (SMQ)	2 (0.7%)	1 (0.3%)	2 (0.6%)	2 (0.6%)	5 (0.7%)	4 (0.6%)
Abdominal abscess	1 (0.3%)	1 (0.3%)	0	0	2 (0.3%)	2 (0.3%)
Appendiceal abscess	1 (0.3%)	0	0	0	1 (0.1%)	0
Enterocutaneous fistula	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Jejunal perforation	0	0	1 (0.3%)	1 (0.3%)	1 (0.1%)	1 (0.1%)
Oesophageal fistula	0	0	1 (0.3%)	1 (0.3%)	1 (0.1%)	1 (0.1%)
Pancreatic fistula	0	0	0	0	1 (0.1%)	1 (0.1%)
Peritonitis	0	0	1 (0.3%)	1 (0.3%)	1 (0.1%)	1 (0.1%)

Effects associated with FGFR Pathway Inhibition

FDA requested additional analyses of potential adverse reactions associated with FGFR pathway inhibition, including vision disorders and hyperphosphatemia. The Applicant provided analyses based on SMQs for vision disorders (optic nerve disorders, retinal disorders, and glaucoma). The USPI for erdafitinib, an inhibitor of FGFR2 and FGFR3, contains warnings for ocular disorders (including central serous retinopathy/retinal pigment epithelial detachment) and hyperphosphatemia. Notably, LIBRETTO-001 did not monitor routine ophthalmologic

examinations. The sponsor provided the following SMQ analyses (FDA modified formatting only):

Table 8.55: SMQ Analysis of Vision Disorders based on 60-Day Safety Update

	MTC Safety (N=299)		NSCLC Safety (N=329)		Overall Safety (N=702)	
AE Category Preferred Term	**All Grades**	**>= Grade 3**	**All Grades**	**>= Grade 3**	**All Grades**	**>= Grade 3**
Glaucoma (SMQ)	25 (8.4%)	1 (0.3%)	23 (7%)	2 (0.6%)	49 (7%)	3 (0.4%)
Vision blurred	16 (5.4%)	0	15 (4.6%)	0	31 (4.4%)	0
Visual impairment	2 (0.7%)	0	2 (0.6%)	0	5 (0.7%)	0
Cataract	1 (0.3%)	0	3 (0.9%)	1 (0.3%)	4 (0.6%)	1 (0.1%)
Photophobia	3 (1%)	0	0	0	3 (0.4%)	0
Eye pain	1 (0.3%)	0	1 (0.3%)	0	2 (0.3%)	0
Glaucoma	0	0	2 (0.6%)	1 (0.3%)	2 (0.3%)	1 (0.1%)
Visual acuity reduced	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	2 (0.3%)	1 (0.1%)
Eye colour change	0	0	0	0	1 (0.1%)	0
Facial pain	0	0	1 (0.3%)	0	1 (0.1%)	0
Halo vision	1 (0.3%)	0	0	0	1 (0.1%)	0
Retinal disorders (SMQ)	24 (8%)	1 (0.3%)	20 (6.1%)	0	47 (6.7%)	1 (0.1%)
Vision blurred	16 (5.4%)	0	15 (4.6%)	0	31 (4.4%)	0
Visual impairment	2 (0.7%)	0	2 (0.6%)	0	5 (0.7%)	0
Vitreous floaters	0	0	2 (0.6%)	0	4 (0.6%)	0
Photophobia	3 (1%)	0	0	0	3 (0.4%)	0
Visual acuity reduced	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	2 (0.3%)	1 (0.1%)
Eye disorder	0	0	1 (0.3%)	0	1 (0.1%)	0
Eye haemorrhage	1 (0.3%)	0	0	0	1 (0.1%)	0
Retinal detachment	1 (0.3%)	0	0	0	1 (0.1%)	0
Retinal oedema	0	0	1 (0.3%)	0	1 (0.1%)	0
Visual field defect	1 (0.3%)	0	0	0	1 (0.1%)	0

Optic nerve disorders (SMQ)	4 (1.3%)	1 (0.3%)	3 (0.9%)	0	8 (1.1%)	1 (0.1%)
Visual impairment	2 (0.7%)	0	2 (0.6%)	0	5 (0.7%)	0
Visual acuity reduced	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	2 (0.3%)	1 (0.1%)
Visual field defect	1 (0.3%)	0	0	0	1 (0.1%)	0

There was one event of retinal detachment in LIBRETTO-001, which was assessed as non-serious. A narrative is provided below:

- Patient (b) (6) This is a 57-year-old male with medullary thyroid cancer previously treated with lenvatinib, ipilimumab, nivolumab, vandetanib, and regorafenib as well as external beam radiation and total thyroidectomy with modified left sided nodal dissection. The patient had an abnormal ophthalmic eye exam documenting, "exudative chronic appearance, rpe depigmentation consistent with previous lesion, inferonasal/ inferotemporal retinal detachment with improved fluid in macula" in the right eye and "large chorioretinal lesion nasal to optic nerve, retinal detachment with pigmented lattia" in the left eye. The physician's summary was 'no change in retinal exam; likely old choroidal metastasis which have responded/ regressed to chemotherapy.' The narrative also notes that the patient is a professional boxer and has sustained repeated trauma due to his profession.
- Patient (b) (6) This is a 57-year-old male with MTC and MEN2B who developed Grade 3 decreased visual acuity considered non-serious and unrelated after approximately 4 months of treatment with selpercatinib. The patient had a history of cataracts and corneal ulceration. An ophthalmologic exam demonstrated increased corneal ulcers due to corneal dryness due to MEN2B, and stable cataracts. Eye drops were prescribed with improvement in visual acuity.

Reviewer note: The event of retinal detachment is confounded by the presence of metastatic tumor and the history of trauma due to the patient's profession. Therefore there do not appear to be reported cases of RPED due to selpercatinib. The event of decreased visual acuity appears to be related to ocular manifestations of the patients' underlying MEN2B syndrome.

FDA also requested a shift analysis for hyperphosphatemia, including the following categories: <5.5 mg/dL, 5.5 mg/dL - 7 mg/dL, > 7 mg/dL – 10 mg/dL, and > 10 mg/dL. (86.4%) of patients in the Overall Safety population retained their baseline phosphate level (based upon the above specified ranges) or better. Additionally, the last post-baseline phosphate lab value available was < 5.5 mg/dL for most of this population (97.2%). Eleven patients were reported to have an AE of hyperphosphatemia and required phosphate binding medication. Seven patients' last post-baseline values had returned to <5.5 mg/dL and the remaining patients had values which were mildly elevated to the level of 5.5-7 mg/dL.

Reviewer note: Increases in phosphate were mild and rarely (in 1.6% of patients) required intervention with phosphate binding medication.

8.2.7 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicants Position:
Not applicable. This application did not include COA analyses informing the safety or tolerability of selpercatinib.

The FDA's Assessment:
FDA agrees with the Applicant. Health-related quality of life (HRQoL) instruments were administered at baseline and at disease assessment visits. Bowel diaries were also included for patients with a diagnosis of MTC. These evaluations were exploratory in nature. Descriptive analyses of Global Health Status were included in the clinical study report, but these analyses are limited by the single-arm nature of the study and were not intended to inform an assessment of safety or tolerability.

The post-marketing study intended to confirm the benefit of selpercatinib in patients with MTC will include analyses of patient-reported outcomes to evaluate the comparative tolerability of selpercatinib compared to physician's choice of available therapies. See Section 13.

8.2.8 Safety Analyses by Demographic Subgroups

The Applicant's Position: [Module 2.7.4.5.6]

Age

Few trends were apparent in the analysis of all AEs by age group (< 65 vs ≥ 65 years) Cough and rash had higher frequencies in the older population. The higher frequency of cough might be attributed, in part, to older patients with NSCLC who may experience disease-related respiratory symptoms. Other than these, AE incidences in the older age group were either similar to or lower than the younger age group.

In the Original NDA, the following AEs occurred with higher frequency in patients < 65 vs ≥ 65 years: dry mouth (34.3% vs 28.2% for younger vs older, respectively), ALT increase (28.0% vs 21.0%), and nausea (21.4% vs 15.5%). In the 60-Day Update, these same AEs occurred with higher frequency in patients < 65 vs ≥ 65 years: dry mouth (39.7% vs 36.8% for younger vs older, respectively), ALT increase (29.6% vs 26.8%), and nausea (25.1% vs 18.0%). Additionally, the AEs of diarrhea (36.9% vs 34.7% for younger vs older, respectively) and headache (24.8% vs 19.2%) also occurred with higher frequency between these populations (60-Day Update SCS Table 14.4.33.1). Due to the disparate sample sizes between the two groups, any differences

should be interpreted with caution. Overall, no substantive age effects were seen in the incidence of AEs.

Sex

The study population had a moderately higher proportion of men (53.9% in the Original NDA; 52.4% in the 60-Day Update). In the Original NDA, relative to men, women tended to have higher frequencies of nausea (23.3% vs 16.1%), diarrhea (34.7% vs 28.3%), pyrexia (15.5% vs 9.8%) and dry mouth (35.1% vs 29.7%), while men displayed a higher incidence of creatinine increase relative to women (21.3% vs 13.1%). In the 60-Day Update, relative to men, women tended to have higher frequencies of dry mouth (44.0% vs 34.0%), diarrhea (38.9% vs 33.7%), nausea (24.9% vs 20.7%), headache (24.9% vs 21.2%), rash (19.5% vs 15.8%), electrocardiogram QT prolonged (18.9% vs 14.1%), and pyrexia (16.5% vs 10.9%); while men displayed a higher incidence of hypertension (36.7% vs 33.2%), creatinine increase (23.9% vs 14.4%), and dyspnea (16.3% vs 11.1%) (60-Day Update SCS Table 14.4.33.2).

Race

Approximately 70.1% of the population were white (69.1% in the 60-Day Update); the largest minority was Asian, which constituted 21.1% of the population (21.9% in the 60-Day Update). Hence, the analysis of AEs by race compared White vs Asian vs All Others.

Several differences between racial groups in the frequency of certain AEs were seen. In the Original NDA, for White vs. Asian patients, AEs with a difference in frequency of 10% or higher were: fatigue (27.2% vs 15.2%), constipation (23.9% vs 12.5%), thrombocytopenia (11.0% vs 21.4%), and ALT increase (24.7% vs 34.8%); In the 60-Day Update, for White vs. Asian patients, AEs with a difference in frequency of 10% or higher were: fatigue (31.8% vs 15.6%), nausea (24.5% vs 13.6%), ALT increased (26.4% vs 39.6%), and rash (14.6% vs 26.6%). (60-Day Update SCS Table 14.4.33.3)

The FDA's Assessment:

FDA agrees with the Applicant that subgroup analyses should be interpreted with caution. In addition to the analyses of specific AEs described above, FDA requested that the Applicant perform analyses to describe the incidence of AEs and SAEs as a whole in these different subgroups. The following tables were provided by the Applicant. FDA notes that there is a higher incidence of serious adverse events in patients 65 years or older, which may be related to increased comorbidities. Otherwise, the incidence of SAEs, fatal AEs, and TEAEs requiring discontinuation appears relatively similar across demographic subgroups.

FDA also requested that the Applicant perform exploratory analyses of patients with MTC with hereditary syndromes. An analysis in the subset of patients who had a germline RET mutation (n=37) was evaluated and compared to the overall MTC safety population (n=299 based on the updated data cut-off). Overall the incidence of any AE, Grade 3 – 4 AE, and SAE were

comparable in the population with germline mutations compared to the overall MTC population. There were no fatal AEs or AEs leading to treatment discontinuation in the subset of patients with germline *RET* mutations. There did not appear to be major differences in the incidences of common AEs between these subsets.

Table 8.67 Incidence of Adverse Events by Age (Applicant's Analysis)

	< 65 years (N=463)	>= 65 years (N=239)	Total (N=702)
Patients with TEAEs	458 (98.9)	237 (99.2)	695 (99.0)
Patients with TEAEs Maximum Severity >= 3	259 (55.9)	156 (65.3)	415 (59.1)
Patients with Serious TEAEs	131 (28.3)	103 (43.1)	234 (33.3)
Patients with Fatal TEAEs	11 (2.4)	10 (4.2)	21 (3.0)
Patients with TEAEs and Action Taken of LOXO-292 Permanently Discontinued	17 (3.7)	20 (8.4)	37 (5.3)

Table 8.68: Incidence of Adverse Events by Sex (Applicant's Analysis)

	Male (N=368)	Female (N=334)	Total (N=702)
Patients with TEAEs	365 (99.2)	330 (98.8)	695 (99.0)
Patients with TEAEs Maximum Severity >= 3	205 (55.7)	210 (62.9)	415 (59.1)
Patients with Serious TEAEs	122 (33.2)	112 (33.5)	234 (33.3)
Patients with Fatal TEAEs	13 (3.5)	8 (2.4)	21 (3.0)
Patients with TEAEs and Action Taken of LOXO-292 Permanently Discontinued	21 (5.7)	16 (4.8)	37 (5.3)

Table 8.69: Incidence of Adverse Events by Race (Applicant's Analysis)

	White (N=485)	Asian (N=154)	All Others (N=63)	Total (N=702)
Patients with TEAEs	482 (99.4)	151 (98.1)	62 (98.4)	695 (99.0)
Patients with TEAEs Maximum Severity >= 3	290 (59.8)	87 (56.5)	38 (60.3)	415 (59.1)
Patients with Serious TEAEs	170 (35.1)	43 (27.9)	21 (33.3)	234 (33.3)
Patients with Fatal TEAEs	13 (2.7)	6 (3.9)	2 (3.2)	21 (3.0)
Patients with TEAEs and Action Taken of LOXO-292 Permanently Discontinued	24 (4.9)	8 (5.2)	5 (7.9)	37 (5.3)

8.2.9 Specific Safety Studies/Clinical Trials

The Applicants Position:

There were no additional studies performed to evaluate any specific safety concerns.

The FDA's Assessment:
FDA agrees with the Applicant's statement and has no further comments.

8.2.10 Additional Safety Explorations

Human Carcinogenicity or Tumor Development
The Applicants Position:

Carcinogenicity studies were not conducted or required to support the use of selpercatinib in the proposed indication.

The FDA's Assessment:
FDA agrees with the Applicant's statement and has no further comments.

Human Reproduction and Pregnancy
The Applicants Position

Women who were known to be pregnant or breast-feeding were excluded from the study; birth-control measures during treatment and ongoing pregnancy screening were enforced to ensure that no fetus was exposed to selpercatinib. Hence, no information on the use of selpercatinib in pregnancy or lactation are available. Additionally, no pregnancies occurred during the development of the program and there was no known drug exposure of breastfed infants of lactating women. [Module 2.7.4.8.2]

The FDA's Assessment:
FDA agrees with the Applicant's statement and has no further comments.

Pediatrics and Assessment of Effects on Growth
The Applicants Position

Five pediatric patients with ages ranging from 1 to 10 years were treated with selpercatinib for compassionate use on single patient protocols (SPP). Tumor types represented included MTC, papillary thyroid, lipofibromatosis, infantile myofibroma, and infantile fibrosarcoma (1 patient each). [Module 2.7.4.10]

A pediatric trial (LOXO-RET-18036) was initiated and is ongoing, no patients were enrolled at the time of the NDA submission data cut-off date of 17 June 2019. The assessment of effects on growth have not been conducted.

The FDA's Assessment:
The Applicant provided information on six patients treated under single patient protocols in the Summary of Clinical Safety. There were no trends in adverse events experienced by these patients based on the information presented by the Applicant.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicants Position:

Overdose

For the Original NDA, no overdoses, defined as a daily exposure which exceeded the maximum daily assigned dose of 320 mg, 400 mg or 480 mg (dependent on assignment of 160 mg BID, 200 mg BID or 240 mg BID, respectively), had occurred by the 17 June 2019 data cutoff. At the 60-Day Update, 1 patient (b) (6) unintentionally took 240 mg (instead of 160 mg) in the AM and took 160 mg in the PM, resulting in a relative dose intensity of 100.1%. There were no AEs or SAEs reported from this overdose. (Original NDA Module 2.7.4.8.3; 60-Day Update SCS Table 14.3.1)

Abuse Potential

No information is available at this time on selpercatinib abuse or misuse, nor is there evidence that selpercatinib would be a candidate for such. [Module 2.7.4.8.4]

Withdrawal

No studies or analyses specifically addressed clinical issues related to selpercatinib withdrawal and/or rebound. Over one-half of treated patients (58.7%) had their treatment interrupted either for AE or other reasons at the time of the 60-Day Update. Treatment was reinstated successfully without known sequelae. [Original NDA Module 2.7.4.8.5; 60-Day Update Section **Error! Reference source not found.**]

The FDA's Assessment:
FDA agrees with the Applicant's statement and has no further comments.

8.2.11 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicants Position:
To date, selpercatinib has not been granted market authorization.

The FDA's Assessment:
FDA agrees there is no postmarketing safety experience to consider in this review.

Expectations on Safety in the Postmarket Setting

The Applicants Position:

Safety of selpercatinib in the post-market setting is not expected to differ significantly from that observed in LOXO-RET-17001 as assessed during the safety review of this NDA submission.

The FDA's Assessment:
Selpercatinib is expected to be administered by oncologists; management of and monitoring for adverse effects of anti-cancer medications including potentially serious adverse effects is standard practice in oncology. FDA does not anticipate that the safety of this product will differ significantly in the post-market setting.

8.2.12 Integrated Assessment of Safety

The Applicants Position: [Module 2.7.4.2 & 2.7.4.11]

[Original NDA Modules 2.7.4.2 and 2.7.4.11; 60-Day Update Assessment Aid Addendum 8.2.4]

For this 60-Day Update the primary safety analysis set is based on all 702 patients who received at least one dose of selpercatinib (OSAS) as of the data cutoff of 16 December 2019. Ninety-five percent (667 of 702) received a dose of 160 mg BID of selpercatinib —609 (86.8%) patients received 160 mg BID as a starting dose, and 58 (8.2%) patients received 160 mg BID as a protocol-specified dose adjustment. Thus, the safety experience described should be reasonably representative of real-world use.

The median time on treatment in the Original NDA was 5.9 months, with a longest time on treatment of 25.1 months. With the additional follow up, the median time on treatment in the 60-Day Update was 8.7 months, with a longest time on treatment of 31.0 months (and ongoing as of the data cutoff for the 60-Day Update).

In the 60-Day Update, the median age of patients receiving selpercatinib was 59.0 years for the OSAS, and encompassed a wide range (15–92), with 3 (0.4%) patients younger than 18 years of age and 48.0% of patients in the 45-64 years age group. The majority of patients carried the 2 different tumor diagnoses of NSCLC (47.3%) and MTC (43.6%). Most patients had received prior cancer therapy: 65.7% had undergone surgery, 74.8% had received 1 or more systemic therapies and 46.9% had received radiotherapy.

The most common AEs of any grade for the OSAS (for the Original NDA and for the 60-Day Update, respectively) AEs were dry mouth (32.2% and 38.7%), diarrhea (31.3% and 36.2%), hypertension (28.8% and 35.0%), AST increase (27.5% and 29.9%), ALT increase (25.6% and 28.6%), fatigue (24.3% and 28.1%), and constipation (21.8% and 25.4%). Three additional AEs occurred at a frequency greater than 20% in the 60-Day Update: edema peripheral (23.5%), headache (22.9%), and nausea (22.6%). All other AEs occurred at a frequency of less than 20%.

In the 60-Day update, selpercatinib safety was generally consistent across NSCLC and MTC patients with the following exceptions: the NSCLC population (relative to the MTC population) had a higher incidence of diarrhea (40.4% vs 31.8%, respectively), pyrexia (19.8% vs 6.4%), and thrombocytopenia (17.3% vs 8.7%), while the MTC population (relative to the NSCLC population) had a higher incidence of hypertension (37.8% vs 31.9%, respectively), constipation (31.1% vs 20.1%), fatigue (31.1% vs 23.7%), abdominal pain (20.1% vs 14.0%), and arthralgia (17.1% vs 8.2%). As there is no known explanation for these differences, the pooled analyses (n = 702) is considered the most comprehensive evaluation of selpercatinib.

Investigators reported an AE of Grade 3 or 4, regardless of attribution, in 271 (51.0%) patients in the Original NDA and 394 (56.1%) patients in the 60-Day Update. Of these, 132 (24.9%) were deemed related to selpercatinib in the Original NDA and 206 (29.3%) were deemed related in the 60-Day Update.

In the OSAS, AEs deemed related to selpercatinib and leading to dose reductions occurring in > 1% of patients (for the Original NDA and for the 60-Day Update, respectively) included ALT increase (5.8%; and 6.4%), AST increase (4.3%; and 5.6%), ECG QT prolonged (2.6%; and 2.3%), fatigue (1.7%; and 2.1%), and drug hypersensitivity (1.1%; and 1.7%). Five additional AEs deemed related to selpercatinib and leading to dose reductions occurred at a frequency greater than 1% in the 60-Day Update: thrombocytopenia (1.4%), rash (1.3%), diarrhea (1.3%), hypertension (1.3%), and hypersensitivity (1.1%).

In the OSAS, AEs deemed related to selpercatinib and resulting in discontinuations of selpercatinib occurred in 9 (1.7%) patients in the Original NDA and in 14 (2.0%) patients in the 60-Day Update. In the 60-Day Update, the AEs deemed related to selpercatinib and leading to patient discontinuation included: ALT increased (3 patients), AST increased and drug hypersensitivity (2 patients each), and thrombocytopenia, abdominal pain, blood bilirubin increased, drug eruption, erythema, hepatitis acute, hypersensitivity, pneumatosis intestinalis, rash, retroperitoneal hematoma, sensation of foreign body, skin ulcer, tachycardia, and tumor lysis syndrome (1 patient each).

Early in the clinical program, three AESIs were observed and explored. All of these AEs are monitorable and reversible. In the 60-Day Update in the OSAS, AST or ALT increases were observed in 210 (29.9%) and 201 (28.6%) patients, respectively. These AST and ALT elevations in the 60-Day Update were Grade 1 and 2 in 158 (22.5%) and 137 (19.5%) patients, respectively, and Grade 3 and 4 in 52 (7.5%) and 64 (9.1%) patients, respectively. Frequent monitoring of LFTs, together with the implementation of a dose modification strategy when the elevations occurred, allowed a majority of patients with AST/ALT increases to experience normalized AST/ALT and stay on study. Permanent discontinuation from study due to AST/ALT increases occurred in only 3 patients (2 patients had increased AST and ALT, 1 patient had increased ALT only). No patients met the Hy’s Law criteria of drug induced liver injury.

Drug hypersensitivity in the 60-Day Update was 4.3% (the PT terms include 'Drug hypersensitivity' and 'Hypersensitivity’). Permanent discontinuation from study due to

hypersensitivity occurred in only 3 patients. In the 60-Day Update, 25 of the 30 patients in the 60-Day Update with treatment-emergent hypersensitivity were NSCLC patients, and 4 of the 30 patients were MTC patients.

In the 60-Day update, of the 24 patients with a selpercatinib-related drug hypersensitivity reaction as defined herein, 17 had received prior IO therapy.

Hypertension in the 60-Day Update, was reported in 35.9% of patients. Almost half of those patients had Grade 3-4 events (17.8%) and the minority of patients required dose interruption (4.7%) and/or reduction (1.3%). No patients discontinued therapy due to an AE of hypertension.

In summary, the overall tolerability of selpercatinib in adult cancer patients is characterized by recognizable toxicities, which are either monitorable, reversible with dose interruption or addressable through dose reduction or concomitant medication when necessary. In the context of the durable response rates reported, the Sponsor believes that the safety data summarized here support a favorable risk-benefit determination for selpercatinib.

The FDA's Assessment:
FDA agrees with the description of the safety database provided above by the Applicant and refers to product labeling and FDA's analysis for specific incidences of adverse events.

In addition to the adverse events of special interest described by the Applicant, FDA identified a safety signal for the risk of hemorrhagic events. Grade 3 or greater hemorrhagic events occurred in 2.3% of patients, including three patients with fatal hemorrhagic events. Although confounding factors were present in some events, in a single arm trial it is difficult to assess what may be attributable to factors in the underlying population. Given the potential severity of these events, as well as a plausible biologic rationale through inhibition of VEGF, a Warning for hemorrhagic events has been included in the product label.

In addition, although there was not an identifiable safety signal for issues with wound healing, this has been observed in patients with other VEGF pathway inhibitors. Given the implications for patients undergoing surgical procedures, a Warning has been included in the product label to describe standard advice for withholding selpercatinib in the perioperative period. These recommendations were based on literature review and expert opinion. Overall, the toxicity profile of selpercatinib is considered acceptable when considering the anti-tumor effects in patients with serious and life-threatening conditions. The major safety risks of selpercatinib are toxicities that oncologists frequently manage.

8.3 Statistical Issues

The FDA's Assessment:

No major statistical issues were identified by FDA when reviewing this application. The application included data from a single-arm, multi-center, dose escalation and expansion study, and the primary analysis populations included patients with metastatic *RET* fusion-positive NSCLC who had been previously treated with platinum chemotherapy, and patients with *RET* mutant MTC previously treated with cabozantinib or vandetanib. The SAP for LIBRETTO-001 included statistical assumptions based on the cohorts in the expansion phase of the study which included patients with *RET* fusion-positive solid tumors with or without standard first line therapy, and patients with *RET* mutant MTC with or without prior therapy. The pre-defined populations based on the SAP therefore did not include analyses based on tumor type in patients with *RET* fusions. However, the analysis populations included in the application, including the primary analysis populations and supplemental analysis populations, were discussed with FDA prior to submission of the application, as described in Section 3. During the course of the review, based on the magnitude and durability of responses observed in patients in the supplemental analysis sets (i.e., patients with metastatic *RET* fusion-positive NSCLC and *RET* mutant MTC who had not received prior therapy, and patients with *RET* fusion-positive thyroid cancer who are RAI refractory) the review team determined that line-agnostic indications should be granted.

8.4 Conclusions and Recommendations

The FDA's Assessment:

In the opinion of the review team, the submitted evidence meets the statutory evidentiary standard for accelerated approval. The recommendation for accelerated approval is based on the results from a single multicenter, single-arm, open-label, first-in-human, dose escalation and expansion study (LIBRETTO-001) which enrolled patients with advanced solid tumors with a *RET* fusion or mutation as detected by a CLIA-certified (or equivalent) laboratory. This study enrolled patients with three primary tumor types which form the basis of this application: patients with metastatic *RET* fusion-positive NSCLC, patients with advanced or metastatic *RET* mutant MTC, and patients with *RET* fusion-positive thyroid cancer. The primary efficacy populations for each tumor type included patients with a documented RET mutation or fusion, measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, sufficient follow-up to make a determination of efficacy and safety, and who received at least one dose of selpercatinib. The primary efficacy populations for each tumor type included 105 patients with *RET* fusion-positive NSCLC previously treated with platinum chemotherapy, 39 patients with *RET* fusion-positive NSCLC who were naïve to systemic therapy, 55 patients with *RET* mutant MTC previously treated with cabozantinib or vandetanib, 88 patients with *RET* mutant MTC who were naïve to systemic therapy, and 27 patients with *RET* fusion-positive thyroid cancer

who were RAI-refractory (if appropriate for their tumor histology). The analysis of efficacy in each tumor type demonstrated a large, clinically meaningful, and durable ORR per BICR.

RET fusion-positive NSCLC

The confirmed ORR in patients with metastatic, treatment-naïve RET fusion-positive NSCLC (n=39) per BICR was 84.6% (95% CI: 69.5%, 94.1%), with 42.4%, 12.1%, and 3% of the 33 responders having observed DOR of of 6 – 12, 12 – 18, and ≥18 months, respectively. The lower limit of the 95% CI for ORR with selpercatinib (69.5) in the treatment naïve patients excludes the ORR observed in clinical trials of other therapies approved for the first-line treatment of an unselected population of patients with NSCLC or non-squamous NSCLC (i.e., chemotherapy plus anti-PD-(L)1 antibody, ORR 48% to 58%). In 105 patients with metastatic RET fusion-positive NSCLC (the primary analysis set, or PAS), the ORR per BICR was 63.8% (95% CI: 53.9%, 73.0%) and with 44.8%, 29.9%, and 4.5% of responders having observed DOR of 6 – 12, 12 – 18, and ≥18 months, respectively. The lower limit of the 95% CI for ORR for selpercatinib in the treatment of platinum-treated patient (59.8%) excludes the ORR observed in clinical trials of approved therapies for second-line treatment of an unselected population of patients with NSCLC (i.e., ramucirumab plus docetaxel, ORR 23%).

Assessment of the anti-tumor activity of selpercatinib in the CNS was pre-specified in the plan for analysis specifically as descriptive analyses of intracranial ORR (IC-ORR) and IC-DOR as secondary endpoints. The PAS in NSCLC (n=105) included 11 patients with measurable CNS metastases at baseline per BICR and who had not received radiation to the brain within 2 months of first dose of selpercatinib; 10 of these patients had confirmed IC response (ORR 90.9%). Given the limited number of patients, the point estimate for these results needs to be interpreted with caution; however, the results do support a conclusion that selpercatinib has anti-tumor activity in the CNS in patients with RET fusion-positive NSCLC with brain metastases. Given the rarity of RET fusion-positive NSCLC and the magnitude of the response observed in LIBRETTO-001, a randomized trial may not be feasible. The review team considers that the ORR, which is large in magnitude, along with the observed duration of responses, in patients treated with selpercatinb is sufficient to establish clinical benefit in the genetically defined (RET fusion-positive), rare subgroup of patients with metastatic NSCLC. Data from additional patients with NSCLC (treatment naïve and platinum-treated) including overall response rate and duration of response, will be required as a post-marketing requirement to confirm clinical benefit.

RET mutant MTC

Confirmed ORR per BICR in patients 12 years of age and older with advanced or metastatic treatment-naïve RET mutant MTC was 72.7% (95% CI: 62.2%, 81.7%), with 37.5%, 20.3%, and 3.1% of responders having observed DOR of 6 – 12, 12 – 18, and ≥18 months, respectively. The lower bound of the 95% CI for ORR in this population excludes that of available therapy (i.e., vandetanib, ORR 45%) for a biomarker unselected population with MTC. In patients who had previously received an approved therapy (cabozantinib, vandetanib, or both, n=55), the ORR per BICR was 69.1% (95% CI: 55.2%, 80.9%) with 21.2%, 36.8%, and 18.4% of responders having an observed DOR of of 6 – 12, 12 – 18, and ≥18 months, respectively. These patients have no approved therapies, and there are no approved therapies specifically for RET mutant MTC. The

review team considers that the ORR, which is large in magnitude, along with the observed duration of responses, in patients treated with selpercatinb is sufficient to establish clinical benefit in the genetically defined subgroup of patients with advanced or metastatic MTC. Data from additional patients with treatment-naïve MTC will be required as a post-marketing requirement to confirm clinical benefit.

RET fusion-positive thyroid cancer

Patients ages 12 years of age and older with advanced *RET* fusion-positive thyroid cancer included patients who were RAI-refractory (if appropriate), and patients who were RAI refractory and had received a subsequent systemic therapy (hereafter referred to as "previously treated") and patients who had received RAI alone. The 19 patients who were previously treated demonstrated an ORR 78.9% (95% CI: 54.4%, 93.9%), with 40%, 26.7%, and 20% of responders having an observed DOR of 6 – 12, 12 – 18, and ≥18 months, respectively. Among 8 patients with *RET* fusion-positive thyroid cancer who had received RAI but not a subsequent therapy, 100% (95% CI 63%, 100%) demonstrated a response, with 62.5% and 12.5% of patients demonstrating an observed DOR of 6 – 12 and 12 – 18 months, respectively. Responses were observed in patients with distinct subtypes of thyroid cancer, including papillary, Hurthle cell, poorly-differentiated, and anaplastic histologies, though patients with papillary thyroid cancer formed the majority of the study population (n=21 of 27 patients). Both lenvatinib and sorafenib are approved in patients with differentiated thyroid cancer who are RAI-refractory, but there are no approved therapies in the second-line post-RAI setting for DTC or for RET fusion-positive thyroid cancers specifically. The response rate in this rare molecularly-defined subset of patients compares favorably to the response rates observed in studies of lenvatinib (65%) and sorafenib (12%) for a broader population of patients with RAI-refractory differentiated thyroid cancer, regardless of *RET* mutation status. Given the observation of partial responses in all histologic subtypes of *RET* fusion-positive thyroid cancer studied, the review team considered that an indication which encompassed multiple histologic subtypes of thyroid cancer with *RET* fusions was appropriate. The review team considered that the evidence of efficacy in *RET* fusion-positive thyroid cancer is supported by the comparably high, durable response rates observed in response to selpercatinib in the other *RET*-driven cancers described in the application. Data from additional patients to confirm clinical benefit will be required as a post-marketing requirement.

The safety review of selpercatinib included data from 702 patients from LIBRETTO-001. The primary risks related to selpercatinib are QT prolongation, hepatotoxicity, hypertension, hypersensitivity, and hemorrhagic events. These serious risks, which are described in detail in sections above, are adequately addressed in the Warnings and Precautions and Dose Modifications sections of the selpercatinib product labeling. Overall, the toxicity profile of selpercatinib is considered acceptable in patients with advanced or metastatic cancer, some of whom have no available approved therapies.

Although no specific safety risks were identified in the few adolescent patients enrolled on LIBRETTO-001, or in the limited data provided regarding pediatric patients who are receiving selpercatinib via expanded access programs, additional data is needed to characterize the

effect of selpercatinib on growth and development. Given the available safety and pharmacokinetic data, as well as the unmet medical need in adolescent patients with *RET*-driven cancers, the review team recommends approval of selpercatinib in patients 12 years of age and older with *RET*-mutant MTC and *RET* fusion-positive thyroid cancer. Additional data regarding the effect of selpercatinib on growth and development will be collected post-marketing.

A companion diagnostic for selpercatinib was not available at the time of approval, but is under development. Given the availability of local tests to identify *RET* alterations, the unmet medical need in the populations considered for approval, and the magnitude and durability of the responses observed, the review team agreed that selpercatinib should be approved in the absence of a companion diagnostic, with the Applicant's commitment to develop such a test. The final product labeling will reflect the lack of an approved companion diagnostic for the selection of patients for treatment with selpercatinib.

We recommend approval of this application under Subpart H (accelerated approval) pending agreement regarding final labeling and agreement regarding post-marketing requirements and commitments.

X X

Primary Statistical Reviewer Statistical Team Leader

X X

Primary Clinical Reviewer Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

FDA did not hold an advisory committee meeting for these applications because no review issues were identified that raised significant public health questions regarding the risk:benefit assessment of selpercatinib for the proposed indications.

10 Pediatrics

The Applicants Position:

In September 2019, the sponsor initiated a Phase 1/2 clinical trial of selpercatinib in pediatric patients (age ≥ 6 months of age to ≤ 21 years of age) with advanced *RET*-altered solid or primary central nervous system tumors (Study LOXO-RET-18036). As of November 2019, 2 patients had been enrolled to the Phase 1 portion of the study. [Module 2.5.1.2 (NSCLC); Module 2.5.1.2 (MTC)]

The FDA's Assessment:

Selpercatinib was granted orphan designation for the treatment of patients with:

- RET fusion positive non-small cell lung cancer
- RET fusion-positive or RET mutant thyroid cancers including poorly differentiated thyroid cancer, undifferentiated or anaplastic thyroid cancer, medullary thyroid cancer and locally advanced or metastatic follicular or papillary thyroid cancer

NDA 213246 is therefore exempt from PREA requirements.

Data from Study LOXO-RET-18036 was not submitted in support of this application. Three adolescent patients (ages 15 – 17 years old) with MTC enrolled on study LIBRETTO-001 and the data for these patients is included in the application. Safety summary information, but not efficacy data, is provided for six pediatric patients who received selpercatinib via expanded access programs. These patients ranged in age from 1 – 10 years old and had the following diagnoses: infantile myofibroma, papillary thyroid cancer, medullary thyroid cancer, infantile fibrosarcoma, and lipofibromatosis.

The Applicant proposed an indication which included adolescent as well as adult patients. Medullary thyroid cancer occurs in children and adolescents usually in the setting of an inherited or sporadic germline *RET* mutation such as in MEN2 syndromes or familial MTC. As discussed in Section 2.1, thyroid cancers other than MTC (particularly papillary thyroid cancer) also occur in pediatric patients, though no patients <17 years of age were included in the efficacy population for *RET* fusion-positive thyroid cancer as part of this application. As of the June 2019 data cut-off date, two of the three adolescent patients (all with MTC) enrolled on study LIBRETTO-001 had experienced partial responses, demonstrating the potential for clinical benefit in adolescent patients. Given the unmet medical need in pediatric patients 12 years of age and older with advanced or metastatic *RET* mutant MTC and *RET* fusion-positive thyroid cancer, the biological similarity of the diseases in adolescent and adult patients, and preliminary evidence of safety and efficacy in this population, the indications for both populations will include adolescent patients 12 years of age and older. Additional data regarding the safety of administration of selpercatinib in adolescent patients is needed to

better characterize the potential for toxicities specific to pediatric patients, such as the potential for effects on growth and development.

Epiphyseal growth plate thickening was observed in the nonclinical studies of rats and minipigs exposed to selpercatinib. Due to the potential impact on bone development, Study LOXO-RET-18036 incorporates growth plate monitoring. The study also includes dental evaluations in patients ages 5 years and older without a full set of permanent teeth and Tanner staging in patients ages 7 years and older who are not yet sexually mature. Given the uncertain impact of selpercatinib on growth in adolescents with growing bones, a post-marketing study will be required to further assess this risk. However, given the unmet medical need in adolescent patients with RET-altered thyroid cancer, and the durable responses observed with selpercatinib, it is the opinion of this reviewer that the risk:benefit assessment in this population is favorable.

11 Labeling Recommendations

Data:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
Section 1, Indications and Usage	Indications proposed by the Applicant were for the treatment of adult (b) (4) patients with: • Metastatic RET fusion-positive NSCLC who require systemic therapy • RET-mutant MTC who require systemic therapy • Advanced RET fusion positive thyroid cancer who require systemic therapy (b) (4)	The indications were revised to only include adults in NSCLC (b) (4) The indications were revised to better reflect the populations studied (i.e., patients with RET fusion-positive thyroid cancer who are RAI-refractory).
Section 2, Dosage and Administration	• The recommended dosage was 160 mg BID (b) (4) • The labeling included recommended dosage modifications for (b) (4) adverse reactions, strong CYP3A (b) (4) inhibitors and severe hepatic impairment.	FDA agreed and provided additional detail regarding mutations which qualified patients to enroll on the study in Section 14. Section 2.2 was added to provide important administration instructions with respect to food, given the variability in exposures in patients who are taking a concomitant PPI. Section 2.4 was added to describe specific dose modification instructions for acid-reducing agents. Section 2.3 was revised to include a lower dose for patients < 50 kg given a concentration-dependent

		risk of QT prolongation. Dose modifications for this lower dose were also added. Sections 2.5, 2.6 and 2.7 were revised to provide recommended dosage modifications for adverse reactions, drug interactions and hepatic impairment (b) (4) Section 2.5 was revised to reflect new Warnings & Precautions. Section 2.6 was revised to provide recommended dosage for moderate CYP3A4 inhibitors. Removed (b) (4)
Section 5, Warnings and Precautions	• The proposed Warnings included (b) (4) QT Interval prolongation, Hypertension, and Embryo-fetal toxicity.	FDA added Warnings for Hemorrhagic events, Hypersensitivity (which was previously described elsewhere in the label) and the Risk of Impaired Wound Healing (which is standard language for agents which inhibit VEGF).
Section 6, Adverse Reactions	• Standard information on Adverse Reactions was included	FDA provided comprehensive advice to revise and reorder the section to be consistent with OOD's Best Labeling Practices. The revisions were made in order to present information for all oncology products in a consistent manner and to make this information more useful to healthcare providers (HCPs). FDA requested additional information regarding the Applicant's claim that

		selpercatinib may increase serum creatinine without affecting glomerular function. Information regarding the effect of selpercatinib on creatinine in healthy subjects was included in the labeling.
Section 7, Drug Interactions	• An interaction with Strong CYP3A4 Inducers was included in the label	Additional information regarding use with acid-reducing agents was added. The interaction with CYP3A inducers was revised to also include moderate inducers given the potential for decreased efficacy with a 70% reduction in exposure predicted with moderate inducers. The interaction with CYP3A inhibitors was expanded to include moderate inhibitors. A section on drugs that prolong the QT interval (7.3) was added given the warning for QT prolongation.
Section 8, Use in Specific Populations		Revisions were made for consistency with PLLR recommendations, with best labeling practices for pediatric labeling (section 8.4), and with guidance for the geriatric section of labeling.
		(b) (4)
Section 12, Clinical Pharmacology	• The Applicant originally described the mechanism of action as including	Section 12.1 was revised to include the alternative names for FLT1 and FLT4, VEGFR1 and VEGFR3. The section was revised

	inhibition of FLT1 and FLT4, as well as RET.	to include inhibition of FGFR 1 and 2. Section 12.2 was revised to describe the results of the thorough QT study in the context of exposures observed in patients. Additional information as included from PBPK models related to moderate CYP3A inhibitors and moderate and weak CYP3A inducers. Section 12.3 was revised to clearly describe interactions with food and acid-reducing agents.
Section 14	• The Applicant (b) (4) subsections, (b) (4) RET fusion-positive NSCLC, (b) (4) RET-mutant MTC, and RET fusion-positive thyroid cancer.	Section 14 was reorganized in 3 subsections, one for each indication, with headings added to separate the results for 1st and 2nd line NSCLC and MTC. (b) (4) was removed given the small number of patients included in the analysis. A table was added to describe the specific mutations which were used to enroll patients with MTC.
Section 17, Patient Counseling Information		The patient counseling information was revised to reflect the changes to the PI and in accordance with best practices.

The Applicant's Position:
Labeling recommendations have been submitted with the initial NDA, no changes from the Sponsor are recommended at this time.

The FDA's Assessment:
The table above describes changes to the proposed prescribing information requested during

the review. Please see the final approved prescribing information for RETEVMO (selpercatinib) accompanying the approval letter for final labeling.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The review teams determined that a REMS was not needed to ensure safe and effective use of selpercatinib in the indicated patient populations. Selpercatinib will be prescribed by oncologists who are skilled in monitoring, diagnosing, and managing serious toxicities caused by antineoplastic drugs including targeted therapies. Standard practice in oncology dictates that patients be apprised of risks related to treatment prior to receiving anti-neoplastic drugs.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

Loxo Oncology has agreed to the following postmarketing requirements and commitments. Please refer to approval letter for expected completion dates.

Clinical PMRs

PMR 3829-1:
Submit the final report including datasets from a multi-center, randomized trial comparing selpercatinib to physician's choice of approved therapies in patients with kinase inhibitor-naïve, progressive, advanced or metastatic RET-mutant medullary thyroid cancer to confirm clinical benefit of selpercatinib with progression-free survival as a key secondary end point-as assessed by blinded independent central review.

> *Rationale: Selpercatinib is being considered under accelerated approval for the treatment of patients with* (b) (4)*, advanced or metastatic RET-mutant medullary thyroid cancer. Conversion to regular approval is contingent upon verification of clinical benefit.*

PMR 3829-2:
Submit a final report including datasets from an ongoing clinical trial to verify and further characterize the clinical benefit of selpercatinib for the treatment of patients with 1) treatment-naïve *RET* fusion-positive NSCLC and with 2) RET fusion-positive NSCLC who have previously received platinum chemotherapy that will provide a more precise estimation of the BICR-assessed overall response rate and duration of response after all responders in the population of at least 65 patients have been followed for at least 12 months from the date of initial response (or until disease progression, whichever comes first) in patients with treatment-naïve NSCLC and after all responders have been followed for at least 6 months in the population of patients (at least 180 patients) with NSCLC previously treated with platinum therapy.

> *Rationale: Selpercatinib is being considered under accelerated approval for the treatment of patients with* (b) (4) *RET fusion-positive NSCLC and with 2) RET fusion-positive NSCLC* (b) (4) *Conversion to regular approval is contingent upon verification of clinical benefit in these two NSCLC populations.*

PMR 3829-3:
Submit a final report including datasets, to verify and further characterize the clinical benefit of selpercatinib for the treatment of patients with RET fusion-positive thyroid cancer who have received radioactive iodine (if appropriate for their tumor histology) to provide a more precise estimation of the BICR-assessed overall response rate and duration of response in at least 50 patients after all responding patients have been followed for 12 months following onset of response or until disease progression, whichever comes first.

> *Rationale: Selpercatinib is being considered under accelerated approval for the treatment of patients with advanced or metastatic RET fusion-positive thyroid cancer that is RAI-refractory. Conversion to regular approval is contingent upon verification of clinical benefit in patients with RET fusion-positive thyroid cancer.*

PMR 3829-4:
Submit the final report, of an integrated safety analysis from clinical studies that further characterize the potential serious risk of long-term adverse effects of selpercatinib on growth and development, including an assessment of growth plate abnormalities in a sufficient number of adolescent patients with RET mutant MTC and RET fusion-positive thyroid cancer. Patients will be monitored for growth and development using age-appropriate screening tools. Evaluations will include growth as measured by height, weight, height velocity and height standard deviation scores, age at adrenarche if applicable (males), age at menarche if applicable (females) and Tanner stage. Patient monitoring will be performed until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first. Include the datasets with the final report. The results from this report may inform labeling.

> *Rationale: The primary adolescent safety population in the registration trial was limited in sample size and selpercatnib is intended for chronic use in this population. The primary aim of this PMR is to evaluate and provide information on the safety of long term administration of selpercatinib to adolescent patients.*

<u>Clinical Pharmacology PMRs</u>

PMR 3829-5:
Submit the analysis and datasets with the final report for an ongoing hepatic impairment clinical trial to evaluate the pharmacokinetics and safety of selpercatinib in patients with normal hepatic function and patients with hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry titled: "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*."

> *Rationale: To determine an appropriate safe dose of selpercatinib in patients with hepatic impairment.*

PMR 3829-6:
Submit the analysis and datasets with the final report for an ongoing renal impairment clinical trial to evaluate the pharmacokinetics and safety of selpercatinib in patients with normal renal function and patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry titled "*Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*."

> *Rationale: To determine an appropriate safe dose of selpercatinib in patients with renal impairment.*

PMR 3829-7:
Submit the final report and datasets from a clinical drug-drug interaction study to evaluate the effect of selpercatinib on the pharmacokinetics of a P-gp substrate, and inform appropriate management strategies for clinically relevant drug interactions. Design and conduct the trial in accordance with the FDA Guidance for Industry titled: "*Clinical Drug Interaction Studies - Cytochrome P450 Enzyme and Transporter- Mediated Drug Interactions*."

> *Rationale: Selpercatinib inhibits P-gp in vitro. After administration, high selpercatinib concentrations in the gastrointestinal tract may result in clinically relevant inhibition of P-gp. As a result, the excretion of P-gp substrates back into the gut lumen may be reduced, leading to increasing plasma concentrations of these substrates, which may lead to an increased risk of adverse reactions. A clinical drug interaction study is needed to characterize the effects of selpercatinib on the PK of P-gp substrates and to inform appropriate management strategies for safe coadministration of selpercatinib with P-gp substrates.*

<u>Nonclinical PMRs</u>

PMR 3829-8:
Conduct a rodent carcinogenicity study in mice to evaluate the potential for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

> *Rationale: To determine the risk of carcinogenicity due to selpercatinib because the disease of the intended patient population (MTC) includes some patients with a potentially long life expectancy even in the absence of treatment.*

PMR 3829-9:
Conduct a rodent carcinogenicity study in rats to evaluate the potential for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

Rationale: To determine the risk of carcinogenicity due to selpercatinib because the disease of the intended patient population (MTC) includes some patients with a potentially long life expectancy even in the absence of treatment.

Clinical PMCs

PMC 3829-10:
Submit the final report of an analytical and clinical validation study, using clinical trial data, that is adequate to support labeling of an in vitro diagnostic device that demonstrates the device is essential to the safe and effective use of selpercatinib for patients with RET gene fusions in lung cancer. The results of the validation study may inform product labeling.

Rationale: To assess the ability of RET testing to ensure the safe and effective use of selpercatinib in selecting appropriate patients with RET gene fusion in lung cancer.

PMC 3829-11:
Submit the final report of an analytical and clinical validation study, using clinical trial data, that is adequate to support labeling of an in vitro diagnostic device that demonstrates the device is essential to the safe and effective use of selpercatinib for patients with RET gene fusions and RET mutations in thyroid cancer. The results of the validation study may inform product labeling.

Rationale: To assess the ability of RET testing to ensure the safe and effective use of selpercatinib in selecting appropriate patients with RET gene fusions and RET mutations in thyroid cancer .

14 Division Director (DHOT) (NME ONLY)

X _____

15 Division Director (OCP)

X _____

16 Division Director (OB)

X _____

17 Division Director (Clinical)

X _____

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X_____

19 Appendices

19.1 References

The Applicant's References:

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19.2 Financial Disclosure

The Applicant's Position:

Financial disclosure information was collected for all 951 investigators and sub-investigators participating in LOXO-RET-17001. In the table below, the total number of investigators for LOXO-RET-17001 and the number of investigators with disclosable financial interests are provided. The description of the category of financial interest is provided as well for those investigators who have disclosable financial interests/arrangements. [Module 1.3.4].

The FDA's Assessment:

The disclosures noted above involving significant payments made to study investigators were reviewed. The Applicant has provided a description of steps taken to minimize bias; specifically, these investigators were not the Principal Investigators (PIs) and were thus acting under oversight by the PI, and the efficacy data was reviewed by a blinded independent review committee. (b) (6)

Covered Clinical Study (Name and/or Number):* LOXO-RET-17001 (LIBRETTO-001)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 951		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table was filled by the applicant, and confirmed/edited by the FDA.

19.3 Nonclinical Pharmacology/Toxicology

Not applicable

The FDA's Assessment:
See Section 5 for the FDA Nonclinical review

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1 Population PK Analysis

Population PK analysis was conducted by the applicant to characterize the PK of selpercatinib, identify covariate factors that could affect selpercatinib disposition and estimate the individual exposures for the subsequent exposure-response analysis. Data was collected from ongoing Study LOXO-RET-17001 (LIBRETTO-001, an open-label, multicenter, global Phase1/2 study in patients with advanced solid tumors, including *RET* fusion-positive solid tumors, *RET*-mutant MTC and other tumors with *RET* activation).

The PK analysis dataset included 6246 non-BLQ PK observations and 133 BLQ PK observations from 512 patients. PK observations are summarized by dose level in Table 19.1.None of the non-BLQ PK observations were excluded from the analysis for the final model, and all the BLQ PK observations were excluded from the analysis, resulting in all 512 patients being included in the analysis.

Table 19.1. Summary of PK Observations in the Analysis

Parameter	Count (%)									
Category	20 mg QD	20 mg BID	40 mg BID	60 mg BID	80 mg BID	120 mg BID	160 mg BID	200 mg BID	240 mg BID	Overall
Patients										
Total[a]	4 (0.8%)	16 (3.1%)	28 (5.5%)	33 (6.5%)	57 (11%)	34 (6.6%)	465 (91%)	3 (0.6%)	6 (1.2%)	512 (100%)
Excluded	0	0	0	0	0	0	0	0	0	0
PK observations										
Non-BLQ	81 (1.3%)	218 (3.4%)	363 (5.7%)	366 (5.7%)	818 (13%)	435 (6.8%)	3787 (59%)	53 (0.8%)	125 (2.0%)	6246 (98%)
BLQ	2 (0.03%)	14 (0.2%)	15 (0.2%)	8 (0.1%)	16 (0.3%)	14 (0.2%)	56 (0.9%)	2 (0.03%)	6 (0.1%)	133 (2%)
Included in the final model	81 (1.3%)	218 (3.4%)	363 (5.7%)	366 (5.7%)	818 (13%)	435 (6.8%)	3787 (59%)	53 (0.8%)	125 (2.0%)	6246 (98%)

Abbreviations: BLQ=below the lower limit of quantitation; PK=pharmacokinetic.
[a] Due to the planned dose adjustment procedures in the protocol, some patients received multiple dose levels of LOXO-292 during the study and are counted more than once in the Total row above.
Source: PK-figures-report-2019-10-26.R

Source: loxo-292-dmpk-050, Page 31, Table 4.

The main population of the subjects were Caucasian (69.9%) and Asian (21.5%). The median age of all subjects was 59 years old (range: 15-90), 54.1% were males and the median body weight, BSA and BMI were 68.0 kg (range: 26.8-177), 1.79 m^2 (range: 1.11-2.75) and 23.7 kg/m^2 (range: 11.6- 59.1), respectively. The median value of the calculated creatinine clearance was 91.2 mL/min (range: 20.7-566). The majority (259, 50.6%) of the 512 cancer participants were of normal renal function, 175 (34.2%) were of mild renal dysfunction, 74 (14.4%) were of moderate renal dysfunction and 4 (0.8%) were of severe renal dysfunction. The majority (488; 95.3%) of the participants were of normal liver function, 17 (3.3%) were of mild hepatic

impairment, and 8 (1.6%) were of moderate hepatic impairment based on NCI hepatic impairment classification. No severe hepatic impairment participant was enrolled in the study. Demographic data and laboratory values for subjects in the population PK analysis are shown in **Table 19.2.**.

Table 19.2. Demographics and Baseline Characteristics and Covariates of the PK Data

Covariate Statistic/Category	Female (n=235)	Male (n=277)	Overall (n=512)
Race			
Caucasian	154 (65.5%)	204 (73.6%)	358 (69.9%)
Asian	57 (24.3%)	53 (19.1%)	110 (21.5%)
Black or African American	10 (4.3%)	5 (1.8%)	15 (2.9%)
American Indian/Alaskan Native	1 (0.4%)	1 (0.4%)	2 (0.4%)
Other	11 (4.7%)	14 (5.1%)	25 (4.9%)
Missing	2 (0.8%)	0 (0%)	2 (0.4%)
Age (years)			
Mean (SD)	57.2 (14.2)	57.9 (13.0)	57.6 (13.5)
Median [Min, Max]	59.0 [15.0, 88.0]	59.0 [17.0, 90.0]	59.0 [15.0, 90.0]
Body weight (kg)			
Mean (SD)	62.0 (16.1)	79.6 (19.3)	71.6 (19.9)
Median [Min, Max]	58.4 [26.8, 120]	77.5 [45.9, 177]	68.0 [26.8, 177]
Body Surface Area (m^2)			
Mean (SD)	1.64 (0.197)	1.94 (0.222)	1.80 (0.259)
Median [Min, Max]	1.61 [1.11, 2.26]	1.93 [1.48, 2.75]	1.79 [1.11, 2.75]
Missing	6 (2.6%)	10 (3.6%)	16 (3.1%)
Body Mass Index (kg/m^2)			
Mean (SD)	23.9 (5.83)	25.9 (5.99)	25.0 (6.00)
Median [Min, Max]	22.4 [11.6, 51.8]	25.2 [13.4, 59.1]	23.7 [11.6, 59.1]
Missing	6 (2.6%)	10 (3.6%)	16 (3.1%)
ALT (U/L)			
Mean (SD)	22.8 (18.6)	27.6 (19.8)	25.4 (19.4)
Median [Min, Max]	17.0 [5.00, 158]	22.0 [4.00, 130]	19.0 [4.00, 158]
AST (U/L)			
Mean (SD)	27.2 (18.0)	28.2 (20.6)	27.7 (19.5)
Median [Min, Max]	22.0 [11.0, 142]	23.0 [6.00, 233]	22.0 [6.00, 233]

Covariate Statistic/Category	Female (n=235)	Male (n=277)	Overall (n=512)
Bilirubin (mg/dL)			
Mean (SD)	9.06 (5.10)	10.8 (6.84)	9.98 (6.15)
Median [Min, Max]	6.84 [3.42, 37.0]	8.55 [3.00, 56.4]	8.55 [3.00, 56.4]
Creatinine Clearance (mL/min)			
Mean (SD)	89.2 (38.0)	104 (47.8)	97.1 (44.1)
Median [Min, Max]	81.5 [20.7, 311]	99.8 [27.3, 566]	91.2 [20.7, 566]

Source: loxo-292-dmpk-050, Page 43-45, Table 6.

The population PK analysis was conducted via nonlinear mixed-effect modeling with NONMEM, version 7.4 using first-order conditional estimation with INTERACTION option (FOCE+I). Observed concentration below the limit of quantification (BLQ) were excluded.
The plasma concentrations of selpercatinib data were described by a two-compartment disposition model with sequential zero- and first-order absorption, and linear elimination. IIV terms were included on CL/F, V_c/F, ka, and duration of zero-order absorption (Dur), with a correlation between the IIV terms for CL/F and V_c/F. The residual error model included both additive and proportional error terms. Several covariates including selpercatinib dose, gender, race, age, bodyweight at baseline, alanine aminotransferase, aspartate aminotransferase, total bilirubin, creatinine clearance at baseline and concomitant medications of CYP3A4 inhibitors/inducers were explored.

The final population PK parameters for selpercatinib are presented in **Table 19.3.**. The final PK model was parameterized in terms of k_a, Dur, CL/F, V_c/F, Q/F, and V_p/F. Fixed and random effect parameters were estimated with good precision (%RSE < 24%). Residual variability was moderate. The PK of selpercatinib is affected by the administered dose and body weight. The clearance decreases with increasing dose levels. This leads to greater-than-proportional increases in selpercatinib exposure with increasing dose levels. Body weight was included in the final population PK model following allometric principles, where volume parameters increase proportional to body weight (exponent is 1.0) and clearance parameters increase slightly less than proportional to body weight (exponent is 0.75).

Table 19.3. Parameters of the Final Population PK Model

	Estimate		Interindividual Variability		
Parameter (unit)	Typical Value	RSE[a]	Typical Value	RSE[a]	Shrinkage[b]
Apparent clearance (CL/F, L/hr)	6.0	2.4%	49%	4.1%	2.9%
Effect of Dose on CL/F (%/mg)[c]	-0.3%	24%	—	—	—
Apparent distributional clearance (Q/F, L/hr)	27	8.0%	—	—	—
Apparent central volume of distribution (Vc/F, L)	101	5.8%	69%	7.2%	27%
Apparent peripheral volume of distribution (Vp/F, L)	90	4.5%	—	—	—
First-order absorption rate constant (ka, 1/hr)	1.51	6.7%	78%	13%	50%
Zero-order absorption duration (Dur, hr)	1.04	3.1%	56%	5.6%	50%
Correlation between IIV-CL/F and IIV-Vc/F	—	—	34%	10%	—
Residual variability					
Proportional residual error	28%	4.3%	—	—	7.1%
Additive residual error SD (ng/mL)	47	16%	—	—	7.1%

CV=coefficient of variation; CL/F=apparent clearance; Dur=duration of zero-order absorption; IIV=interindividual variability; ka=first-order first-order absorption rate constant; PK=pharmacokinetic; Q/F=apparent intercompartmental clearance; RSE=relative standard error; SD=standard deviation; SE=standard error; Vc/F=apparent central volume of distribution; Vp/F=apparent peripheral volume of distribution.

[a] RSE of parameter estimate are calculated as 100×(SE/typical value); RSE of between-patient variability magnitude are presented on %CV scale and approximated as 100×(SE/variance estimate)/2.

[b] Shrinkage (%) is calculated as 100×(1 – SD of post hocs/estimated variance).

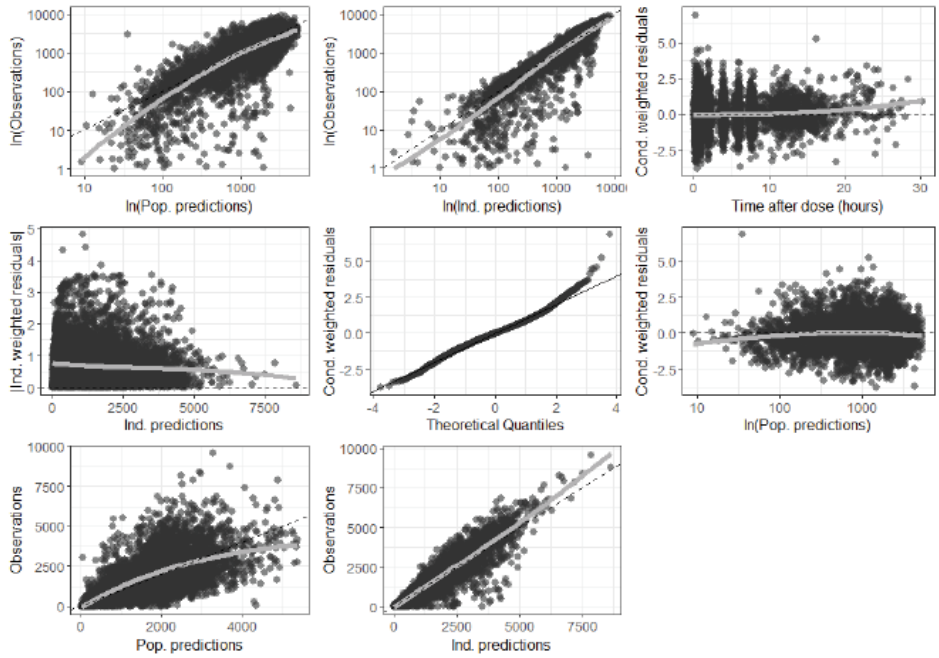
[c] Effect of dose on CL/F is relative to a 160 mg dose of LOXO-292.

Source: allofd3-sumo.txt

Source: loxo-292-dmpk-050, Page 61, Table 16.

The diagnostic plots for the final PK model are shown in **Figure 19.1.**. The prediction-corrected visual predictive check (pcVPC) is shown on **Figure 19.2.** and pcVPC stratified by dose is shown on **Figure 19.3**. The model described the observed data well and the model predictions were generally within the 90% prediction intervals. No apparent bias was observed except at time points more than 24 hours after the last dose. There is some overprediction at the very first-time interval (within 1 hour) and for the subjects in 200 mg BID dose group. Bootstrap results are in good concordance with the final model parameter estimates (**Table 19.4.**).

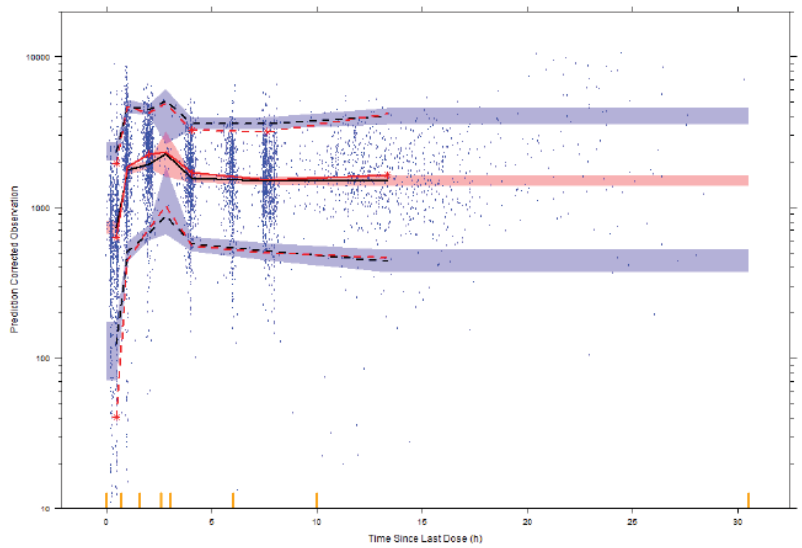
Figure 19.1. Diagnostic Plots for the Final Population PK Model for Selpercatinib.



Abbreviations: Cond=conditional; Ind=individual; ln=natural logarithm; PK=pharmacokinetic; Pop=population.
Note: The circles represent individual data points, the gray lines represent loess smooth curves, and the dashed and solid lines represent the line of unity (y=x) or the x-axis (y=0).
Source: PK-figures-report-2019-10-26.R

Source: loxo-292-dmpk-050, Page 63, Figure 15.

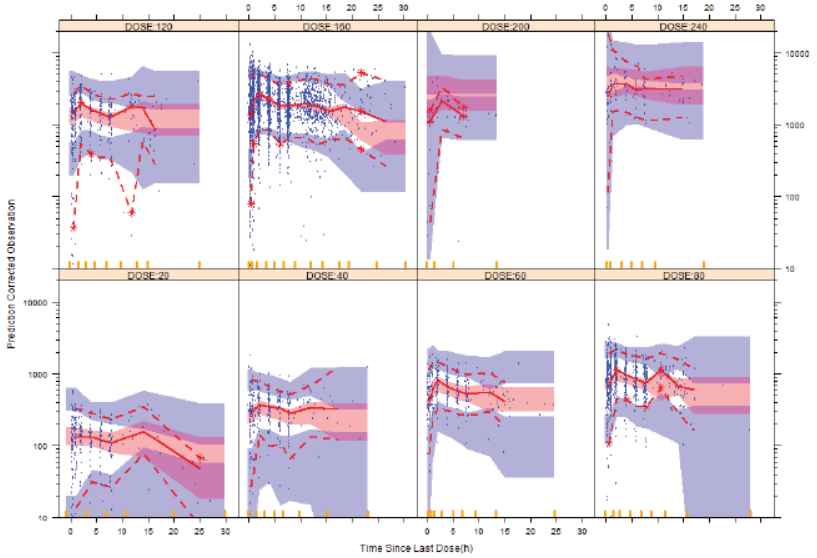
Figure 19.2. Prediction-corrected VPC of the Final Population PK Model for Selpercatinib.



Abbreviations: h=hour; PK=pharmacokinetic; VPC=visual predictive check.
Note: The blue circles represent prediction-corrected observed data, the red solid line represents the median of the prediction-corrected observed data, and the red dashed lines represent the 5th and 95th percentiles of the prediction-corrected observed data. The red stars represent observed values that lie outside the 90% prediction interval. The black solid line represents the median of the prediction-corrected simulation data, and the black dashed lines represent the 5th and 95th percentiles of the prediction-corrected simulation data. The blue shaded areas represent the 90% prediction interval for the 5th and 95th percentiles of the predicted data, and the red shaded areas represent the 90% prediction interval for the median of the predicted data. The yellow vertical ticks on the x-axis represent the edges of the bins used to group the data for calculation of the quartiles.
Source: PK-figures-report-2019-10-26.R

Source: loxo-292-dmpk-050, Page 64, Figure 16.

Figure 19.3. Prediction-corrected VPC of the Final Population PK Model for Selpercatinib Stratified by Dose.



Abbreviations: h=hour; PK=pharmacokinetic; VPC=visual predictive check.
Note: The blue circles represent prediction-corrected observed data, the red solid line represents the median of the prediction-corrected observed data, and the red dashed lines represent the 5th and 95th percentiles of the prediction-corrected observed data. The red stars represent observed values that lie outside the 90% prediction interval. The black solid line represents the median of the prediction-corrected simulation data, and the black dashed lines represent the 5th and 95th percentiles of the prediction-corrected simulation data. The blue shaded areas represent the 90% prediction interval for the 5th and 95th percentiles of the predicted data, and the red shaded areas represent the 90% prediction interval for the median of the predicted data. The yellow vertical ticks on the x-axis represent the edges of the bins used to group the data for calculation of the quartiles. Doses are in mg.
Source: PK-figures-report-2019-10-26.R

Source: loxo-292-dmpk-050, Page 65, Figure 17.

Table 19.4. Bootstrap Parameter Estimates from the Final Population PK Model

Parameter	Model Estimate	Bootstrap Median[a]	Bootstrap 95% CI[a]
Apparent clearance (CL/F, L/hr)	6.0	6.0	(5.7, 6.3)
Effect of dose on CL/F (%/mg)[b]	-0.3%	-0.3%	(-0.4%, -0.2%)
Apparent distributional clearance (Q/F, L/hr)	27	27	(22, 32)
Apparent central volume of distribution (Vc/F, L)	101	101	(88, 113)
Apparent peripheral volume of distribution (Vp/F, L)	90	90	(83, 99)
First-order absorption rate constant (ka, 1/hr)	1.51	1.52	(1.30, 1.73)
Zero-order absorption duration (Dur, hr)	1.04	1.04	(0.95, 1.13)
Interindividual variability in CL/F	49%	49%	(45%, 53%)
Interindividual variability in Vc/F	69%	69%	(59%, 79%)
Interindividual variability in ka	78%	77%	(48%, 100%)
Interindividual variability in Dur	56%	56%	(49%, 63%)
Correlation between IIV-CL/F and IIV-Vc/F	34%	34%	(27%, 41%)
Residual variability			
Proportional residual error	28%	28%	(26%, 30%)
Additive residual error SD (ng/mL)	47	47	(34, 68)

CV=coefficient of variation; CI=confidence interval; CL/F=apparent clearance; Dur=duration of zero-order absorption; IIV=interindividual variability; ka=first-order first-order absorption rate constant; PK=pharmacokinetic; Q/F=apparent intercompartmental clearance; RSE=relative standard error; Vc/F=apparent central volume of distribution; Vp/F=apparent peripheral volume of distribution.
[a] Bootstrap parameters based on 1000 bootstrap replicates, of which 954 (95%) were minimized successfully.
[b] Effect of dose on CL/F is relative to a 160 mg dose of LOXO-292.
Source: bootstrap_summary.csv

Source: loxo-292-dmpk-050, Page 62, Table 17.

To evaluate the renal impairment and hepatic impairment on drug clearance and exposure, stepwise covariate method search was performed, and no hepatic or renal impairment category was found to be statistically significant. The models with hepatic or renal impairment category forced onto the selpercatinib clearance parameters showed no significant reductions in clearance in subjects with mild or moderate renal and hepatic impairment. Mild, moderate, and severe renal impairment showed a reduction in clearance of 1%, 14%, and 23%, respectively.
Besides the covariates of dose and body weight, factors such as sex, race, age, creatinine clearance, liver function tests, and coadministration of CYP3A4 inhibitors or inducers had no impact on the PK of selpercatinib in this analysis.

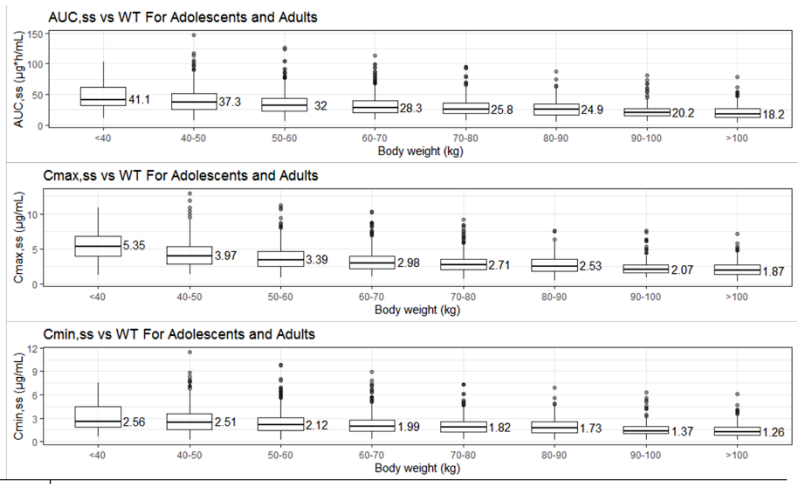
Reviewer's comments:

The population PK model developed by the applicant was verified by the reviewer. The model appears to be reasonable in general because there was a good agreement between observations and predictions.

Using the final population PK model, individual post hoc clearances (CL/F) in patients with 160 mg BID dosage were used to estimate the influence of renal impairment and hepatic impairment by the reviewer. The η-shrinkage of CL/F is 2.9% and the data is informative to estimate the individual CL/F. Hepatic impairment showed that no reduction in clearance in subjects with mild or moderate hepatic impairment. Renal impairment showed that no statistically significant reductions in clearance were found in subjects with mild and moderate renal impairment. The influence of severe renal impairment is not adequately studied as there are only 4 subjects in this group.

The reviewer conducted an independent simulation analysis to compare the exposure for adolescent and adult subjects. The simulation was done with 1000 adolescent and 1000 adult subjects from NHANES datasets (2012-2016) using the final population PK model developed by Applicant. The exposure of selpercatinib vs body weights were shown in ***Figure 19.4.****. Subjects with bodyweight lower than 50 kg had higher AUC_{0-12} and C_{max} than subjects with bodyweight 70-80 kg group. Lower dose might be required for patients with bodyweight lower than 50 kg.*

Figure 19.4. Exposure Simulation of Selpercatinib with Adolescent and Adult Subjects



Adolescents	48	194	260	219	127	68	30	54
Adults	3	42	114	191	235	157	103	155

Source: Reviewer's analysis

19.4.2 Tumor Size Analysis

A population PD model was developed by the applicant to describe the changes in tumor size following treatment with selpercatinib, identify covariate factors that could affect tumor growth. Data was collected in all tumor types from the ongoing Study LOXO-RET-17001. The PD analysis dataset included 2598 tumor size observations from 476 patients. The majority tumor

types were *RET* fusion NSCLC (47.9%) and *RET* mutant MTC (42.2%). Demographics and tumor type data for subjects in the population PD analysis are shown in **Table 19.5.**.

Table 19.5. Demographics and Tumor Type Data for Subjects in the Population PD Analysis

	PAS (n=152)		Not PAS (n=324)			Overall (n=476)		
Covariate Statistic/Category	**RET Fusion NSCLC (n=101)**	**RET Mutant MTC (n=51)**	**RET Fusion NSCLC (n=127)**	**RET Mutant MTC (n=150)**	**Other (n=47)**	**RET Fusion NSCLC (n=228)**	**RET Mutant MTC (n=201)**	**Other (n=47)**
Sex								
Female	59 (58.4%)	16 (31.4%)	71 (55.9%)	52 (34.7%)	20 (42.6%)	130 (57.0%)	68 (33.8%)	20 (42.6%)
Male	42 (41.6%)	35 (68.6%)	56 (44.1%)	98 (65.3%)	27 (57.4%)	98 (43.0%)	133 (66.2%)	27 (57.4%)
Race								
Caucasian	52 (51.5%)	46 (90.2%)	65 (51.2%)	132 (88.0%)	38 (80.9%)	117 (51.3%)	178 (88.6%)	38 (80.9%)
Asian	39 (38.6%)	0 (0%)	53 (41.7%)	5 (3.3%)	3 (6.4%)	92 (40.4%)	5 (2.5%)	3 (6.4%)
Black or African American	5 (5.0%)	1 (2.0%)	6 (4.7%)	1 (0.7%)	2 (4.3%)	11 (4.8%)	2 (1.0%)	2 (4.3%)
American Indian/Alaskan Native	0 (0%)	0 (0%)	1 (0.8%)	1 (0.7%)	0 (0%)	1 (0.4%)	1 (0.5%)	0 (0%)
Other	4 (4.0%)	4 (7.8%)	2 (1.6%)	11 (7.3%)	3 (6.4%)	6 (2.6%)	15 (7.5%)	3 (6.4%)
Missing	1 (1.0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)	1 (0.4%)	0 (0%)	1 (2.1%)
Age (years)								
Mean (SD)	58.3 (12.0)	56.6 (15.0)	60.1 (11.4)	56.3 (14.6)	55.3 (15.9)	59.3 (11.7)	56.4 (14.7)	55.3 (15.9)
Median [Min, Max]	61.0 [23.0, 81.0]	57.0 [17.0, 84.0]	61.0 [23.0, 86.0]	58.0 [15.0, 90.0]	55.0 [20.0, 88.0]	61.0 [23.0, 86.0]	58.0 [15.0, 90.0]	55.0 [20.0, 88.0]
Body weight (kg)								
Mean (SD)	67.9 (17.4)	76.8 (24.2)	69.1 (17.9)	72.0 (18.4)	77.3 (27.5)	68.6 (17.6)	73.2 (20.1)	77.3 (27.5)
Median [Min, Max]	64.0 [42.2, 148]	74.0 [42.3, 177]	63.8 [38.9, 131]	71.1 [26.8, 148]	73.9 [33.9, 165]	63.9 [38.9, 148]	71.7 [26.8, 177]	73.9 [33.9, 165]
Alteration type								
CCDC6	22 (21.8%)	0 (0%)	26 (20.5%)	0 (0%)	15 (31.9%)	48 (21.1%)	0 (0%)	15 (31.9%)
Extracellular cysteine mutation	0 (0%)	7 (13.7%)	0 (0%)	29 (19.3%)	2 (4.3%)	0 (0%)	36 (17.9%)	2 (4.3%)
KIF5B	57 (56.4%)	0 (0%)	87 (68.5%)	0 (0%)	0 (0%)	144 (63.2%)	0 (0%)	0 (0%)
M918T	0 (0%)	30 (58.8%)	0 (0%)	90 (60.0%)	2 (4.3%)	0 (0%)	120 (59.7%)	2 (4.3%)
NCOA4	2 (2.0%)	0 (0%)	3 (2.4%)	0 (0%)	9 (19.1%)	5 (2.2%)	0 (0%)	9 (19.1%)
Other	8 (7.9%)	9 (17.6%)	5 (3.9%)	23 (15.3%)	12 (25.5%)	13 (5.7%)	32 (15.9%)	12 (25.5%)
Unknown	12 (11.9%)	0 (0%)	6 (4.7%)	0 (0%)	0 (0%)	18 (7.9%)	0 (0%)	0 (0%)
V804M/L	0 (0%)	5 (9.8%)	0 (0%)	8 (5.3%)	0 (0%)	0 (0%)	13 (6.5%)	0 (0%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (14.9%)	0 (0%)	0 (0%)	7 (14.9%)

Tumor type								
Adrenal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (4.3%)	0 (0%)	0 (0%)	2 (4.3%)
Kidney	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	1 (2.1%)
MTC	0 (0%)	51 (100%)	0 (0%)	150 (100%)	6 (12.8%)	0 (0%)	201 (100%)	6 (12.8%)
NSCLC	101 (100%)	0 (0%)	127 (100%)	0 (0%)	3 (6.4%)	228 (100%)	0 (0%)	3 (6.4%)
Pancreatic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (8.5%)	0 (0%)	0 (0%)	4 (8.5%)
Prostate gland	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	1 (2.1%)
Rectal neuroendocrine	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	1 (2.1%)
Salivary	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	1 (2.1%)
Small intestine	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	1 (2.1%)
Thyroid	0 (0%)	0 (0%)	0 (0%)	0 (0%)	27 (57.4%)	0 (0%)	0 (0%)	27 (57.4%)

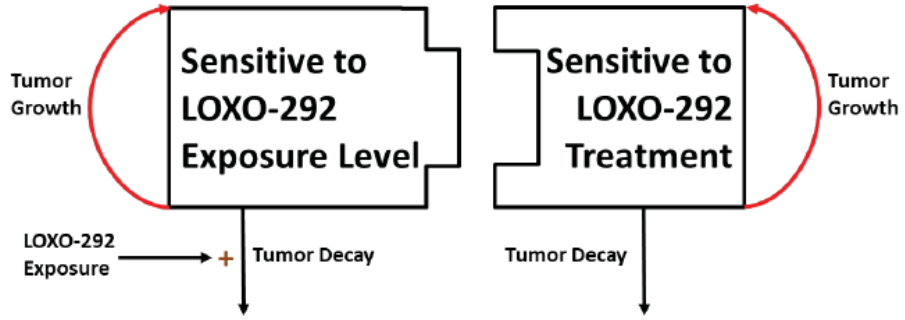
Abbreviations: Max=maximum; Min=minimum; n=sample size; MTC=medullary thyroid cancer; PAS=primary analysis set; n=sample size; NSCLC=non-small cell lung cancer; PK=pharmacokinetic; SD=standard deviation.
Note: The complete PAS includes 155 patients; however, tumor size and PK data were available only for 152 of those patients, thus only 152 patients were included in the survival analysis.
Source: Tumor-figures-report-2019-10-26.R

Source: loxo-292-dmpk-050, Page 46-48, Table 7.

The population PD analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software, version 7.4 using first-order conditional estimation with INTERACTION option (FOCE+I).

The tumor size model includes two theoretical portions of the tumor: one portion is sensitive to selpercatinib exposure levels and the other is sensitive only to selpercatinib treatment, but not the exposure level. Each of these portions includes an exponential growth term (KG) and exponential decay term (KD) which are shared for both portions of the tumor. The effect of drug exposure was described by Emax model on KD in the portion of the tumor that is sensitive to selpercatinib exposure levels. The exposure level used in the tumor model is the 24-hour AUC ($AUC_{0\text{-}24}$) at steady state. A schematic representation of the structural tumor size model is shown in **Figure 19.5.**

Figure 19.5. Schematic Representation of Tumor Size Model



Source: loxo-292-dmpk-050, Page 68, Figure 19.

The mathematical equations for the model are as follows:

$$\frac{dSEL}{dt} = KG * SEL - \left(KD + \frac{KDAUCmax * AUC24}{KDAUC50 + AUC24}\right) * SEL$$

$$\frac{dST}{dt} = KG * ST - KD * ST$$

where AUC24 is area under the plasma concentration-time curve over 24 hours at steady state; KD is tumor decay rate constant; KDAUC50=AUC24 that gives 50% of maximal effect; KDAUCmax is maximal increase in KD due to selpercatinib treatment; KG is tumor growth rate constant; ST is sensitive to selpercatinib treatment; SEL is sensitive to selpercatinib exposure level.

IIV terms are included on tumor growth rate constant (KG), tumor decay rate constant (KD), and total tumor decay rate constant for the portion of the tumor that is sensitive to selpercatinib exposure levels and the fraction of tumor that is sensitive only to selpercatinib treatment. The residual error model includes both additive and proportional error terms. Several covariates including age, gender, race, tumor location, tumor type and tumor size at baseline were explored.

The final population PD model for tumor size parameter estimates are shown in **Table 19.6.**. Estimated fixed and random effect parameters were estimated with acceptable precision (%RSE < 46%). The magnitude of the IIV was high for KG, KD for portion of tumor sensitive to selpercatinib exposure, KD for portion of tumor sensitive only to selpercatinib treatment and fraction tumor that is sensitive to selpercatinib exposure level. Residual variability was moderate. The maximum effect of selpercatinib exposure on tumor decay are different for patients with different tumors. For the *RET* Fusion NSCLC group, the tumor decay rate for the portion of the tumor that is sensitive to selpercatinib exposure levels was 76% higher than for the portion of the tumor that is only sensitive to selpercatinib treatment. For the *RET* Mutant MTC group, the tumor decay rate for the portion of the tumor that is sensitive to selpercatinib exposure levels was 28% higher than for the portion of the tumor that is only sensitive to selpercatinib treatment. The steady-state selpercatinib exposure for 50% maximal increasing in tumor decay rate for the sensitive portion of the tumor was 6526 ng*hr/mL and was independent of tumor type.

Table 19.6. Parameters of the Final Population Tumor Size Model

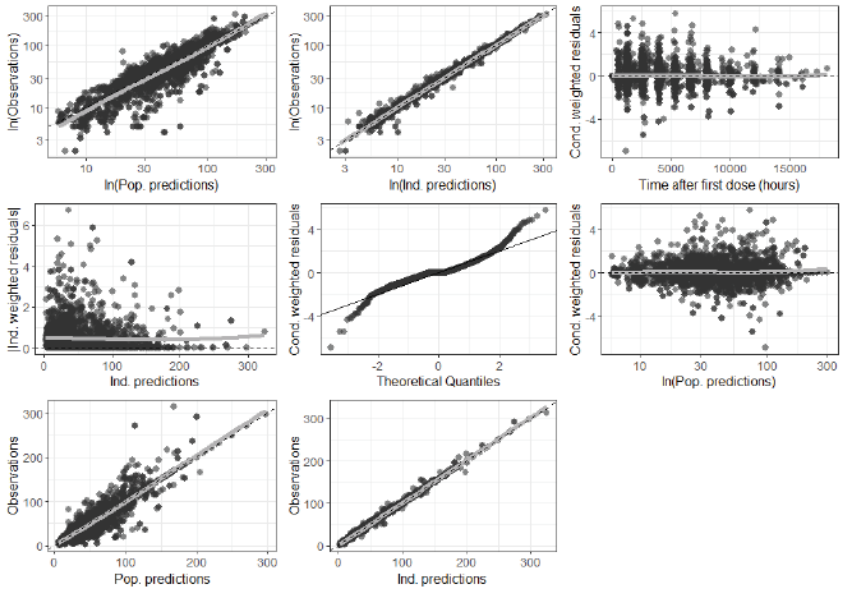
Parameter	Estimate		Interindividual Variability		
	Typical Value	RSE[a] (%)	Magnitude (%CV)	RSE[a] (%)	Shrinkage[b] (%)
Tumor growth rate (KG, 1/wk)	0.0012	23%	136%	8.6%	42%
Tumor decay rate (KD, 1/wk)	0.0027	22%	—	—	—
IIV in KD for portion of tumor sensitive to LOXO-292 exposure level	—	—	131%	5.9%	36%
IIV in KD for portion of tumor sensitive only to LOXO-292 treatment	—	—	206%	7.2%	48%
Maximum increase in decay rate for NSCLC (KDAUCmax, 1/wk)	0.0021	15%	—	—	—
Effect of MTC on KDAUCmax	-64%	9.9%	—	—	—
Effect of Other on KDAUCmax	-38%	46%	—	—	—
AUC24 required for 50% maximal effect (KDAUC50, ng·hr/mL)	6526	33%	—	—	—
Fraction tumor that is sensitive to LOXO-292 exposure level	38%	3.9%	88%	5.2%	34%
Residual variability					
Proportional residual error	4.4%	0.9%	—	—	15%
Additive residual error SD (mm)	1.6	1%	—	—	15%

Abbreviations: CV=coefficient of variation; IIV=interindividual variability; KD=tumor decay rate constant; KDAUC50=AUC24 that gives 50% of maximal effect; KDAUCmax=maximum increase in decay rate; KG=tumor growth rate constant; RSE=relative standard error; SD=standard deviation; wk=week.
[a] RSEs of parameter estimate are calculated as 100×(SE/typical value); RSEs of between-patient variability magnitude are presented on %CV scale and approximated as 100×(SE/variance estimate)/2.
[b] Shrinkage (%) is calculated as 100×(1 – SD of post hocs/estimated variance).
Source: tcovfd1-sumo.txt

Source: loxo-292-dmpk-050, Page 73, Table 21.

The final model adequately describes the tumor size-time profile following oral administration of selpercatinib in patients with advanced solid tumors. Tumor size decreases over time in the presence of selpercatinib. The diagnostic plots (**Figure 19.6.**) show no significant bias in the model, and the pcVPCs (**Figure 19.7.** and **Figure 19.8.**) suggest that the model describes the observed data well and can be useful for predictions. Bootstrap results (**Table 19.7.**) are also in good concordance with the final model parameter estimates.

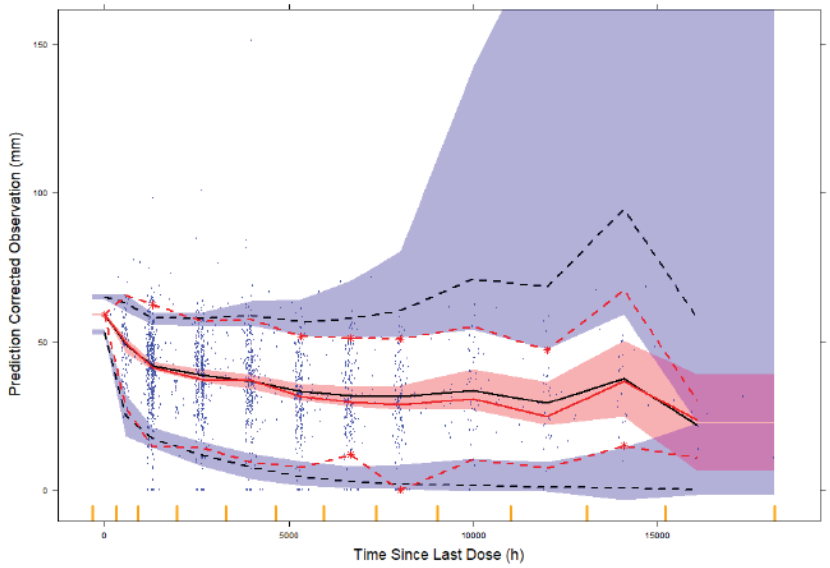
Figure 19.6. Diagnostic Plots for the Final Population Tumor Size Model for Selpercatinib.



Abbreviations: Cond=conditional; Ind=individual; ln=natural logarithm; Pop=population.
Note: The circles represent individual data points, the grey lines represent loess smooth curves, and the dashed and solid lines represent the line of unity (y=x) or the x-axis (y=0).
Source: Tumor-figures-report-2019-10-26.R

Source: loxo-292-dmpk-050, Page 75, Figure 22.

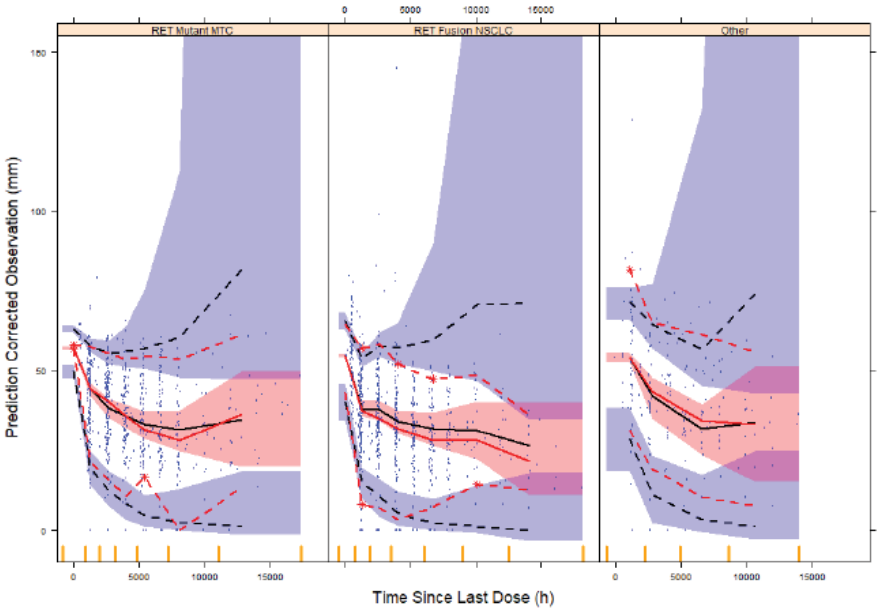
Figure 19.7. Prediction-corrected VPC of the Final Population Tumor Size model for Selpercatinib



Abbreviations: h=hour; VPC=visual predictive check.
Note: The blue circles represent prediction-corrected observed data, the red solid line represents the median of the prediction-corrected observed data, and the red dashed lines represent the 5th and 95th percentiles of the prediction-corrected observed data. The red stars represent observed values that lie outside of the 90% prediction interval. The black solid line represents the median of the prediction-corrected simulation data, and the black dashed lines represent the 5th and 95th percentiles of the prediction-corrected simulation data. The blue shaded areas represent the 90% prediction interval for the 5th and 95th percentiles of the predicted data, and the red shaded area represent the 90% prediction interval for the median of the predicted data. The yellow vertical ticks on x-axis represent the edges of the bins used to group the data for calculation of the quartiles.
Source: Tumor-figures-report-2019-10-26.R

Source: loxo-292-dmpk-050, Page 76, Figure 23.

Figure 19.8. Prediction-corrected VPC of the Final Population Tumor Size Model for Selpercatinib Stratified by Tumor Group.



Abbreviations: h=hour; VPC=visual predictive check.
Note: The blue circles represent prediction-corrected observed data, the red solid line represents the median of the prediction-corrected observed data, and the red dashed lines represent the 5th and 95th percentiles of the prediction-corrected observed data. The red stars represent observed values that lie outside of the 90% prediction interval. The black solid line represents the median of the prediction-corrected simulation data, and the black dashed lines represent the 5th and 95th percentiles of the prediction-corrected simulation data. The blue shaded areas represent the 90% prediction interval for the 5th and 95th percentiles of the predicted data, and the red shaded areas represent the 90% prediction interval for the median of the predicted data. The yellow vertical ticks on x-axis represent the edges of the bins used to group the data for calculation of the quartiles.
Source: Tumor-figures-report-2019-10-26.R

Source: loxo-292-dmpk-050, Page 77, Figure 24.

Table 19.7. Bootstrap Parameters Estimates from the Final Population Tumor Size Model.

Parameter	Model Estimate	Bootstrap Median[a]	Bootstrap 95% CI[a]
Tumor growth rate (KG, 1/wk)	0.0012	0.0013	(0.0004, 0.0022)
Tumor decay rate (KD, 1/wk)	0.0027	0.0027	(0.0015, 0.004)
Maximum increase in decay rate for NSCLC (KDAUCmax, 1/wk)	0.0021	0.0021	(0.0015, 0.0031)
Effect of MTC on KDAUCmax	-64%	-63%	(-75%, -48%)
Effect of other on KDAUCmax	-38%	-38%	(-67%, 6.9%)
AUC24 required for 50% maximal effect (KDAUC50, ng·hr/mL)	6526	6419	(1814, 16593)
Fraction tumor that is sensitive to LOXO-292 exposure level	38%	38%	(34%, 42%)
Interindividual variability in KG	136%	137%	(107%, 192%)
Interindividual variability in KD for portion of tumor sensitive to LOXO-292 exposure level	131%	129%	(107%, 157%)
Interindividual variability in KD for portion of tumor sensitive only to LOXO-292 treatment	206%	205%	(159%, 260%)
Interindividual variability in Fraction tumor that is sensitive to LOXO-292 exposure level	88%	88%	(73%, 105%)
Residual variability			
Proportional residual error	4.4%	4.4%	(2.9%, 5.7%)
Additive residual error SD (mm)	1.6	1.6	(1.2, 2.1)

Abbreviations: CI=confidence interval; IIV=interindividual variability; KD=tumor decay rate constant; KDAUC50=AUC24 that gives 50% of maximal effect; KDAUCmax=maximum increase in decay rate; KG=tumor growth rate constant; MTC=medullary thyroid cancer; NSCLC=non-small cell lung cancer; RSE=relative standard error; SD=standard deviation.
[a] Bootstrap parameters based on 1000 bootstrap replicates, of which 307 (31%) minimized successfully. Parameter estimates from all 1000 bootstrap replicates were included in the summary.
Source: bootstrap_summary_all.csv

Source: loxo-292-dmpk-050, Page 74, Table 22.

Reviewer's comments:

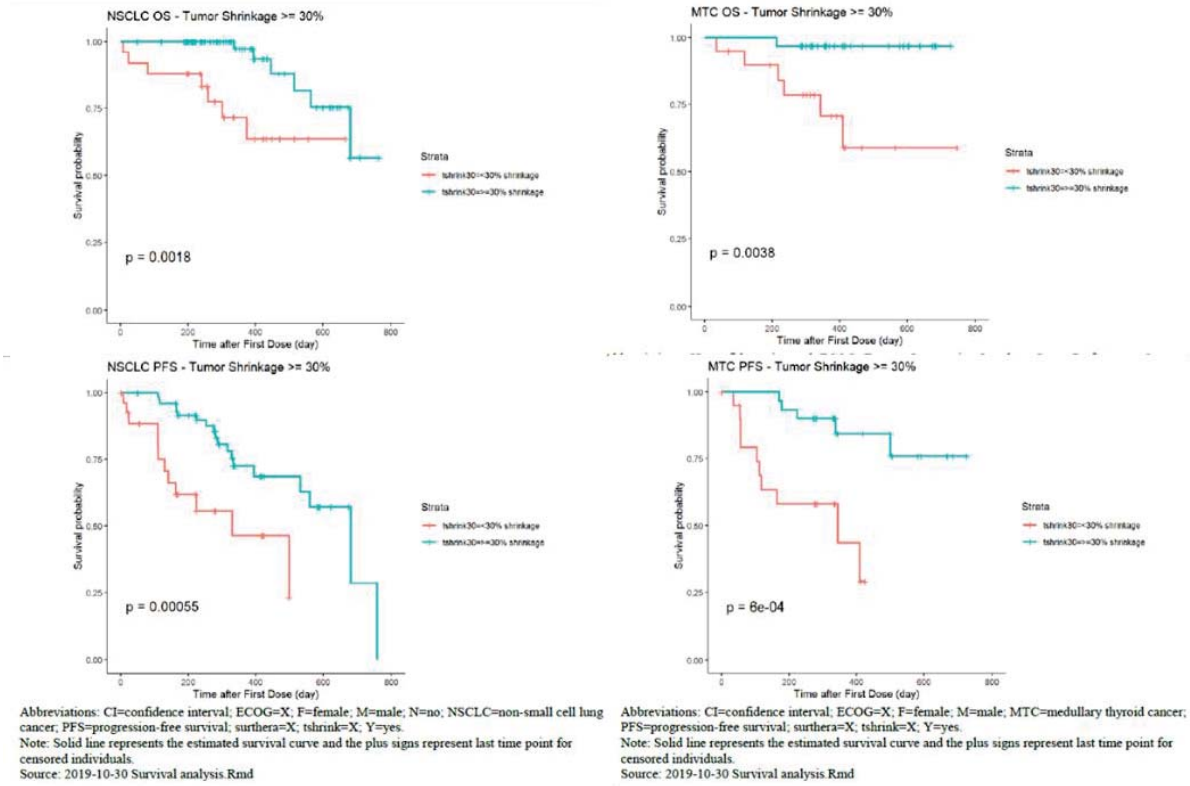
The results of final tumor size model were checked by the reviewer. In general, the final model could describe the tumor size-time profile following oral administration of selpercatinib in patients with advanced solid tumors because of the agreement of observation and prediction. There were two theoretical portions of the tumor included in the applicant's tumor size model. One portion is sensitive to the selpercatinib exposure level while the other portion is not sensitive to selpercatinib exposure level. As there is no placebo control to describe the natural tumor growth in the model, the tumor will always shrink no matter what dose of selpercatinib is used. The current tumor model is not valid for extrapolation.

19.4.3 Survival Analysis

Survival analysis was performed with both OS and PFS data for patients with *RET* Fusion NSCLC (n=105) and *RET* Mutant MTC (n=55) separately. Tumor shrinkage ≥30% was a significant (p<0.01) predictor of survival for both OS and PFS for both tumor groups in Kaplan-Meier analysis. The results were shown in **Figure 19.9.**. Parametric survival models were further

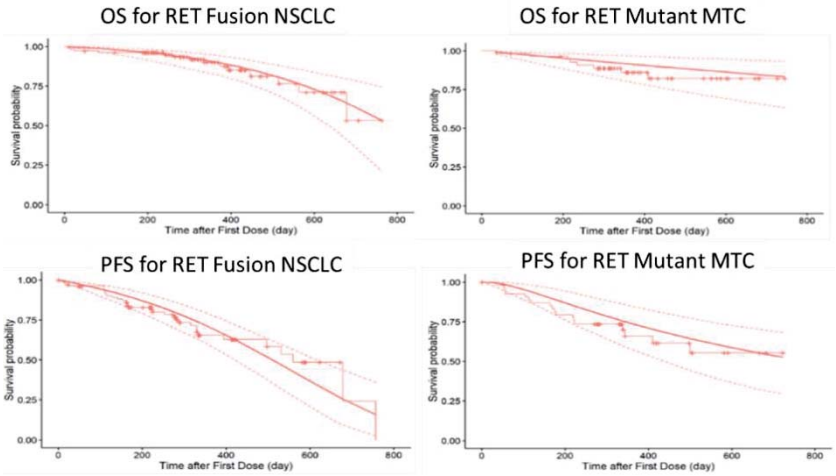
developed to further explore the tumor shrinkage as predictors for both OS and PFS for both tumor groups (**Figure 19.10.**).

Figure 19.9. Univariate Survival Curves with the Kaplan-Meier Method for Tumor shrinkage ≥30%.



Source: loxo-292-dmpk-050, Page 228-247, Figure 53-56

Figure 19.10. Parametric Survival Curve and Model Fit for PFS/OS for RET Fusion NSCLC/MTC

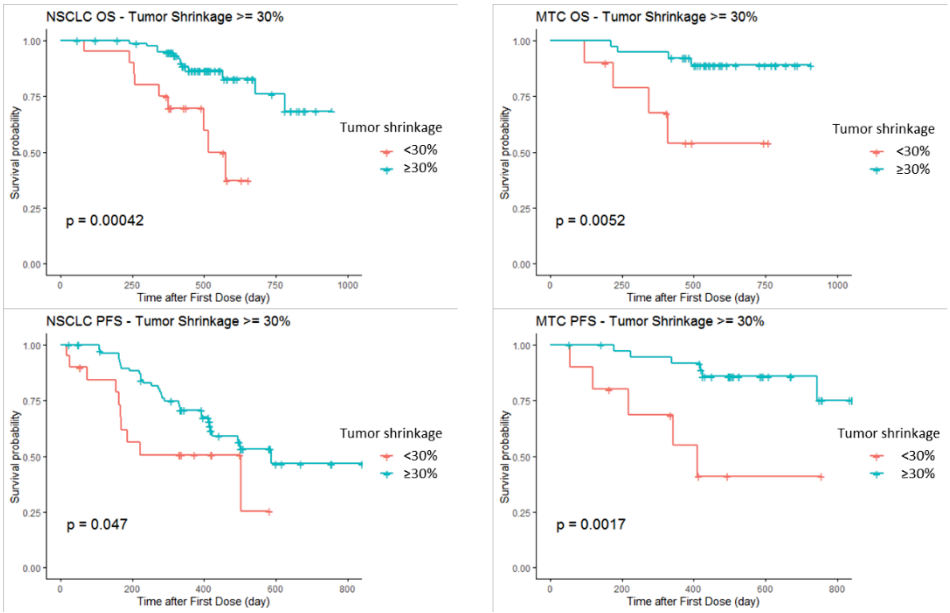


Source: loxo-292-dmpk-050, Page 81-84, Figure 26-29.

Reviewer's comments:

*The results of survival analysis for OS and PFS were verified by reviewer. Tumor shrinkage ≥ 30% was identified as a significant predictor of both OS and PFS for both RET fusion NSCLC and RET mutant MTC. Parametric survival models for PFS/OS for RET fusion NSCLC and RET mutant MTC are acceptable. An independent analysis was done by the reviewer with the 60-day update observed tumor size and time to event data assessed by IRC. Tumor shrinkage was calculated based the smallest observed tumor size and baseline tumor size. Tumor shrinkage ≥30% was a significant (p<0.01) predictor of survival for both OS and PFS in both tumor groups except for PFS in RET fusion NSCLC in Kaplan-Meier analysis (**Figure 19.11.**).*

Figure 19.11. Univariate Survival Curves with the Kaplan-Meier Method for Tumor shrinkage ≥30% based on reviewer's analysis.

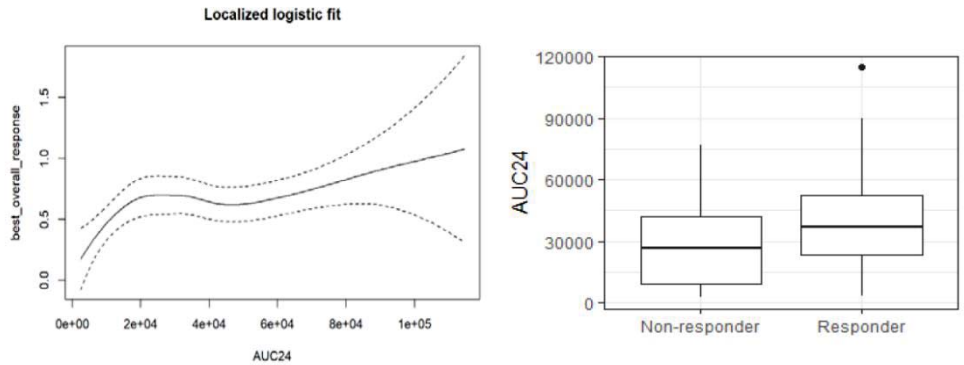


Source: Reviewer's analysis

19.4.4 Exposure-Response Analysis

The exposure-response relationship of Overall Response Rate (ORR) and selpercatinib dose and exposure (AUC_{24}, C_{max} & C_{min}) were evaluated with participants with *RET* fusion NSCLC (n=105) and *RET* mutant MTC (n=55) in study LOXO-RET-17001 by the applicant. Selpercatinib exposure parameters were estimated with the individual post hoc parameter from the population PK analysis at time of most recent response for the responder and last treatment period for the non-responder for each individual patient. The steady-state AUC_{0-24} is selected as the significant predictor in the sensitivity analysis (**Figure 19.12.**).

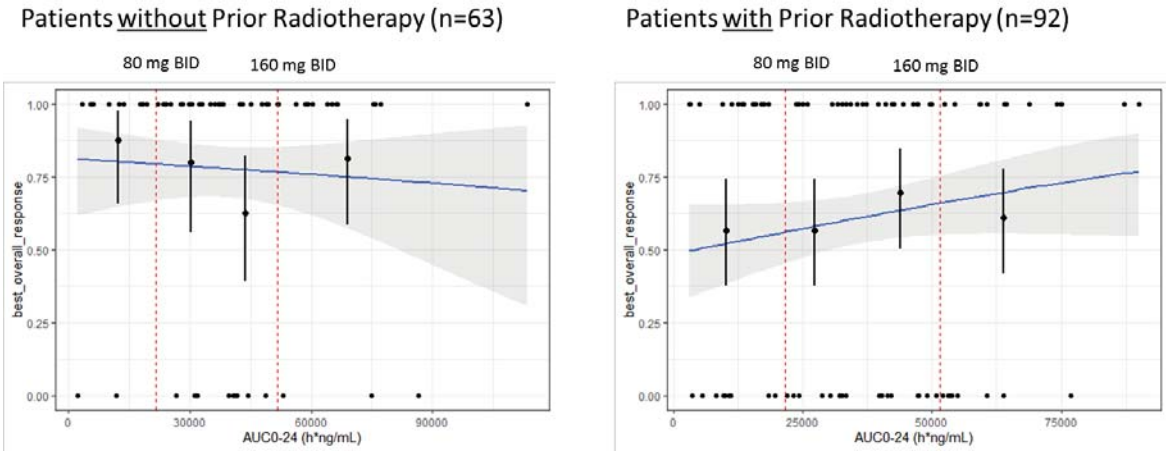
Figure 19.12. Box Plots and Logistic Regressions for Response versus AUC24



Source: loxo-292-dmpk-050-supplement-2, Page 19, Figure 1

Reviewer's comments:
*The result of the logistic regression models for ORR vs. selpercatinib exposure were checked by the reviewer. Selpercatinib exposure parameters were selected from the time of most recent response for the responder and last treatment period for the non-responder for each individual patient. This might not reflect the exposures at steady-state as the exposure simulation file provided by the applicant showed that some responders have temporary dose adjustment at the time of the most recent response and some non-responders had dose reduction for 1-2 last dose. The reviewer did an independent ER analysis with the applicant's simulated exposure data. To avoid temporary dose adjustment and decrease, the exposure parameters were selected from the average of last 10 treatment periods from the time of most recent response for the responder and last 10 treatment periods for the non-responder for each individual patient. The analysis identified a shallow and non-significant ER relationship between ORR and selpercatinib exposures (**Figure 19.13.*** Logistic Regression Analysis*). While patients without prior radiotherapy have higher ORR than patients with prior radiotherapy.*

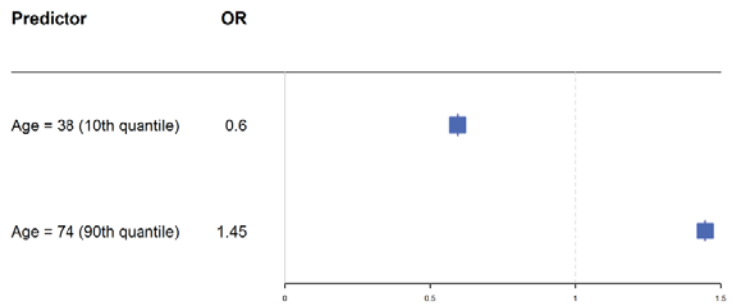
Figure 19.13. Logistic Regression Analysis of Selpercatinib AUC_{0-24} vs. ORR.



Source: Reviewer's analysis

The relationships between adverse event (AE) responses (increases in ALT, increases in AST, hypersensitivity, and hypertension) and selpercatinib exposures (AUC_{0-24}, C_{max}, C_{min}) at steady state, age, body weight were evaluated in patients with advanced tumors in the study LOXO-RET-17001. No statistically significant correction was identified for steady-state selpercatinib exposures and any AEs evaluated in this analysis except for the significant correlation between age and hypertension AE. The probability of a hypertension AE increases with age. The reference patient in this analysis is 59 years of age and has a 13.8% probability of experiencing a hypertension AE (**Figure 19.14.**).

Figure 19.14. Odds Ratio for incidence of Hypertension Adverse Events Based on 10th and 90th Quartiles of Age



Abbreviations: AE=adverse event; OR=odds ratio.
Note: The reference patient is 59 years of age and has a probability of a hypertension AE of 13.8%.
Source: Safety-ER-Analysis-updated-2019-10-09.Rmd

Source: loxo-292-dmpk-050, Page 90, Figure 32.

Reviewer's comments:
The ER analysis for AEs (increases in ALT, increases in AST, hypersensitivity, and hypertension) with selpercatinib were checked by the reviewer. An independent analysis was done by the reviewer. The exposure parameters were selected from the average of last 10 treatment period from the time of most recent incident of AEs for the patients with AEs and the highest exposure for the patients without AEs for each individual patient. No significant ER relationships were identified for steady-state selpercatinib exposures and any AEs evaluated in this analysis except for the significant correlation between age and hypertension AE.

19.4.5 Physiologically Based Pharmacokinetic (PBPK) Modeling Analysis

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses to evaluate the drug-drug interaction (DDI) potentials:

- The effects of strong and moderate CYP3A inhibitors on selpercatinib PK
- The effects of strong, moderate and weak inducers of CYP3A on selpercatinib PK

The Division of Pharmacometrics has review the PBPK analyses reports (loxo-292-dmpk-052 and loxo-292-dmpk-058), responses to FDA's information requests (IRs) submitted on February 11,

February 18, and March 11, 2020, and the modeling supporting files, and concluded that the PBPK models are adequate to predict the effects of the following CYP3A perpetrators on selpercatinib PK.

- strong CYP3A inhibitors (itraconazole, ketoconazole, ritonavir and clarithromycin)
- moderate CYP3A inhibitors (diltiazem, fluconazole and verapamil)
- a strong CYP3A inducer (rifampin), moderate CYP3A inducers (bosentan, efavirenz) and a weak CYP3A inducer (modafinil)

Following co-administration of selpercatinib 160-mg twice daily with CYP3A perpetrators, the model predicted that moderate CYP3A4 inhibitors may increase the selpercatinib exposure (AUC) by approximately 60% to 99% at steady state, a moderate CYP3A inducer may decrease the selpercatinib exposure by approximately 40%-70%, and a weak CYP3A inducer may decrease the selpercatinib exposure by approximately 30%.

Background

The proposed selpercatinib dosing regimen is 160-mg twice daily (BID) given as 40- or 80-mg capsules. Following oral administration of selpercatinib twice daily, steady-state selpercatinib AUC and C_{max} increased in a slightly greater than dose proportional manner across the dose range of 20-mg to 240-mg. At 160-mg, cancer patients had lower selpercatinib exposure (AUC and C_{max}) than healthy subjects.

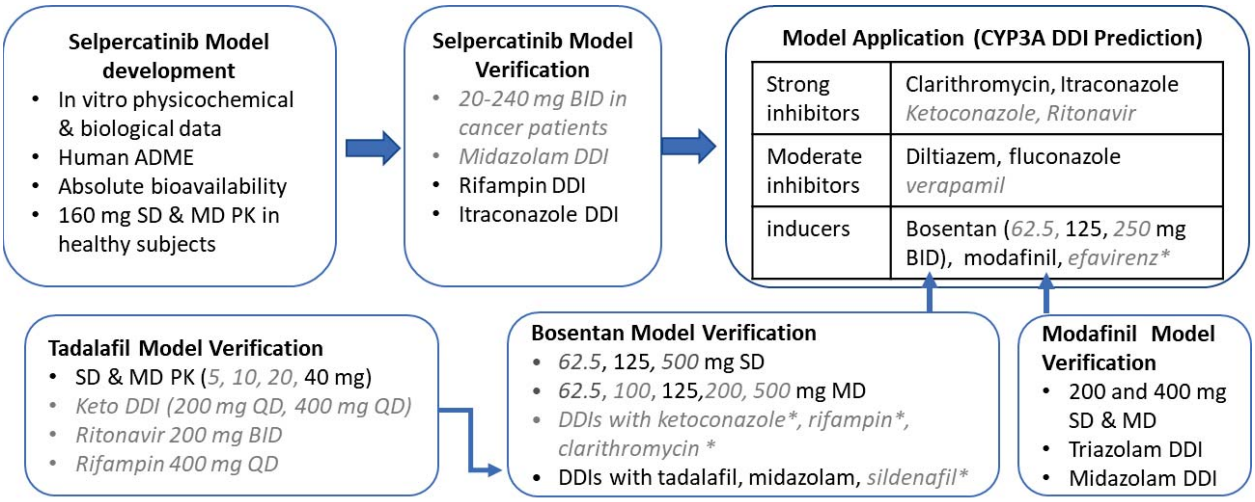
Selpercatinib is a substrate of CYP3A, P-gp and BCRP. Selpercatinib was determined in vitro to be a time-dependent inhibitor and an inducer of CYP3A, and an inhibitor of OATP1B1/3, P-gp and BCRP. At the clinically relevant concentration of 0.153 μM, the unbound steady-state C_{max} at 160 mg BID in cancer patients, selpercatinib may not be an inducer of CYP3A nor an inhibitor of OATP1B1/3 but its effects on intestinal P-gp and BCRP cannot be ruled out. The applicant conducted clinical DDI studies with itraconazole, rifampin, midazolam and repaglinide to evaluate some of the in vitro findings. Refer to the Clinical Pharmacology review section for detail information on selpercatinib regarding ADME properties, in vitro and clinical studies used in PBPK modeling.

Methods

All simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Version 18 Certara, Sheffield, UK). A scheme of the PBPK simulation strategy is shown in **Figure 19.15,** which summarizes the studies used for model development and verification, and model applications in CYP3A-related DDI prediction. Based on results from in vitro metabolism, human ADME and absolute bioavailability studies, the proposed elimination pathways and their contribution in selpercatinib disposition are depicted in **Figure 19.16**. The model structure,

model optimization and final model parameters for the selpercatinib PBPK model in healthy subjects are summarized in **Table 19.8**.

Figure 19.15. Modeling and simulation strategy

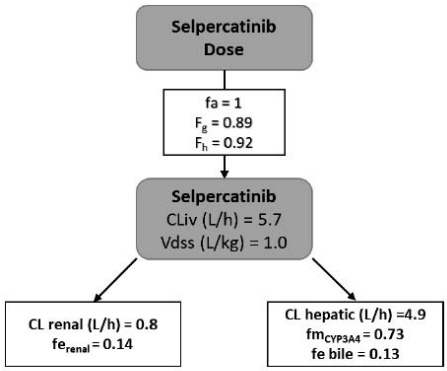


Studies in grey Italicized text were requested by the reviewer. * Reviewer's analyses

Source: This flow chart was generated by the reviewer.

Simcyp library files of midazolam, triazolam, sildenafil, clarithromycin (CLAR), diltiazem (DTZ), verapamil (VER), fluconazole (FLUC), rifampin MD (RIF), efavirenz (EFV), and ritonavir (RTV) were used for DDI simulations without any modification except that the ADAM absorption model of verapamil was changed to a 1st order absorption model and CYP3A4 inhibition constant (K_i) was removed from the rifampicin model. Recently published models were used for simulating DDIs with itraconazole, the IQ itraconazole PBPK model [Chen et al, 2019], and ketoconazole [Guo et al, 2020]. Version comparison for the IQ itraconazole PBPK model was performed with limited number of itraconazole and midazolam interaction studies. Tadalafil, bosentan and modafinil PBPK models were developed by the applicant.

Figure 19.16. Proposed diagram of selpercatinib disposition



Abbreviations: CL = clearance, fa = fraction absorbed, fe = fraction excreted in the urine or bile, F_g = gut wall availability, F_h = hepatic bioavailability, fm = fraction metabolized, V_{dss} = volume of distribution at steady state.

Source: PBPK report loxo-292-dmpk-058 submitted by the Applicant on Feb 14, 2020 in response to the information request.

Table 19.8. Final input parameters of selpercatinib PBPK model in healthy subjects

Property	Value	Source
Molecular weight (g/mol)	525.61	
cLogP	3.1	Predicted Chemaxon;
pKa (diprotic base)	3.19, 7.3	Measured; Appendix 2 of LOXO-292-DMPK-052-
B:P	0.7	Measured; LOXO-292-DMPK-013
Fu, plasma	0.027	Measured; LOXO-292-DMPK-012
Absorption model	First Order	
fa	1	Based on assumption that parent drug in feces is excreted via the biliary route and is not unabsorbed drug
ka (h^{-1})	1	Manually estimated to match T_{max} and C_{max} from single dose studies.
MDCK P_{app} (10^{-6} cm/s)	22.35	Measured; Mean of apical to basolateral and basolateral to apical flux in MDCK/BRCP cells in the presence of the BCRP inhibitor Ko143 (LOXO-292-DMPK-019, Table 5.2). Propranolol permeability from Lilly's reference library[a].
Qgut (L/h)	12.491	Predicted by system based on permeability
Fg	0.89	Predicted by system based on permeability and CYP3A4-mediated intrinsic clearance
V_{dss} (L/kg)	1	Measured after IV administration of selpercatinib (LOXO-RET-18016, Part 2)
CYP3A4 CL_{int} (µL/min/pmol)	0.358	Calculated using the Simcyp retrograde calculator to achieve fm_{CYP3A4} of 0.73.
Biliary CL_{int} (µL/min/10^6 cells)	2.869	
CL_{renal} (L/h)	0.789	ADME/ABA study (LOXO-RET-18016, Part 2)
K_I (µM)	9	Measured (LOXO-292-DMPK-010); time-dependent inhibition parameters were included in multiple dose simulations only.
K_{inact} (h^{-1})	0.78/0.25	Measured (LOXO-292-DMPK-010)/Fitted clinical concentration plasma profiles from study (LOXO-RET-18017) Note: time-dependent inhibition parameters were included in multiple dose simulations only (auto-inhibition does not affect selpercatinib pharmacokinetics after a single dose; Table 4.1).
fu_{inc}	0.418	Measured value (LOXO-292-DMPK-014).

[a] See Report LOXO-292-DMPK-052 for details.
Abbreviations: ABA = absolute bioavailability study, ADME = absorption, distribution, metabolism and excretion, B:P = blood to plasma ratio, CL_{int} = intrinsic clearance, CL_{renal} = renal clearance, cLogP = calculated octanol/water partition coefficient, fa = fraction absorbed, Fg = fraction of the dose that escapes first pass gut metabolism, fu_{mic} = fraction unbound in the incubation, Fu, plasma = fraction unbound in plasma, IV = intravenous, ka = absorption rate constant, MDCK = Madin-Darby Canine Kidney, P_{app} = apparent permeability, P_{eff} = predicted effective permeability, pKa = acid dissociation constant, Q_{gut} = hybrid term that includes villous blood flow and permeability through the enterocyte, V_{dss} = volume of distribution at steady state.

Source: PBPK report loxo-292-dmpk-058 submitted by the Applicant on Feb 14, 2020 in response to the information request.

Reviewer's comment: *For the intended use of model application, model verifications provided in the initial report were insufficient. Additional verifications were requested and are shown in italics (**Figure 19.15**).*

- *In the initial report, CYP3A contribution in the selpercatinib PBPK model was verified using clinical PK and DDI studies conducted with a single oral dose of 160-mg selpercatinib. This*

verified model overpredicted selpercatinib PK following 160-mg BID. To reproduce the observed multiple-dose PK of selpercatinib, the CYP3A time-dependent inhibition parameter k_{inact} was optimized. This optimized selpercatinib PBPK model was used to predict the effects of CYP3A inhibitors and inducers without further verification. The applicant was requested to submit further model verifications against clinical observations including multiple-dose PK in cancer patients and drug interaction with midazolam (responses to IRs on Feb. 18 and March 11, 2020).

- *The tadalafil PBPK model was not verified before it was used to evaluate the induction potential of the bosentan PBPK model. The applicant was requested to verify the ability of the tadalafil PBPK model to predict tadalafil PK at other doses and confirm the contribution of CYP3A to tadalafil disposition using available PK and DDI data (**Figure 19.15**) (response to IR on Feb 11, 2020).*
- *Bosentan is mainly metabolized by CYP3A and CYP2C9 and is a substrate of OATP1B1/3 and P-gp. Selpercatinib has the potential to affect these enzymes and transporters. Based on the FDA in vitro DDI Guidance, the potential of selpercatinib to be an inhibitor of hepatic transporters (OATP1B1/3 and P-gp) is low at the recommended dose of selpercatinib (160-mg), but its effect on intestinal P-gp cannot be ruled out. Due to the uncertainty in translating in vitro kinetic parameters of transporters into in vivo, the applicant was requested to provide the predicted effect of 250-mg bosentan on selpercatinib PK as the worst-case scenario. The ability of the bosentan PBPK model to predict CYP3A induction and the contribution of CYP3A to bosentan disposition was shown in **Table 19.9**.*

Table 19.9. Predicted and observed drug interactions with bosentan

Dosing Regimen		AUC_{0-inf} ratio			C_{max} ratio			References
Perpetrators	**Victims**	**Observed**	**Predicted**	**Pred/obs**	**Observed**	**Predicted**	**Pred/obs**	
Bosentan 125 mg BID 10d	**Midazolam** 3 mg QD 10d	0.45	0.28	1.61	NA	0.34	NA	Markert 2014
Bosentan 125 mg BID 10d	**Tadalafil** 40 mg QD 10 d	0.59	0.64	0.92	0.73	0.76	0.96	Wrishko 2008
Bosentan 125 mg BID 10d	**Sildenafil*** 20 mg tid 3d + 80 mg tid 3d	0.37	0.31	1.19	0.45	0.35	1.29	Burgess 2008
Ketoconazole* 200 mg QD 6d	Bosentan 62.5 mg BID 5.5d	2.3	2.48	1.08	2.1	2.13	1.01	Van Giersbergen 2002
Clarithromycin* 500 mg BID 4d on D11	Bosentan 125 mg BID 14d	3.7	2.16	0.58	3.8	1.91	0.50	Markert 2014
Rifampin* 600 mg QD 7d	Bosentan 125 mg BID 6.5d	0.42	0.45	1.07	0.47	0.58	1.23	van Giersbergen 2007

Sim-ketoconazole-200 mg QD, SV-rifampin-MD and SV-clarithromycin in SImcyp V18 were used in the simulations.

Source: Reviewer's analyses (*) and the Applicant's PBPK report loxo-292-dmpk-052

- *Efavirenz, an inducer of CYP2B6 and CYP3A, is commonly used to evaluate drug interaction potential of a new molecular entity with a moderate CYP3A inducer. To evaluate the potential effect of efavirenz on selpercatinib PK, additional verification of*

*the efavirenz PBPK model in the Simcyp library (V18) was performed to assess its ability to induce the CYP3A pathway, and the results are summarized in **Table 19.10**.*

Table 19.10. Predicted and observed induction effects on CYP3A substrates by efavirenz

Dosing Regimen		AUC_{0-t} Ratio			C_{max} Ratio			Observed Data
Efavirenz	**Victims**	**Observed**	**Predicted**	**Pred/obs**	**Observed**	**Predicted**	**Pred/obs**	**References**
400 mg SD	Midazolam 4 mg po 12h after	0.6	0.76	1.27	NA	0.85	NA	Mikus et al 2017
600 mg qd 14d	Simeprevir 150 mg qd 14d	0.29	0.31	1.07	0.49	0.62	1.27	Snoey et al 2016
600 mg qd 9d	Daclatasvir 60 mg qd 9d	0.68	0.63	0.93	0.83	0.81	0.98	Bifano et al 2013
600 mg qd 14d	Maraviroc 100 mg bid 14d	0.49	0.3	0.61	0.44	0.32	0.73	Abel et al 2008

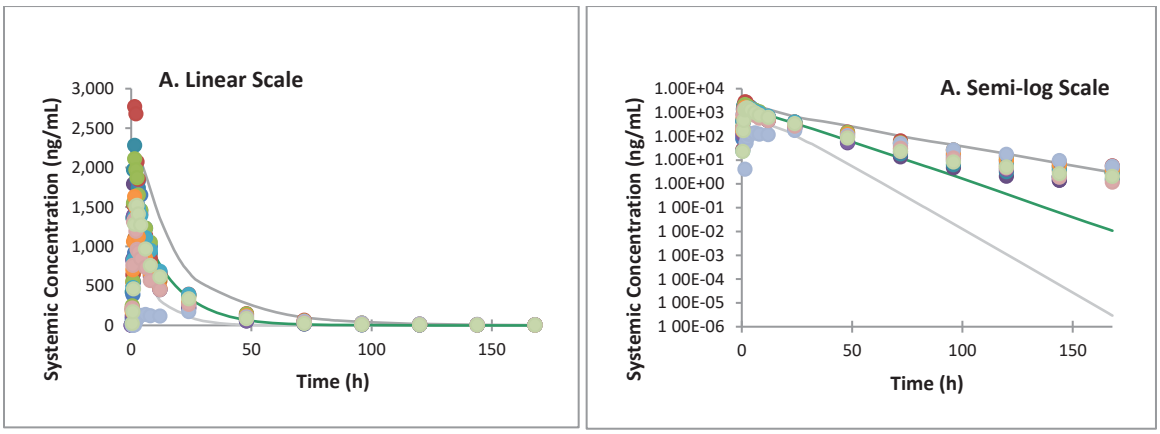
Source: Reviewer's analyses

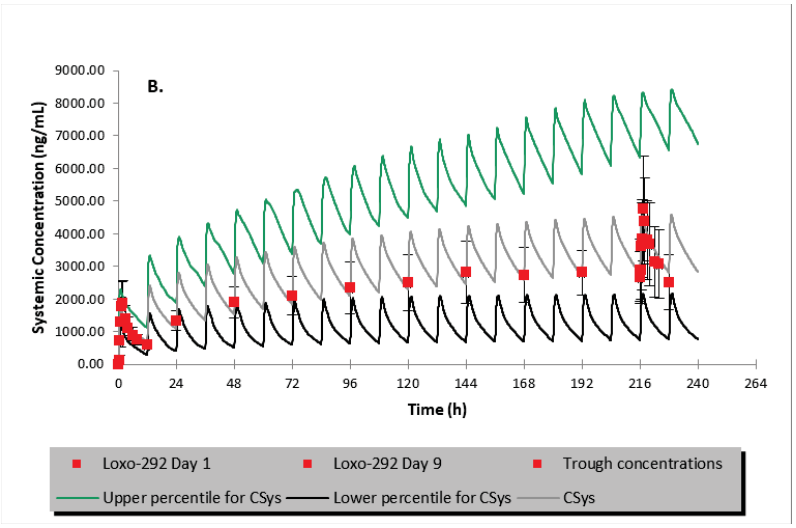
Results

1. Can the PBPK model adequately describe the PK profiles of selpercatinib?

Yes, the PBPK models of selpercatinib described selpercatinib PK following administration of a single-dose and multiple doses of 160-mg selpercatinib in healthy subjects (**Figure 19.17**) and following administration of 20-mg QD or 20 mg to 240-mg selpercatinib twice daily for 8 days (LOXO-RET-17001) in cancer patients (**Figure 19.18** and **Table 19.11**).

Figure 19.17. Simulated and observed PK profiles following (A) 160-mg single dose of selpercatinib in healthy subjects (LOXO-RET -18014); (B) 160-mg of selpercatinib twice daily for 10 days (LOXO-RET-18017) in healthy subjects

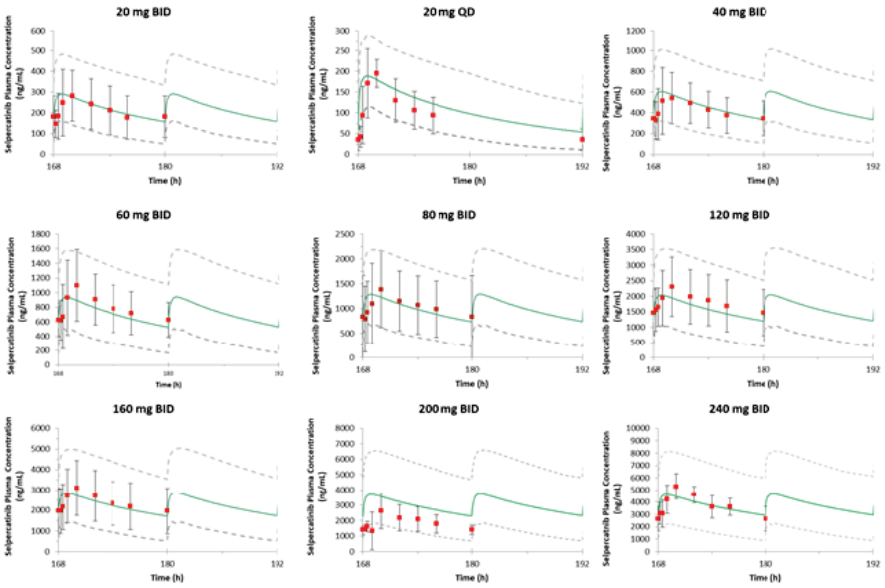




Sim-healthy subject population aged 18 -60, female ratio 0.5

Source: The Applicant (B) and reviewer (A)'s simulation output.

Figure 19.18. Predicted and observed PK profiles following 20-mg QD or 20 mg to 240-mg selpercatinib twice daily for 8 days (LOXO-RET-17001) in cancer patients using the modified model with the f_a value of 0.625.



Sim-NEurCaucasian population aged 18 -90, female ratio 0.5

Source: The applicant's response to information request on March 11, 2020.

Table 19.11. Predicted and observed PK parameters (geometric mean) following 20-mg QD or 20 mg to 240-mg selpercatinib twice daily for 8 days (LOXO-RET-17001) in cancer patients using the modified model with the f_a value of 0.625.

		Cycle 1 Day 8[a,b,c]		
Dose	Geometric Mean	AUC_{tau} (h*ng/mL)	CL_{ss}/F (L/h)	C_{max} (ng/mL)
20 mg QD	Observed	1330	15.1	123
	Predicted	2320	8.62	186
	Pred/Obs	1.74	0.57	1.51
20 mg BID	Observed	2290	8.73	275
	Predicted	2407	8.31	278
	Pred/Obs	1.05	0.95	1.01
40 mg BID	Observed	4600	8.7	546
	Predicted	5078	7.88	581
	Pred/Obs	1.10	0.91	1.06
60 mg BID	Observed	8870	6.76	1070
	Predicted	7968	7.53	905
	Pred/Obs	0.90	1.11	0.85
80 mg BID	Observed	10800	7.39	1340
	Predicted	11066	7.23	1246
	Pred/Obs	1.02	0.98	0.93
120 mg BID	Observed	19100	6.27	2300
	Predicted	17854	6.72	1983
	Pred/Obs	0.93	1.07	0.86
160 mg BID	Observed	25800	6.2	2980
	Predicted	25386	6.3	2784
	Pred/Obs	0.98	1.02	0.93
200 mg BID	Observed	22000	9.1	2650
	Predicted	33597	5.95	3643
	Pred/Obs	1.53	0.65	1.37
240 mg BID	Observed	43900	5.46	5270
	Predicted	42426	5.66	4555
	Pred/Obs	0.97	1.04	0.86

AUC_{0-tau} = Area under the concentration-time curve of the dosing interval, C_{max} = maximum plasma concentration, CL_{ss}/F = apparent clearance (after oral administration) at steady state, QD: once a day, BID: twice a day.

Sim-NEurCaucasian population aged 18 -90, female ratio 0.5

Source: The applicant's response to information request on March 11, 2020.

Reviewer's comment:

*Based on the FDA in vitro DDI Guidance, at 30-fold of steady-state $C_{max,u}$ (0.153 μM) at 160-mg BID in cancer patients, selpercatinib showed minimal induction effect in the CYP3A hepatocyte induction study, thus CYP3A induction was not incorporated in the selpercatinib PBPK model. It should be noted that the single-dose and the multiple-dose PK profiles of 160-mg selpercatinib in healthy subjects (**Figure 19.17**) were used to optimize the parameter k_a and k_{inact}, respectively, in the model development process (**Table 19.8**). Therefore, the applicant was requested to provide further verifications to show the ability of the model to predict selpercatinib PK at doses other than the 160-mg dose and drug interaction with midazolam.*

*The model developed with clinical data from healthy subjects (**Table 19.8**) significantly overpredicted selpercatinib exposure (C_{max} and AUC) by 1.2 to 3.3- fold following multiple-dose administration of selpercatinib (20-240 mg BID) in cancer patients (data not shown, PBPK report loxo-292-dmpk-058 submitted by the Applicant on Feb 14, 2020 in response to the information request). It was observed that, at 160-mg, selpercatinib exposure in healthy subjects was higher than that in cancer patients, and*

*the difference between the observed and the predicted exposure in cancer patients was mainly driven by the overprediction of C_{max}. Assuming the exposure difference between the observed and the predicted in cancer patients was mostly due to overestimation of the fraction absorbed, f_a was reduced to 0.625 based on the C_{max} difference between the observed and the predicted at 160-mg BID. As a result, the predicted and observed profiles on Day 1 (data not shown, reviewer's analyses) and Day 8 (**Figure 19.18**) were superimposed, and predicted PK parameters were within the bioequivalent bounds for most of the doses ranging from 20 mg BID to 240 mg BID (**Table 19.11**). This modified model could be used to adequately predict the exposure of selpercatinib in cancer patients. The applicant was requested to adjust their PBPK model and predict the exposure and DDIs of selpercatinib in cancer patients using the modified model.*

2. Can PBPK analyses predict the effects of CYP3A inhibitors on the PK of selpercatinib?

Yes. CYP3A is solely responsible for the metabolism of selpercatinib. Based on results from the human ADME and absolute bioavailability studies, fraction metabolized by CYP3A was estimated to be 0.73. The predicted ratios of AUC and C_{max} of selpercatinib following a single dose of 160 mg selpercatinib in the presence vs. absence of itraconazole in healthy subjects were consistent with clinical observations (**Table 19.12**), confirming the contribution of CYP3A to selpercatinib disposition.

Following multiple-dose administration of 160-mg selpercatinib, the effects of itraconazole on selpercatinib AUC and C_{max} were comparable to that observed following a single dose of selpercatinib (**Table 19.13**). When 160-mg selpercatinib was co-administered with CYP3A inhibitors, the predicted AUC of selpercatinib was increased by 126 to 188% with strong CYP3A inhibitors (shaded in **Table 19.13**) and was increased by 60 to 99% with moderate CYP3A inhibitors (**Table 19.13**). The predicted steady-state AUC of selpercatinib was within 50% of that observed in cancer patients at 160-mg (**Table 19.11**) following dose adjustment to 80-mg or 120-mg when coadministration with a strong CYP3A inhibitor or moderate CYP3A inhibitor, respectively.

Table 19.12. Predicted and Observed drug interactions of selpercatinib in healthy subjects*

Dosing Regimens		$AUC_{0\text{-}inf}$ Ratio (GeoMean)			C_{max} Ratio (GeoMean)		
CYP3A Inhibitors	**Victims**	**Obs.**	**Pred.**	**Pred/obs**	**Obs.**	**Pred.**	**Pred/obs**
Itraconazole 200 mg QD 11d	selpercatinib 160 mg **SD** D5	2.33	2.13	0.91	1.30	1.28	0.98
Rifampin 600 mg QD 16d	selpercatinib 160 mg **SD** D10	0.13	0.13	1.00	0.30	0.35	1.17
Selpercatinib 160 mg BID 10d	**Midazolam po** 2 mg SD D10	1.54	2.16	1.40	1.39	1.75	1.26

*using the PBPK model shown in **Table 19.9** and sim-healthy subject population aged 24 -47, female ratio 0.42.

Source: PBPK report loxo-292-dmpk-058 submitted by the Applicant on Feb 14, 2020 in response to the information request

Table 19.13. Predicted effects of CYP3A inhibitors on selpercatinib PK and selpercatinib exposure in the presence of the inhibitors in cancer patients following multiple-dose administration of both selpercatinib and inhibitors

CYP3A inhibitors	Selpercatinib BID	$AUC_{tau,inh}$ (ng/mL.h)	$C_{max,inh}$ (ng/mL)	$C_{min,inh}$ (ng/mL)	AUC_{tau} Ratio	Cmax Ratio	Cmin Ratio

ITRA 200 mg QD	80 mg	25530	2512	1731	2.32	2.03	2.73
RTV 100 mg BID	80 mg	35172	3258	2582	3.19	2.63	4.06
CLAR 500 mg BID	80 mg	28423	2716	2011	2.58	2.19	3.16
Keto 400 mg QD	80 mg	35932	3332	2640	3.26	2.69	4.15
DTZ 60 mg TID	80 mg	19330	1954	1281	1.76	1.58	2.02
VER 80 mg TID	80 mg	24456	2385	1693	2.22	1.92	2.67
FLUC 200 mg QD	80 mg	22941	2255	1569	2.08	1.82	2.47
DTZ 60 mg TID	120 mg	29736	2994	1980	1.67	1.52	1.89
VER 80 mg TID	120 mg	37129	3613	2576	2.08	1.83	2.46
FLUC 200 mg QD	120 mg	36301	3541	2508	2.04	1.79	2.39
ITRA 200 mg QD	160 mg	57270	5521	3995	2.26	1.99	2.64
RTV 100 mg BID	160 mg	70443	6526	5172	2.77	2.35	3.40
CLAR 500 mg BID	160 mg	57656	5495	4092	2.27	1.97	2.69
Keto 400 mg QD	160 mg	73328	6782	5406	2.88	2.44	3.55
DTZ 60 mg TID	160 mg	40569	4070	2713	1.60	1.46	1.79
VER 80 mg TID	160 mg	50064	4864	3482	1.97	1.75	2.30
FLUC 200 mg QD	160 mg	50508	4896	3517	1.99	1.76	2.32

Multiple doses of selpercatinib were given twice daily for 24 days, and CYP3A inhibitors were given on Day 10 for 15 days. Sim-NEurCaucasian population aged 18 -90 with female ratio of 0.5 was used in these simulations. Geometric mean was reported. Strong CYP3A inhibitors are shaded.

Source: The applicant's response to information request on March 11, 2020.

3. Can PBPK analyses predict the effects of CYP3A inducers on the PK of selpercatinib?

Yes. The predicted ratios of AUC and C_{max} of selpercatinib following a single oral dose of 160-mg selpercatinib in the presence vs. absence of rifampin in healthy subjects were consistent with that observed in the clinical trial (**Table 19.12**).

Following multiple-dose administration of 160-mg selpercatinib, the predicted effects of rifampin on selpercatinib AUC and C_{max} were comparable to that observed following a single dose of selpercatinib (**Table 19.14**). When 160-mg selpercatinib was co-administered with CYP3A inducers, the predicted geometric mean AUC was decreased by 40 to 70% with moderate CYP3A inducers (bosentan and efavirenz) and was decreased by 33% with a weak CYP3A inducer (modafinil) (**Table 19.14**).

Table 19.14. Predicted effects of CYP3A inducers on selpercatinib PK and selpercatinib exposure in the presence of the inducers in cancer patients following multiple-dose administration of both selpercatinib and inducers

CYP3A inducers	Selpercatinib (BID)	$AUC_{tau,ind}$ (ng/mL.h)	$C_{max,ind}$ (ng/mL)	$C_{min,ind}$ (ng/mL)	AUC_{tau} Ratio	C_{max} Ratio	C_{min} Ratio
Rifampin 600 mg QD*	160 mg	3191	586	80	0.13	0.21	0.05
Modafinil 400 mg QD	160 mg	17231	2076	898	0.67	0.74	0.58
Bosentan 62.5 BID	160 mg	15242	1846	793	0.60	0.66	0.53

Bosentan 125 BID	160 mg	12074	1541	581	0.48	0.55	0.39
Bosentan 250 BID	160 mg	9233	1257	402	0.36	0.45	0.27
Efavirenz 500 mg QD*	160 mg	7764	1192	268	0.30	0.43	0.18

Multiple doses of selpercatinib were given twice daily for 24 days, and CYP3A inducers were given on Day 10 for 15 days except that modafinil 200 mg QD was given on Day 11 for 7 days followed by 400 mg QD for 7 days. Sim-NEurCaucasian population aged 18 -90 was used in these simulations.

Source: Reviewer's analyses (*) and the applicant's response to information request on March 11, 2020.

Reviewer's comment:

*Most of the CYP3A perpetrators (ITRA, RTV, Keto, CLAR, DTZ, VER, bosentan, efavirenz) used in this study are CYP3A substrates, thus mutual interactions are expected between these perpetrators and selpercatinib, a weak time-dependent inhibitor of CYP3A. The contribution of CYP3A to the disposition of these perpetrators in their PBPK models has not been verified except for bosentan (**Table 19.9**). Therefore, following multiple doses of selpercatinib, the effects of selpercatinib on these perpetrators may not be accurately predicted, which may, in turn, affect the predicted effects of these perpetrators on selpercatinib PK.*

*The predicted effects shown in **Table 19.12** and **Table 19.13** are considered applicable based on the observations that 1) results from the midazolam interaction study showed that, following multiple doses of 160-mg selpercatinib, selpercatinib had only a weak effect on midazolam (**Table 19.12**), a more sensitive CYP3A substrate than the perpetrators mentioned above. 2) the predicted effects of itraconazole on selpercatinib PK are similar following single and multiple doses of selpercatinib and are similar to that observed in the itraconazole DDI study (**Table 19.12**). These observations suggest that selpercatinib may not significantly alter the exposure of these CYP3A perpetrators and the predicted impacts of these CYP3A perpetrators on selpercatinib PK.*

Conclusions

The PBPK analyses are adequate to evaluate the effects of CYP3A inhibitors and inducers on the PK of selpercatinib.

- When 160-mg selpercatinib was co-administered with CYP3A inhibitors, the predicted geometric mean AUC was increased 126 to 188% by strong CYP3A inhibitors and was increased 60 to 99% by moderate CYP3A inhibitors (**Table 19.12**).
- When 160-mg selpercatinib was co-administered with CYP3A inducers, the predicted geometric mean AUC was decreased by 40 to 70% with moderate CYP3A inducers (bosentan and efavirenz) and was decreased by 33% with a weak CYP3A inducer (modafinil) (**Table 19.13**).

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19.4.6 Genomics Appendix

RET alterations in LIBRETTO-001: Patients were selected based on the presence of certain qualifying RET alterations. For RET fusions and NSCLC please refer to section 8. The section below summarizes the type of mutations identified in patients with advanced MTC (PAS (N=55) and treatment-naïve (N=88) subgroups).

RET mutation types and response in advanced MTC:
Per protocol, qualifying RET mutations were identified based on patients' documented results from local testing in CLIA-certified (or equivalent) laboratories by NGS (80%) (tumor (mainly), blood or plasma), PCR (17%) or by an unknown test (3%). Qualifying RET mutations included

mutations known to be activating. Synonymous, frameshift and nonsense mutations were excluded. Mutations with unknown status could be eligible in Phase 1 and, with Applicant's approval, in Cohort 5 of Phase 2. The protocol included an appendix with examples of qualifying activating mutations spanning from RET exons 5 to 16 (**Table 19.15**). Although both somatic and germline mutations were qualifying, the Applicant was unable to determine for most patients whether the patient's RET mutations were germline or somatic by reviewing molecular pathology reports and eligibility packets [response to an FDA information request (18 March 2020)].

Table 19.15: Examples of RET activating mutations per LIBRETTO-001 protocol

Exon	RET mutation
5	V292M, G321R
8	A510V, E511K, C515S, C531R, G533C
10	V591I, R600Q, K603E/Q, Y606C, C609F/G/R/S/W/Y, C611F/G/R/S/W/Y, C618F/G/R/S/W/Y,C620F/G/R/S/W/Y
11	C630R/Y, D631Y, E632K, C634F/G/R/S/W/Y, S649L, K666E/M
13	E768D, R770Q, N777S, V778I, Q781R, L790F, Y791F/N
14	V804L, V804M, Y806C, E819K, R833C, R844Q, R866W, M848T
15	L881V, A883F/S/T/V, R886W, S891A, S904F
16	S904C/F, G911D, R912P, M918T, E921K, S922P, T930M
Complex	D631del, E632-L633del, D898-E901del, E632-A639> HR
Other	Because the list of published activating *RET* mutations is constantly being updated, other mutations (e.g. other complex mutations, overlapping deletions, substitutions with different amino acids at the same site) may be eligible if a compelling rationale is provided by the Investigator and approved by the Sponsor.

Source: Applicant's Table 11-2-Appendix B, LIBRETTO-001 Clinical Protocol LOXO-RET-17001 [18 October 2018]

The number of patients and the number of responses (CR or PR) in subgroups defined by identified mutation(s) are summarized in **Table 19.16**. For analyses, the Applicant categorized RET mutations in 4 main types. The most common RET mutation in both PAS and treatment-naïve patients (N=143) was M918T (approximately 57.3%) in the tyrosine kinase domain, followed by mutations affecting cysteine residues within the extracellular domain (ECD) of RET (approximately 18.9%). These mutations are associated with hereditary MEN2B (M918T) and MEN 2A (cysteine ECD mutations) and are the most prevalent in sporadic MTC (Romei et al, 2016). Confirmed responses (CR or PR) were observed in both PAS and treatment-naïve patients with different RET mutations and across the 4 mutation types (**Table 19.16**), supporting the proposed broad target population [advanced RET-mutant MTC]. Of note, approximately 10% of patients had mutations that were not included in the protocol list (**Table 19.15**).

Table 19.16: IRC-Assessed Responses in patients with advanced MTC with RET mutations enrolled into LIBRETTO-001 (60-Day Update)

RET Mutation[1]	Number of patients (PAS)	Number of responses by IRC (ORR)	Number of patients (treatment naïve[2])	Number of responses by IRC (ORR)
Overall	**55**	**38 (69%)**	**88**	**64 (72.7%)**
RET Mutation Type				
M918T	**33**	**21 (63.6%)**	**49**	**39 (79.6%)**
Extracellular Cysteine Mutation[3]	**7**	**5 (71.4%)**	**20**	**12 (60%)**
C618Y	1	1	0	0
C618F/R/S	0	0	4	4
C620G	0	0	1	1
C620F/R/S	3	2	1	1
D627_L633delinsAH[§]	0	0	1	1
P628_L633del[§]	0	0	1	0
C630G[§]	1	1	0	0
C630R/Y	1	1	2	1
C634F/G/R/S/W/Y	0	0	10	4
Mutation at exon 10 splice variant [µ§]	1	0	0	0
V804M or V804L	**5**	**3 (60%)**	**6**	**3 (50%)**
V804L	1*	1	1	1
V804M	4	2	5	2
Other	**10**	**9 (90%)**	**13**	**10 (76.9%)**
D378_G385delinsE[§]	1	1	0	0
D631_L633delinsV[§]	1	1	1	0
D631_L633delinsE[§]	2	2	3	3
E632_L633del	1	1	3	2
T636_V637insCRT[§]	0	0	1	0
K666N[§]	1	1	0	0
L790F	0	0	2	2
A883F	2	1	2	2
D898_E901del	2	2	0	0
D898_E901del + D903_S904delinsEP[§]	0	0	1	1

Source: Reviewer table based on ADSL and ADRS [60-Day Update data cut (16 December 2019)] datasets, mutation types as categorized by the Applicant; **1**:Somatic or germline, protein change; **2**:Carbozantinib and vandetanib naïve; **3**:"Extracellular Cysteine Mutation" defined as involving at least one cysteine at C609, C611, C618, C620, C630, C634; **§**:Not included in the protocol list of qualifying mutations; **µ**:uncharacterized, predicted by the Applicant to lead to

the skipping of exon 10 and the disruption of disulfide bond formation; *:Patient also had a M918T mutation; del=deletion, ins=insertion; PAS: Primary Analysis Set; ORR: Objective Response Rate; Responses (CR or PR)

References

1.Romei C, Ciampi R, Elisei R. A comprehensive overview of the role of the RET proto-oncogene in thyroid carcinoma. Nat Rev Endocrinol. 2016 Apr;12(4):192-202.

19.5 Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
Please refer to Section 8 for a discussion of safety.

An analysis of adverse events using combined terms to accurately reflect the incidence of common adverse events was performed. The analysis of AEs occurring at an incidence of ≥ 15 % is included below, as reflected in the product label.

Table 19.17 Adverse Reactions (≥ 15%) in Patients Who Received Selpercatinib in LIBRETTO-001

Adverse Reaction	Selpercatinib (n = 702)	
	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal		
Dry Mouth	39	0
Diarrhea[1]	37	3.4*
Constipation	25	0.6*
Nausea	23	0.6*
Abdominal pain[2]	23	1.9*
Vomiting	15	0.3*
Vascular		
Hypertension	35	18
General		
Fatigue[3]	35	2*
Edema[4]	33	0.3*
Skin		
Rash[5]	27	0.7*
Nervous System		

Adverse Reaction	Selpercatinib (n = 702)	
	Grades 1-4 (%)	Grades 3-4 (%)
Headache[6]	23	1.4*
Respiratory		
Cough[7]	18	0
Dyspnea[8]	16	2.3
Investigations		
Prolonged QT interval	17	4*
Blood and Lymphatic System		
Hemorrhage[9]	15	1.9

[1]Diarrhea includes diarrhea, defecation urgency, frequent bowel movements, and anal incontinence
[2]Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain
[3]Fatigue includes fatigue, asthenia, malaise.
[4]Edema includes edema, edema peripheral, face edema, eye edema, eyelid edema, generalized edema, localized edema, lymph edema, scrotal edema, peripheral swelling, scrotal swelling, swelling, swelling face, eye swelling, peripheral swelling
[5]Includes rash, rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash pruritic
[6]Headache includes headache, sinus headache, tension headache
[7]Includes cough, productive cough
[8]Includes dyspnea, dyspnea exertional, dyspnea at rest
[9]Hemorrhage includes epistaxis, hematuria, hemoptysis, contusion, rectal hemorrhage, vaginal hemorrhage, ecchymosis, hematochezia, petechiae, traumatic hematoma, anal hemorrhage, blood blister, blood urine present, cerebral hemorrhage, gastric hemorrhage, hemorrhage intracranial, spontaneous hematoma, abdominal wall hematoma, angina bullosa hemorrhagica, diverticulum intestinal hemorrhagic, eye hemorrhage, gastrointestinal hemorrhage, gingival bleeding, hematemesis, hemorrhagic anemia, intraabdominal hemorrhage, lower gastrointestinal hemorrhage, melena, mouth hemorrhage, occult blood positive, pelvic hematoma, periorbital hematoma, pharyngeal hemorrhage, pulmonary contusion, purpura, retroperitoneal hematoma, subarachnoid hemorrhage, subdural hemorrhage, upper gastrointestinal hemorrhage, vessel puncture site hematoma
*Only includes a grade 3 adverse reaction.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Amy Skinner, Ph.D.	OOD/DHOT	Sections: 4.2, 5	**Select one:** X Authored ___ Approved
	Signature: Amy M. Skinner -S Digitally signed by Amy M. Skinner -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amy M. Skinner -S, 0.9.2342.19200300.100.1.1=2002675349 Date: 2020.05.04 18:23:38 -04'00'			
Nonclinical Team Leader	Whitney S. Helms, PhD	OOD/DHOT	Sections: 4.2, 5	**Select one:** X Authored X Approved
	Signature: Whitney S. Helms -S Digitally signed by Whitney S. Helms -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9 2342.19200300.100.1.1=2000585776, cn=Whitney S. Helms -S Date: 2020.05.04 10:16:28 -04'00'			
Nonclinical Team Division Director	John K. Leighton, Ph.D., DABT	OOD/DHOT	Sections: 4.2, 5	**Select one:** ___ Authored X Approved
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Clinical Pharmacology Team Leader	Jeanne Fourie Zirkelbach	OCP/DCPII	Sections: 6, 19	**Select one:** ___ Authored X Approved
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Genomics Reviewer	Rosane Charlab Orbach	OCP/DTPM/ Genomics	Sections: 6, Appendix 19.4.6	**Select one:** _X_ Authored ___ Approved
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DTPM/Genomics Division Director	Michael A. Pacanowski	OCP/DTPM/ Genomics	Sections: 6, Appendix 19.4.6	**Select one:** ___ Authored _X_ Approved
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Pharmacometrics Reviewer	Yangbing Li	OCP/DPM	Sections:6, 19.4	**Select one:** _X_ Authored ___ Approved
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Pharmacometrics Team Leader	Jiang Liu	OCP/DPM	Sections:6, 19.4	**Select one:** _X_ Authored _X_ Approved
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PBPK Reviewer	Xinyuan Zhang	OCP/DPM	Sections: 19.4.5	**Select one:** _X_ Authored ___ Approved
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PBPK Team Leader	Yuching Yang	OCP/DPM	Sections: 19.4.5	**Select one:** ___ Authored X Approved
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Clinical Reviewer	Diana Bradford	OOD/DO2	Sections: 1, 2, 3, 7, 8, 9, 10, 11, 12, 13, 19.5 Section 4: summarized issues from other disciplines	**Select one:** X Authored ___ Approved
	Signature: Diana L. Bradford -S Digitally signed by Diana L. Bradford -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001559418, cn=Diana L. Bradford -S Date: 2020.05.06 19:51:22 -04'00'			

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Statistical Reviewer	Sirisha Mushti	OTS/OB/DBV	Sections: 7, 8.1 and 8.3	**Select one:** X Authored X Approved
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Statistical Team Leader	Lisa Rodriguez	OTS/OB/DBV	Sections: 7, 8.1 and 8.3	**Select one:** ___ Authored X Approved
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Division Director (OB)	Shenghui Tang	OTS/OB/DBV	Sections: 7, 8.1 and 8.3	**Select one:** ___ Authored X Approved
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Associate Director for Labeling (ADL)	Stacy S. Shord, Pharm.D.	OOD IO	Sections: 11	**Select one:** ___ Authored X Approved

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Cross-Disciplinary Team Leader (CDTL)	Diana Bradford	OOD/DO2	Sections: All (Serving as clinical reviewer and CDTL. See also "Clinical Reviewer" for sections authored)	**Select one:** ___ Authored X Approved
	Signature: Diana L. Bradford -S Digitally signed by Diana L. Bradford -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001559418, cn=Diana L. Bradford -S Date: 2020.05.06 19:52:05 -04'00'			
Division Director (Clinical)	Harpreet Singh	OOD/DO2	Sections: All	**Select one:** X Authored X Approved
	Signature: Bonnie H. Moore -S Digitally signed by Bonnie H Moore S DN: c US o U S Government ou HHS ou FDA ou People 0 9 2342 19200300 100 1 1 2001042285 cn Bonnie H Moore S Date: 2020 05 07 13:22:39 04'00'			

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B HARPREET SINGH
05/08/2020 09:10:21 AM

MARC R THEORET
05/08/2020 10:47:16 AM
My signature indicates that I have considered the assessments and recommendations included in this Review in determining the regulatory action.