

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213246Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

<input checked="" type="checkbox"/> Approval
<input type="checkbox"/> Approval with Post-Marketing Commitment
<input type="checkbox"/> Complete Response

NDA 213246 Assessment #1

Drug Product Name	Retevmo (selpercatinib)
Dosage Form	Capsules
Strength	40 mg and 80 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Loxo Oncology, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA	12/04/2019	All
Quality Amendment	12/17/2019	OPMA
Quality Amendment	01/10/2020	DP
Quality Amendment	01/29/2020	OPMA
Quality Amendment	02/11/2020	OPMA
Quality Amendment	02/25/2020	DP
Quality Amendment	03/03/2020	DP
Quality Amendment	03/10/2020	DS
Labeling Amendment	03/20/2020	DP
Quality Amendment	04/01/2020	DP, BIOPHARMA

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Rohit Tiwari	Ali Al Hakim
Drug Product	Tefsit Bekele	Anamitro Banerjee
Manufacturing	Yifan Wang	Zhaoyang Meng
Microbiology	Yifan Wang	Zhaoyang Meng
Biopharmaceutics	Qi Zhang	Banu Zolnik
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xing Wang	
Laboratory (OTR)	N/A	N/A
Environmental	James Laurenson	N/A



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EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

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 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 °F); excursions permitted to 15-30 °C (59°F - 86°F) [See USP Controlled Room Temperature]”. In addition, OPQ grants a (b) (4) re-test period for the drug substance when stored at (b) (4)

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Selpercatinib is a RET receptor kinase inhibitor. Two (b) (4) forms of selpercatinib (b) (4) were discovered. (b) (4)

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

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 (b) (4) with microcrystalline cellulose and colloidal silicon dioxide. Selpercatinib capsules are manufactured (b) (4) (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.

<p>Proposed Indication(s) including Intended Patient Population</p>	<p>Indicated for the treatment of adult (b) (4) patients with:</p> <ul style="list-style-type: none"> • metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy and have progressed following platinum-based chemotherapy and an anti-PD-1 or anti-PD-L1 therapy, • RET-mutant medullary thyroid cancer (MTC) who require systemic therapy, have progressed following prior
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	treatment and have no acceptable alternative treatment options
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	160 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

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)

(b) (4) The manufacturing process description is provided (b) (4) drug substance. 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 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)

(b) (4) The applicant proposed a retest period of (b) (4) based on the stability data when stored (b) (4) and based on the provided that this retest period is acceptable.

Drug Product: Adequate

Retevmo is supplied as 40 mg or 80 mg capsules in HDPE bottles. The drug product is formulated as (b) (4) selpercatinib drug substance 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 are

(b) (4) The drug substance, selpercatinib (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.

Labeling: Adequate

All CMC comments/edits have been conveyed to OND and the applicant.

Manufacturing: Adequate

(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. (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: Adequate

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 (b) (4) 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.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, Stability	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	L		L	
Physical Stability (solid state)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	M	(b) (4)	L	
Content Uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	L		L	
Dissolution – BCS Class II	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	L		L	

Application Technical Lead Name and Date: Xing Wang, Ph.D.



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QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	IV		(b) (4)	Adequate	03/16/2020	DMFs not reviewed per MAPP 5015.5 (Rev. 1).
	IV		Adequate			
	III		Adequate			
	III		Adequate			
	III		Adequate			

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	(b) (4)	Drug development

2. CONSULTS None



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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Retevmo	Adequate
Established name(s)	Selpercantib	Adequate
Route(s) of administration	For oral use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	40 mg 80 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Capsules	Adequate
Strength(s) in metric system	40 mg and 80 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Capsules: <ul style="list-style-type: none"> • 40 mg, gray opaque capsule imprinted with "Lilly", "3977" and "40 mg" in black ink. • 80 mg, blue opaque capsule imprinted with "Lilly", "2980" and "80 mg" in black ink. 	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Retevmo and selpercatinib	Adequate
Dosage form(s) and route(s) of administration	Capsules for oral administration	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	<p>RETEVMO (selpercatinib) is supplied as 40 mg or 80 mg hard gelatin capsules for oral (b) (4)</p> <p>(b) (4) inactive ingredients: microcrystalline cellulose and silicon dioxide. (b) (4)</p> <p>(b) (4)</p>	<p>Change to: RETEVMO (selpercatinib) is supplied as 40 mg or 80 mg hard gelatin capsules for oral (b) (4). Each capsule contains inactive ingredients of microcrystalline cellulose and silicon dioxide. The capsule shell is composed of gelatin, titanium dioxide (b) (4)</p> <p>(b) (4) the 40 mg capsule shell consists of ferric oxide, black (b) (4) and the 80 mg capsule shell consists of FD&C blue #1. The black ink is composed of shellac, (b) (4)</p> <p>(b) (4) potassium hydroxide, ferric oxide, (b) (4) black (b) (4).</p>
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH	N/A	

or make isotonic, include the name and statement of effect.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Pharmacological/therapeutic class	Kinase inhibitor	Adequate
Chemical name, structural formula, molecular weight	<p>Chemical name: 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</p> <p>Structural formula: provided</p> <p>Molecular weight: 525.61 g/mol</p>	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	<p>Selpercatinib is a white to light yellow powder that is slightly hygroscopic. The aqueous solubility of selpercatinib is pH dependent.</p> <p>(b) (4) is (b) (4)</p>	Adequate
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Capsules	Adequate
Strength(s) in metric system	40 mg and 80 mg	Adequate
Available units (e.g., bottles of 100 tablets)	40 mg: bottles of 60 capsules 80 mg: bottles of 60 capsules and bottles of 120 capsules	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	<ul style="list-style-type: none"> • 40 mg, gray opaque capsule imprinted with “Lilly”, “3977” and “40 mg” in black ink; available in bottles of 60 capsules (NDC# 0002-3977-60). • 80 mg, blue opaque capsule imprinted with “Lilly”, “2980” and “80 mg” in black ink; available in bottles of 60 capsules (NDC# 0002-2980-60) or bottles of 120 capsules (NDC# 0002-2980-26). 	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F)	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	N/A	Not relevant for oral dosage forms
Include information about child-resistant packaging	Not provided	(b) (4)

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	(b) (4)	Applicant will be requested to provide a complete address

2.0 PATIENT LABELING

Assessment patient Labeling: Patient Labeling is adequate from the product quality perspective.

3.0 CARTON AND CONTAINER LABELING

Cartons are not used in the packaging of selpercatinib. The container labels are shown below.

3.1 Container Label



Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Provided	Adequate
Dosage strength	Provided	Adequate
Route of administration	Not provided	Not critical for oral drugs
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	Provided	Adequate
"Rx only" displayed on the principal display	Provided	Adequate
NDC number	Provided	Adequate
Lot number and expiration date	Space provided	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Storage conditions provided	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Provided	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Provided	Adequate
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap over seal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: Adequate

Overall Assessment and Recommendation:

The container label and prescribing information comply with all regulatory requirements and they are recommended for approval from a CMC perspective pending revision of what are noted in the Assessor's Comments column above.

Primary Labeling Assessor Name and Date: Tefsit Bekele 3/16/2020

Secondary Assessor Name and Date Anamitro Banerjee 3/17/2020



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Banerjee

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	213246
Assessment Cycle Number	1
Drug Product Name/ Strength	Retevmo™ (selpercatinib), 40 mg and 80 mg capsules
Route of Administration	Oral (160 mg orally twice daily; with or without food)
Applicant Name	Loxo Oncology, a wholly owned subsidiary of Eli Lilly and Company
Therapeutic Classification/ OND Division	Oncology OND/OOD/DO2
RLD/RS Number	This is 505 b (1)-NME
Associated INDs	IND 133193; IND 142299
Proposed Indication	For the treatment of metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC); and RET-mutant medullary thyroid cancer (MTC).
Primary Reviewer	Qi Zhang, Ph.D.
Secondary Reviewer	Banu Zolnik, Ph.D.
Assessment Recommendation	Adequate

Assessment Summary:

1) Dissolution Method and Acceptance Criterion:

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 ^(b)/₍₄₎

Approved dissolution method and acceptance criterion for Retevmo™ (selpercatinib), 40 mg and 80 mg capsules				
USP Apparatus	Speed	Medium	Volume/Temp	Acceptance Criterion
2 (Paddle)	75 rpm	0.1 N HCl	900 mL/37°C	NLT ^(b) / ₍₄₎ % (Q) at 15 minutes

2) Biopharmaceutics Risk Assessment:

The initial risk deemed dissolution as “Moderate” from a Biopharmaceutics standpoint, since the drug substance has pH-dependent solubility and low solubility at higher pH ^(b)/₍₄₎. In addition, the drug substance exhibits polymorphism. The Applicant has included drug substance particle size acceptance criteria ^(b)/₍₄₎.
^(b)/₍₄₎ The risk can be further mitigated with the implementation of the dissolution specification for the proposed drug product.

3) Bridging Throughout Product Development:

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.

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Original Submission	12/04/2019
Response to Information Request	2/25/2020
Response to Information Request	4/2/2020

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

None.

B.1 BCS DESIGNATION

Assessment: Not submitted nor required

(b) (4)

Permeability: The permeability of selpercatinib is not reported by the Applicant. The absolute bioavailability of selpercatinib was 73 ^(b)₍₄₎%, per the proposed labelling.

Dissolution: The proposed selpercatinib 40 mg and 80 mg capsules are very rapidly dissolving in 15 minutes using the proposed dissolution method.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *Adequate*

Dissolution Method Development: The optimal dissolution method parameters, e.g., apparatus 2 (paddles) and agitation speed of 75 rpm, and dissolution medium (0.1 N HCl), were identified as summarized in the Dissolution Overview in Section 2.7.1 and the Dissolution Development Report in Section 3.2.P.2.3.1.5.

(b) (4)

Discriminating Capability of Dissolution Method:

The proposed dissolution method lacks discriminating power toward particle size of drug substance, (b) (4) and manufacturing process variables, due to the high solubility of the drug substance and very rapid dissolution of the drug product in the proposed dissolution medium.

Data from Manufacturing Process Assessment Study: A manufacturing process risk assessment was conducted to investigate manufacturing process parameters (b) (4)

The dissolution data showed that all the capsules batches tested in this study dissolve very rapid.

API Particle Size: The proposed dissolution method can't differentiate toward API particle size, i.e., between the capsules manufactured with the (b) (4) μm drug substance and capsules with (b) (4) particle size (b) (4) μm drug substances (Table 2 and Figure 4a). The Applicant has included a one tier particle size control D90 NMT (b) (4) μm in the drug substance specification.

Stability: The Applicant showed no difference between the dissolution of selpercatinib 80-mg capsules stored for 6 months under accelerated conditions of 40°C/75%RH and the dissolution at 25°C/60%RH for 24 months, and both stability samples dissolve very rapid (b) (4)

Validation of Dissolution Method:

An UPLC assay method (with UV detection at 260 nm) is used to quantify the drug in the dissolution samples. The Applicant reported that the UPLC method was validated with regard to

specificity, linearity, accuracy/recovery, precision, (b) (4), solution stability, and sink conditions, and robustness with respect to UPLC system changes. Refer to the Drug Product Review, for the evaluation of the adequacy of the analytical method validation (including the UPLC method used for dissolution testing).

Dissolution Acceptance Criterion:

The proposed selpercatinib capsules dissolve very rapid and complete for both 40 mg and 80 mg using the proposed dissolution method. The proposed dissolution acceptance criterion of NLT (b) (4)% (Q) in 15 minutes for batch release and stability testing is acceptable. The summary of dissolution profile data generated using the clinical batches and primary stability batches (N = 12) and dissolution datasets (SAS file) are provided in 3.2.P.5.4.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE

CRITERIA (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Assessment: Adequate

Data Evaluating the PK of Different Formulation Variants

Two formulations containing different particle size drug substance lots were evaluated in the BA PK study (LOXO-RET-17001). One formulation was a (b) (4) in capsule using (b) (4) drug substance (D90 = (b) (4) μm). The other formulation was a (b) (4) in capsule formulation using (b) (4) drug substance (D90 = (b) (4) μm). Both formulations were shown to produce similar pharmacokinetic profiles in patients (Figure 5), despite the significant difference in drug substance particle size and the change in formulation.

(b) (4) the proposed release method of 0.1N HCl medium (900 mL in apparatus II at 75 rpm), provide similar relative drug product performance in vitro (b) (4) as is observed in vivo regardless their respective drug substance particle size, while the difference in dissolution at (b) (4) (e.g. pH (b) (4) between the selpercatinib capsules containing different drug substance particle size (D90 = (b) (4) μm vs. D90 = (b) (4) μm) is unlikely to impact in vivo performance, based on the results of the clinical BA PK data.

Physiologically-Based Pharmacokinetics (PBPK) Model

Although, the PBPK model and additional data are deemed not necessary, below is the summary of the PBPK model submitted in the application.

(b) (4)

In addition, the proposed dissolution method and acceptance criterion are deemed acceptable, and the PBPK model was not used as a supportive evidence to accept the proposed dissolution acceptance criterion. Therefore, this Reviewer did not evaluate the PBPK modeling and Division of Biopharmaceutics PBPK committee agreed with this decision and thus did not request the simulation datasets during the review of this NDA. An IR comment was conveyed to the Applicant stating that if in the future the Applicant plans to use this PBPK model to support any post-marketing changes, then the Applicant should submit a complete PBPK report along with all Simcyp files for FDA's review and evaluation.

B.4 BRIDGING OF FORMULATIONS

Assessment: 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.

B.5 BIOWAIVER REQUEST

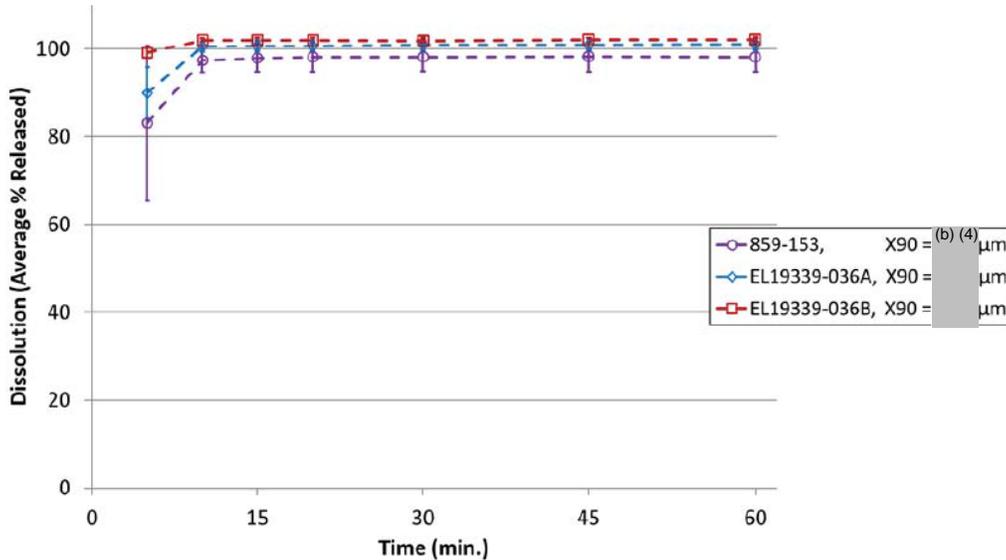
Assessment: Biowaiver is not required since both strengths are used in the clinical studies.

Table 2: Summary of Drug Product Lot and Drug Substance Batch Numbers and Particle Sizes for Drug Substance Particle Size Study

Product Batch Number	Drug Substance Lot Number	Drug Substance Process	(b) (4)	Content (%)	API x90 (µm)
859-153	A0007842 ¹	(b) (4)	(b) (4)	(b) (4)	(b) (4)
EL19339-036A	18-547M-001-181428	(b) (4)	(b) (4)	(b) (4)	(b) (4)
EL19339-036B	19-547-003 ²	(b) (4)	(b) (4)	(b) (4)	(b) (4)
1 (b) (4)					
2 (b) (4)					

Source: Laboratory Notebook AON-H81023-094

Figure 4a: Dissolution Profiles of 80-mg Capsules with Various Drug Substance Particle Size in the Proposed dissolution Medium (0.1 N HCl)



Method conditions: 900 mL media with USP Apparatus 2 at 75 rpm. (b) (4)
 . Error bars represent standard deviations for n = 3.

Figure 5: Mean Plasma Concentration for (b) (4) Selpercatinib in Two Different Drug Product Formulations After Administration of a 40-mg Dose BID on Day 1 and Day 8 in Cycle 1 of Study LOXO-RET-17001.

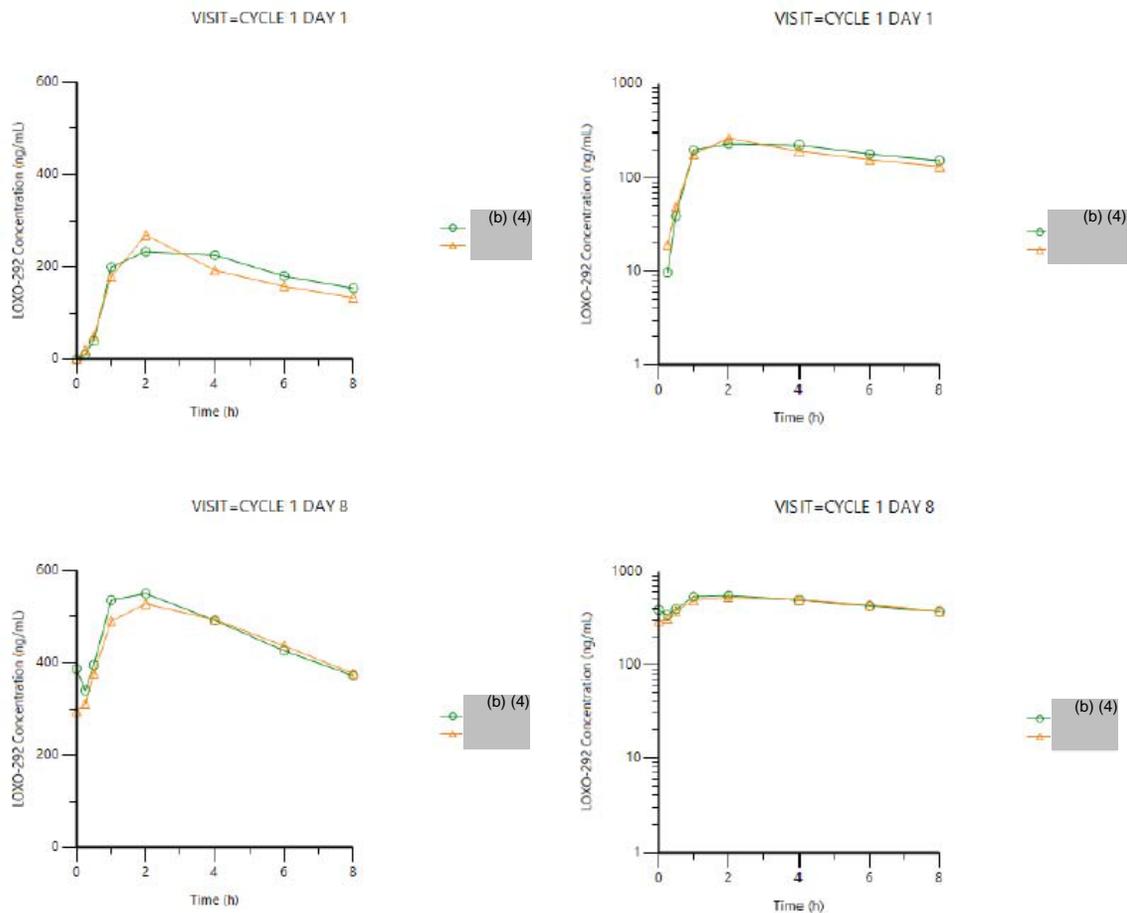


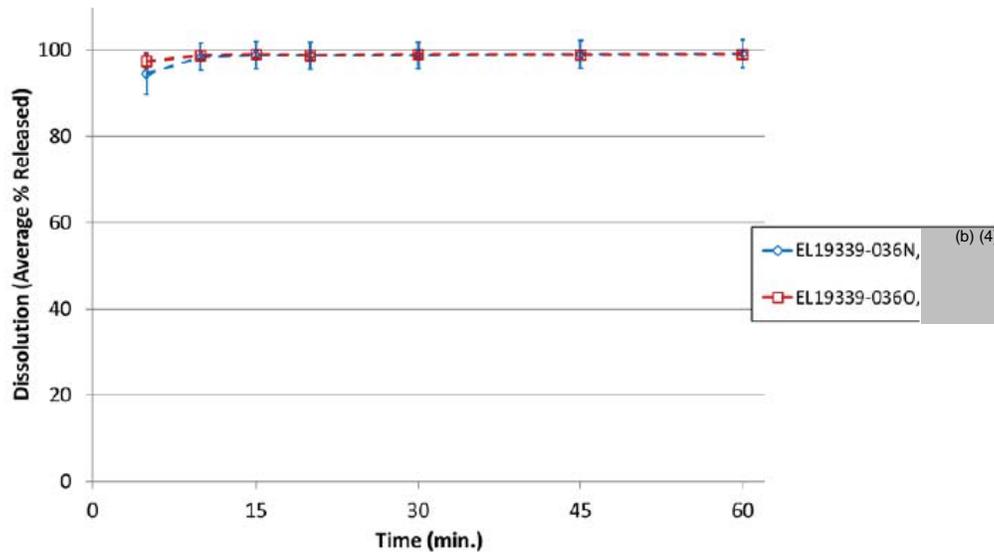
Table 3: Summary of Drug Product Lot and Drug Substance Batch Numbers and Particle Sizes for Drug Substance (b) (4) Study

Drug Product Batch Number	Drug Substance Lot Number	(b) (4) Fraction (%)	API X90 (µm) ¹
EL19339-036N	19-547M-002-191059	(b) (4)	(b) (4)
EL19339-036O	AQQ-H81549-046-PCB ²	(b) (4)	(b) (4)

1 (b) (4)

2 (b) (4)

Figure 6: Dissolution Profiles of 80-mg Capsules Containing (b) (4) Using the Proposed Dissolution Method (0.1 N HCl)



Method conditions: (b) (4)

Error bars represent standard deviations for n = 3.



Qi
Zhang

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Banu
Zolnik

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Date: 3/31/2020 10:35:13AM

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XING WANG
04/02/2020 12:20:26 PM