CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218160Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA	NDA 218160 (SDN 01)
Link to EDR	\\CDSESUB1\EVSPROD\nda218160\0001\m1\us\cover.pdf
Applicant	Loxo Oncology/ subsidiary of Eli Lilly and Company
Submission Date	06/13/2023
Submission Type	NDA 505(b)(1)
Brand Name	RETEVMO®
Generic Name	Selpercatinib
Dosage Form and Strength	Tablets, 40 mg, 80 mg, 120 mg, and 160 mg
Route of Administration	Oral
Indications	• Treatment of Adult patients with locally advanced or metastatic NSCLC with a rearranged during transfection (RET) gene fusion. • Treatment of Adult and pediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a RET mutation • Treatment of Adult and pediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with a RET gene fusion • Treatment of Adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options
Recommended Dosages	• Less than 50 kg: 120 mg orally twice daily • 50 kg or greater: 160 mg orally twice daily
OCP Reviewer	Om Anand, Ph.D.
Master Pharmacokineticist and OCP Secondary Review	Jeanne Fourie Zirkelbach, Ph.D.
Consult	Ethan Stier, Ph.D.
CDTL	Jeanne Fourie Zirkelbach, Ph.D.
OCP Final Signatory	Nam Atiqur Rahman, Ph.D.

I. BACKGROUND and EXECUTIVE SUMMARY

Selpercatinib is a kinase inhibitor. Selpercatinib (RETEVMO®), is currently available as hard gelatin capsules of 40 mg and 80 mg strengths. The Applicant submitted this New Drug Application (NDA) in support of a new immediate release tablet formulation of Retevmo® (Selpercatinib Tablets, 40 mg, 80 mg, 120 mg, and 160 mg). The proposed indications for the tablet formulation are unchanged from those approved for use with the commercial capsule formulation.

This NDA includes data from two clinical studies, in healthy subjects, a bioequivalence (BE) study, Study J2G-MC-JZJZ (JZJZ) and a food-effect study, Study J2G-MC-JZPA (JZPA).

Clinical pharmacology reviewed the results of the BE study (JZJZ) and the food-effect study (JZPA) as well as the rationale for administration of selpercatinib tablets with food when coadministered with a proton-pump inhibitor.

The BE study (JZJZ) demonstrated bioequivalence between the tablet (1 × 160-mg tablet) and the capsule (2 × 80 mg) formulations in healthy participants. The 94.12% CI (accounting for a 2-stage adaptive trial design) for the ratios of the geometric least squares mean $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max} were contained within the prespecified limits of 80% to 125%.).

Based on in vivo BE study, the approved selpercatinib capsule (80- mg capsule) formulation is adequately bridged with the proposed selpercatinib tablet (160-mg tablet) formulation.

Based on the food-effect study (JZPA), no clinically significant differences in selpercatinib AUC or Cmax were observed following administration of a high-fat meal compared to the fasted state in healthy subjects. When administered with a high-fat meal, the AUC(0-∞) and AUC(0-tlast) for selpercatinib tablets was decreased by 5.1% and 4.8%, respectively, compared with the fasted state. When administered with a high-fat meal, the Cmax of selpercatinib tablets decreased by 17.1% compared with the fasted state.

Based on these results selpercatinib tablets may be administered with or without regard to food, unless coadministered with a proton-pump inhibitor (PPI).

A biowaiver was requested for tablet strengths of 40 mg, 80 mg, and 120 mg based on results for the highest strength (160 mg), formulation proportionality, dissolution profiles, and pharmacokinetic dose proportionality. The Division of Biopharmaceutics/OPQ concluded that the information provided in the submission (in vitro dissolution profile similarity, PK linearity, dose proportionality and formulation compositional similarity of the lower strengths to the BE strength 160 mg) supports the biowaiver request for the proposed lower strengths (40 mg, 80 mg, and 120 mg) of selpercatinib tablets, under 21CFR§ 320.22 (d)(2). Taken together, based on review of the combined results from the biopharmaceutics comparison and demonstrated BE between the tablet (160 mg) and the approved capsule (2 x 80 mg) formulations in the current submission, and the in vivo drug-drug interaction study with gastric acid reducing agents reviewed in the original NDA 201346, there is no scientific rationale to expect a different PPI mitigating effect of food when

selpercatinib is dosed as a tablet compared to the approved capsule formulation. Therefore, if coadministration of a PPI is required, selpercatinib tablets should be taken with food, similar to the approved capsule formulation.

II. NDA REVIEW

1. Fasting BE Study J2G-MC-JZJZ (JZJZ): Study to evaluate the bioequivalence (BE) of Selpercatinib formulations

Title: An Open-Label, Randomized Study to Evaluate the Bioequivalence of Selpercatinib Formulations

Design: a Phase 1 open-label, randomized, 2-period, 2-formulation, 2-sequence, 2-stage adaptive crossover study in adult heathy male and female participants (Figure 1). This study was conducted at 4 centers that enrolled 224 participants in the United States.

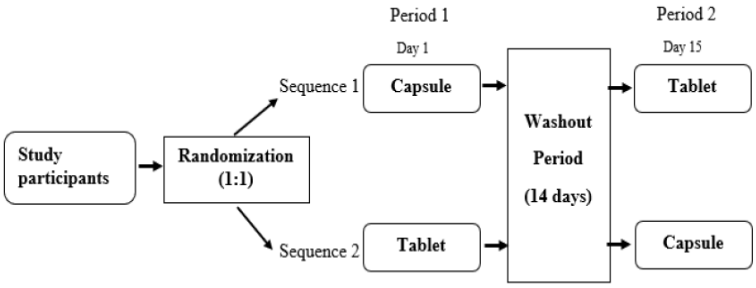
Participants were randomized to receive a single oral dose of 160 mg selpercatinib as the capsule or tablet formulation on Day 1. Participants were dosed following an overnight fast of at least 10 hours. Participants remained resident at the CRU until discharge on Day 7.

Participants received their second single oral dose of 160 mg selpercatinib as the capsule or tablet formulation on Day 15, following an overnight fast of at least 10 hours. Participants remained resident at the CRU until discharge on Day 21.

There was a washout of at least 14 days between doses of selpercatinib.

In Stage 1 only, on Day 1, participants had a nasogastric (NG) tube placed in the stomach prior to dosing to assess gastric pH.

Figure 1: Study design for JZJZ



Blood samples were collected for PK assessments. Safety assessments, including adverse events, concomitant medications, medical assessments, clinical laboratory tests, vital signs, and electrocardiograms (ECGs), were performed.

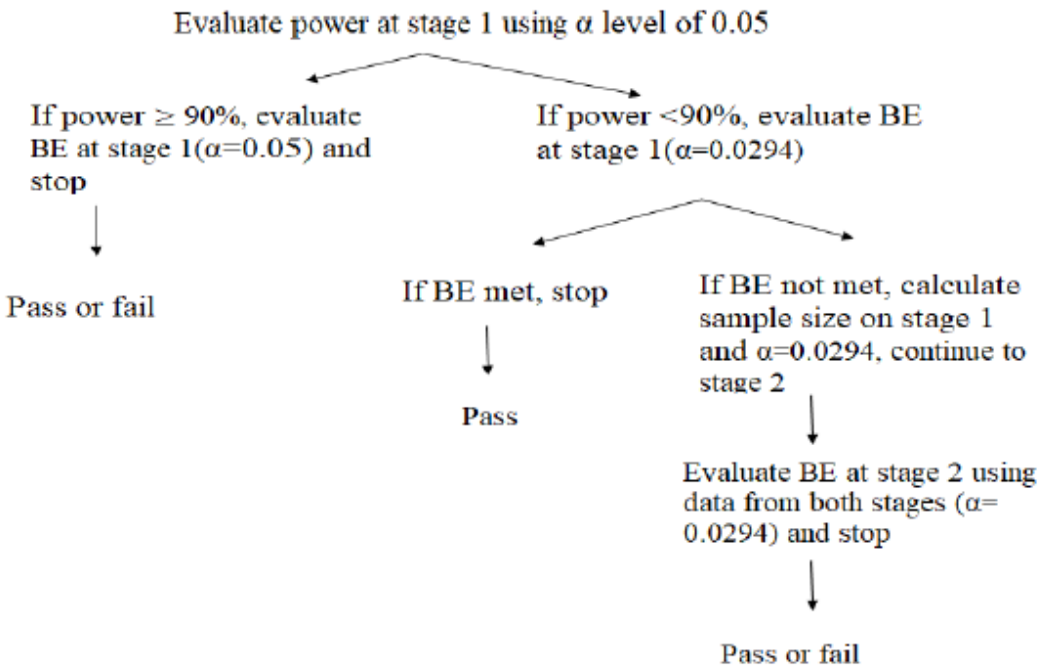
A 2-stage adaptive design was used to evaluate the BE of selpercatinib formulations because the intra-participant variability for Cmax was not well established. Stage 1 determined the intra-participant variability for Cmax and AUC, and the required sample size for Stage 2.

Since at Stage 1, power was less than 90%, BE was tested at an alpha level of 0.0294 and was not met for Cmax, as the 94.12% CI of the ratio of the geometric least squares mean of Cmax was

between 84.0% and 126.0%. Therefore, the study proceeded to Stage 2.

The intra-participant variability for Cmax in Stage 1 was 59.1%. Based on this, a total of 202 participants across Stages 1 and 2 were expected to provide approximately 90% power to meet BE criteria at a 2-sided alpha level of 0.0294, under an assumption of a tablet-to-capsule geometric mean ratio of 1.05. Following the completion of Stage 2, BE was evaluated using data from both stages of the study at an alpha level of 0.0294.

Figure 2: Adaptive sequential design method C (Potvin 2008).



Abbreviation: BE = bioequivalence.

Reviewer's comments on design: *The Applicant used an adaptive design (Potvin Method C) because of high intrasubject variability. Potvin Method (Potvin et al. 2008) is provided as one of the methods mentioned in the FDA draft guidance*[1]*. The Applicant provided details of the adaptive design in the protocol prior to initiation of the study. The use of adaptive design to evaluate the BE of selpercatinib under fasting conditions is acceptable.*

[1] Statistical Approaches to Establishing Bioequivalence Guidance for Industry, Dec 2022, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/statistical-approaches-establishing-bioequivalence

Number of Participants:

Number planned: 50 participants (Stage 1) and 146 (Stage 2)

Number who received at least 1 dose: 224 participants

Number who received all planned doses: 204

Number completed the study: 196

Diagnosis and Main Criteria for Inclusion and Exclusion:

At the time of signing the informed consent form at screening, participants were required to be

- overtly healthy males or females
- aged between 18 and 65 years, inclusive, and
- with a body mass index (BMI) of 19.0 to 35.0 kg/m2, inclusive.

Study Interventions, Dose, and Mode of Administration

On Days 1 and 15, participants received each of the following treatments once according to the randomization scheme:

- Selpercatinib oral 160 mg as 2 × 80-mg Capsules, and
- Selpercatinib oral 160 mg as 1 × 160-mg Tablet

Duration of Study Intervention:

Participants participated in 1 stage of the study only. Study duration for each participant was approximately 56 days, which included a screening period, 2 treatment periods, and a 14-day washout period between doses.

Demographic and Other Baseline Characteristics:

Of the 224 participants enrolled:

- 118 (52.7%) were male and 106 (47.3%) were female,
- Mean age was 42.5 years
- Mean body weight was 80.20 kg
- Mean BMI was 27.83 kg/m^2.

Bioanalytical Assay and Validation

A single bioanalytical method (TM17-410, described in method validation report AV17-LOXO292-01) was used to quantify selpercatinib in human plasma collected from all clinical studies included in the original selpercatinib submission. Method TM17-410 was revalidated to update the validation assay range to 10.0 to 10000 ng/mL (renamed method TM19-544). TM19-544 is a liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method validated to selectively measure selpercatinib in human plasma using K2EDTA as the anticoagulant. A validated Method TM19-544 was used to measure selpercatinib in human plasma in support of Studies JZJZ and JZPA.

Two bioanalytical reports entitled Clinical Bioanalytical Contributor Report for LY3527723 in Study J2G-MC-JZJZ and Clinical Bioanalytical Contributor Report for LY3527723 in Study J2G-MC-JZPA are included in the submission.

All samples for the bioanalytical phase of Study JZJZ were analyzed within 250 acceptable runs for selpercatinib. Calibration standard data, QC sample data, incurred sample reproducibility data, and chromatograms indicate that the method performed acceptably during the sample analysis. All samples for the bioanalytical phase of Study JZPA were analyzed within 29 runs for selpercatinib. Calibration standard data, QC sample data, incurred sample reproducibility data, and chromatograms indicate that the method performed acceptably during the sample analysis.

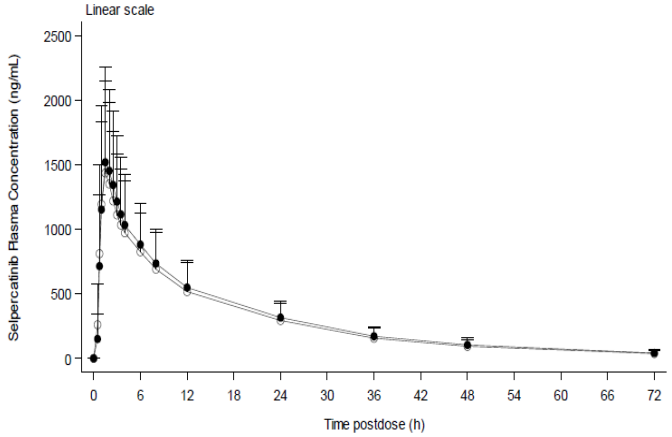
Reviewer's comment: *The Applicant provided bioanalysis results for Quality Control, Calibration, and Incurred Sample Reanalysis runs. The bioanalysis runs met the acceptance criteria as provided in FDA's Bioanalytical Method Validation Guidance for Industry. The Applicant provided summary which identified the root cause of a few failure-runs. Analytical runs were repeated, and reportable data obtained. Incurred sample re-analysis was performed, and 93.9% and 92.6 % of the samples met the pre-specified criteria for study JZJZ and JZPA respectively.*

Given that the bioanalysis runs met acceptance criteria per FDA Guidance, the overall bioanalysis submission for Studies JZJZ and JZPA is acceptable.

Results of fasting BE study JZJZ (PK):

The mean plasma concentration versus time profiles of selpercatinib dosed as 2 × 80-mg capsules or 1 × 160-mg tablet are shown in Figure 3.

Figure 3: Arithmetic mean plasma concentration profile of 160 mg selpercatinib when dosed as 2 × 80-mg capsules or 1 × 160-mg tablet (Study JZJZ).



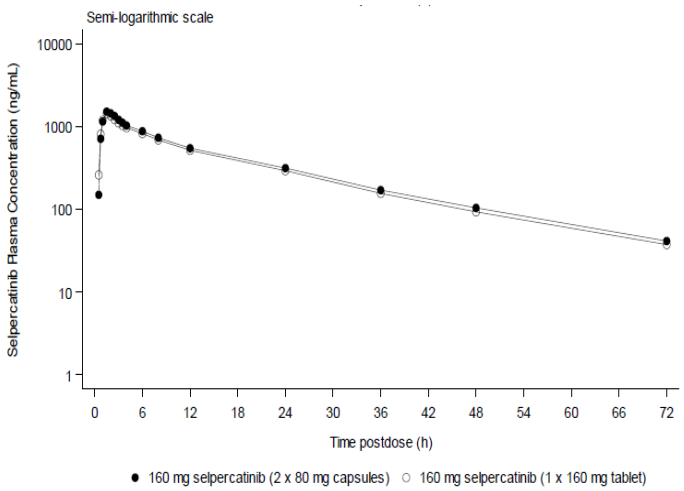


Table 1. Summary of Bioequivalence Study J2G-MC-JZJZ

Study Identifier	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. [M/F]) Type Mean Age (Range)	Geometric Mean (CV [%]) of Parameter Estimates						Study Report Location
					C_{max} (ng/mL)	t_{max}[a] (h)	AUC(0-t_{last}) (ng.h/mL)	AUC(0-∞) (ng.h/mL)	$t_{1/2}$[b] (h)	CL/F (L/hr)	
J2G-MC-JZJZ	To evaluate the bioequivalence of a single 160-mg dose of selpercatinib as the tablet formulation compared to the commercial capsule formulation	Open-label, randomized, 2-period, 2-formulation, 2-sequence, 2-stage adaptive crossover study in adult heathy participants	Tablet formulation: 1×160-mg, tablet on Days 1 or 15, oral, D431420	112 (59/53), healthy participants, mean age 42.8 years (20-65)	1350 (91%) [n=206]	1.50 (0.75-36.00) [n=206]	18100 (65%) [n=204]	19300 (51%) [n=200]	15.3 (8.83-42.7) [n=201]	8.28 (51%) [n=200]	Section 5.3.1.2
			Commercial capsule formulation: 2×80-mg, capsules on Days 1 or 15, oral, D424429	112 (59/53), healthy participants, mean age 42.1 years (18-64)	1520 (61%) [n=209]	1.50 (0.75-36.02) [n=209]	20200 (47%) [n=206]	20700 (45%) [n=206]	15.5 (8.12-47.5) [n=209]	7.73 (45%) [n=206]	

Abbreviations: AUC = area under the curve; AUC(0-∞) = AUC from time 0 to infinity; AUC(0-t_{last}) = AUC from time 0 to time t_{last}, where t_{last} is the last time point with a measurable concentration ; CL/F = apparent total body clearance of drug calculated after extra-vascular administration; C_{max} = maximum observed drug concentration; CV = coefficient of variation; F = female; ID = identifier; M = male; n = number of observations; $t_{1/2}$ = terminal elimination half-life; t_{max} = time of maximum observed drug concentration.

[a] Median (range).

[b] Geometric mean (range).

APPEARS THIS WAY ON ORIGINAL

Table 2: Statistical Summary of the Comparative Bioavailability Data (J2G-MC-JZJZ)

Selpercatinib 160 mg Least Squares Geometric Means, Ratio of Means, and 94.12% Confidence Intervals				
Fasted Bioequivalence Study (JZJZ)				
Parameter	**Tablet Formulation**	**Capsule Formulation**	**Ratio**	**94.12% CI[a]**
AUC(0-t_{last}) (ng.h/mL)	17982	20193	0.891	(0.834, 0.951)
AUC(0-∞) (ng.h/mL)	19203	20707	0.927	(0.882, 0.975)
C_{max} (ng/mL)	1347	1515	0.889	(0.810, 0.976)

Abbreviations: AUC = area under the curve; AUC(0-∞) = AUC from time 0 to infinity; AUC(0-t_{last}) = AUC from time 0 to time t_{last}, where t_{last} is the last time point with a measurable concentration; CI = confidence interval; C_{max} = maximum observed drug concentration; CSR = clinical study report; JZJZ = J2G-MC-JZJZ

[a] Accounting for 2-stage adaptive design.

Safety (Study J2G-MC-JZJZ):

The safety analysis included all 224 participants who were enrolled into the study.

Following administration of 160 mg selpercatinib as 2 × 80-mg capsules**,** 37 (17.1%) participants reported 53 TEAEs. Seven (3.2%) of these participants reported 9 TEAEs that were considered to be related to study treatment.

The most frequently reported TEAEs following dosing with the capsules were headache (7 events), COVID-19 (7 events), complication associated with device (NG tube; 3 events), and dysmenorrhea (3 events). All other TEAEs were reported once or twice each. The majority of TEAEs were considered to be mild in severity, with 4 TEAEs considered to be of moderate severity (headache [2 events], vomiting, and non-cardiac chest pain).

Following administration of selpercatinib as the 1 × 160-mg tablet, 35 (16.5%) participants reported 52 TEAEs. Six (2.8%) of these participants reported 8 TEAEs that were considered to be related to study treatment.

The most frequently reported TEAEs following dosing with the tablet were headache (13 events), COVID-19 (6 events), and blood creatine phosphokinase increased (3 events). All other TEAEs were reported once or twice each. The majority of TEAEs were considered to be mild in severity, with 4 TEAEs considered to be of moderate severity (blood creatine phosphokinase increased [2 events], muscle spasms, and presyncope).

No events of death were reported, and no serious adverse events (SAEs) occurred in this study.

A total of 13 participants (5.80%) discontinued from the study due to TEAEs, which included urinary tract infection, increased ALT, increased blood creatinine phosphokinase, muscle spasms,

and COVID-19 (9 participants, 4.01%).

Five participants had increases in AST and/or ALT, and these were reported as TEAEs of special interest. These findings were generally transient and occurred at isolated time points, or represented small deviations from the reference range.

The incidence of TEAEs reported was similar between the tablet formulation and the capsule formulation.

Clinical Pharmacology Reviewer's assessment of fasting study:

PK of the BE study: The administration of selpercatinib in tablet form at a dosage of 160 mg resulted in slight decreases of 10.9% in AUC(0-tlast), 7.3% in AUC(0-∞), and 11.1% in Cmax compared to when administered as 2 × 80-mg capsules.

Using Potvin design, due to intra-participant variability (59.1 % for Cmax), instead of the 90% CI, a more stringent confidence interval of 94.12% was used to establish the bioequivalence. Based on evaluations of AUC(0-tlast), AUC(0-∞), and Cmax, with the ratios of the geometric least squares means having 94.12% confidence intervals falling within 80% to 125%.it was determined that the single 160-mg tablet of selpercatinib was bioequivalent to the commercial 2 × 80-mg capsules formulation.

The single dose selpercatinib tablet (160-mg) is bioequivalent to the approved selpercatinib capsule (2 × 80-mg) formulation. Based on in vivo BE study, the approved selpercatinib capsule formulation (80-mg) is adequately bridged with the proposed selpercatinib tablet (160-mg).

Though the data are limited, throughout the study, there were no fatalities or serious adverse events reported. No safety signals were observed after single oral doses of selpercatinib, and no clinically significant observations were noted in the vital signs.

2. Food effect study J2G-MC-JZPA (JZPA): Title: An open-label, randomized, two-period crossover study to investigate the effect of food on the pharmacokinetics of Selpercatinib in healthy participants

Design: Study JZPA was an open-label, randomized, 2-period, 2-sequence crossover study of the PK of selpercatinib in the fed and fasted states in healthy participants. Each participant received the first dose of 160 mg selpercatinib tablet formulation either in the fasted or with high-fat meal on Day 1. After a washout period of 7 days, the participants received the second dose of 160 mg selpercatinib under the alternate treatment condition (fasted or fed).

Objective:

This study was conducted to assess:

- the effect of food on the PK of selpercatinib after a high-fat meal in healthy participants,
- safety and tolerability of 160 mg of selpercatinib tablet formulation.

This study was conducted at 1 center that enrolled 46 participants in Singapore.

On day one, all participants were randomized to receive either a single dose of 160 mg selpercatinib in the fasted or with high-fat meal on Day 1, and were to have the alternate treatment (that is, fasted or fed, per the randomization schedule) on Day 8. Participants remained resident at the CRU from Day -1 until Day 11.

There was a washout period of 7 days between dosing on Days 1 and 8. The doses were administered at approximately the same times on Days 1 and 8.

Blood samples were collected for PK assessments. Safety assessments, including adverse events, concomitant medications, medical assessments, clinical laboratory tests, vital signs, and electrocardiograms (ECGs), were performed.

Number of Participants: planned: 46, randomized: 46, completed the study: 44

Diagnosis and Main Criteria for Inclusion and Exclusion:

At the time of signing the informed consent form at screening, participants were required to be

- healthy males or females
- aged between 21 and 65 years, inclusive, and
- healthy, as determined by medical history, physical examination, vital signs, and laboratory assessments at screening.

Study Interventions, Dose, and Mode of Administration

Participants received 2 × single oral doses of 160 mg selpercatinib, with each dose administered as 1 × 160-mg tablet:

Duration of Study Intervention:

The total duration of the study was up to 49 days (Screening: up to 28 days; Treatment Period: 11 days; Safety Follow-up: up to 10 days after the last dose of selpercatinib.

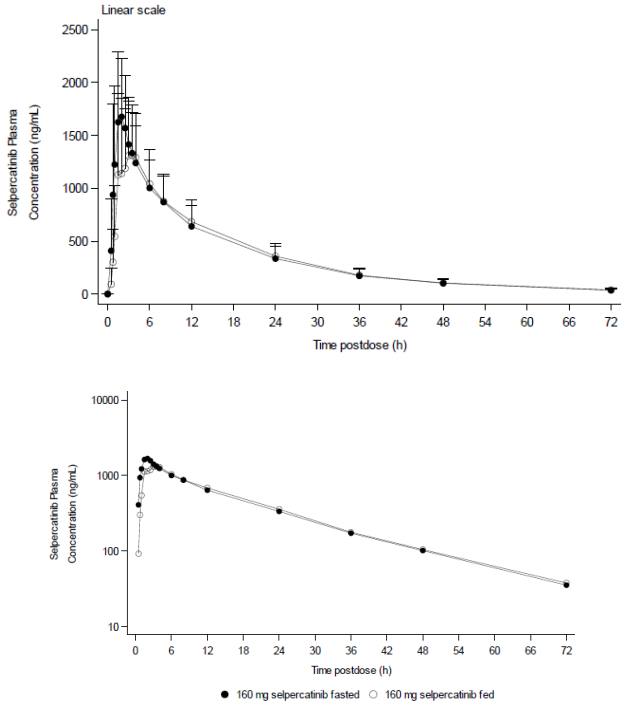
Demographic and Other Baseline Characteristics:

Thirty-six males (36), and 10 females aged 22 to 65 years were enrolled overall. The majority (97.8%) of participants were Asian. The body mass index ranged from 18.8 kg/m2 to 33.4 kg/m2.

Results food effect study JZPA (PK):

The mean plasma concentration versus time profiles of selpercatinib dosed in the fasted state or with high-fat meal are shown in Figure 4.

Figure 4: Arithmetic mean plasma concentration of 160 mg selpercatinib when dosed in the fasted state or with high-fat meal (Study JZPA).



Summaries of the PK parameters for selpercatinib dosed in the fasted state or with high-fat meal are shown in Table 3. Statistical analysis of the PK parameters is shown in Table 4.

Table 3. Summary of Food Effect Study J2G-MC-JZPA

Study Identifier	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) (Product ID)	Subjects (No. [M/F]) Type Mean Age (Range)	Geometric Mean (CV [%]) of Parameter Estimates						Study Report Location
					C_{max} (ng/mL)	t_{max}[a] (h)	AUC(0-t_{last}) (ng.h/mL)	AUC(0-∞) (ng.h/mL)	$t_{1/2}$[b] (h)	CL/F (L/hr)	
J2G-MC-JZPA	To assess the effect of food on the PK of selpercatinib after a high-fat meal in healthy participants To assess the safety and tolerability of 160 mg of selpercatinib	Open-label, randomized, 2-period, 2-sequence crossover study of the PK of selpercatinib in the fed and fasted states in healthy participants	Tablet formulation in fasted state: 1×160 mg, tablet on Days 1 and 8, oral, D458387	45 (35/10), healthy participants, mean age 40.5 years (22-65)	1840 (39%) [n=44]	1.50 (0.75-4.00) [n=44]	22700 (32%) [n=44]	23400 (32%) [n=44]	14.6 (9.01-21.2) [n=44]	6.83 (32%) [n=44]	Section 5.3.3.4
			Tablet formulation in fed state: 1×160 mg, tablet on Days 1 and 8, oral, D458387	45 (35/10), healthy participants, mean age 40.5 years (22-65)	1540 (45%) [n=44]	2.75 (1.00-6.00) [n=44]	21700 (46%) [n=44]	22500 (44%) [n=44]	14.9 (9.47-19.5) [n=44]	7.10 (44%) [n=44]	

Abbreviations: AUC(0-∞) = AUC from time 0 to infinity; AUC(0-t_{last}) = AUC from time 0 to time t_{last}, where t_{last} is the last time point with a measurable concentration; C_{max} = maximum observed drug concentration; CL/F = apparent total body clearance of drug calculated after extra-vascular administration; CV = coefficient of variation; F = female; ID = identifier; M = male; n = number of observations; PK = pharmacokinetics; $t_{1/2}$ = terminal elimination half-life; t_{max} = time of maximum observed drug concentration.

[a] Median (range).

[b] Geometric mean (range).

On administration of selpercatinib tablets with the high-fat meal, the Cmax decreased by 17.1%, median Tmax increased by a1 hour, and AUC0-∞ and AUC0-tlast decreased by 5.1% and 4.8%, respectively, as compared to the administration under the fasted state.

The Applicant claimed that the study results support that selpercatinib may be taken with or without food.

Table 4: Statistical Summary of the Pharmacokinetic Parameters of Selpercatinib (Study J2G-MC-JZPA)

Selpercatinib 160 mg, Tablet (1X 160 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Study (JZPA)				
Parameter	**Fasted**	**Fed**	**Ratio**	**94.12% CI[a]**
AUC(0-t_{last}) (ng.h/mL)	22932	21765	0.949	(0.869, 1.04)
AUC(0-∞) (ng.h/mL)	23737	22603	0.952	(0.876, 1.03)
C_{max} (ng/mL)	1863	1545	0.829	(0.744, 0.925)

Abbreviations: AUC = area under the curve; AUC(0-∞) = AUC from time 0 to infinity; AUC(0-t_{last}) = AUC from time 0 to time t_{last}, where t_{last} is the last time point with a measurable concentration; CI = confidence interval; C_{max} = maximum observed drug concentration;

Safety (Study JZPA):

Following administration of selpercatinib in the fasted state, 32 (71.1%) participants reported 105 TEAEs. Eighteen (18 [40.0%]) of these participants reported 48 TEAEs that were considered to be related to study treatment.
The most frequently reported TEAEs following dosing in the fasted state were general disorders and administration site conditions[2].
The majority of TEAEs were considered to be mild in severity, with 2 TEAEs, both in the same participant, considered to be of moderate severity (catheter site pain and peripheral swelling) reported.

Table 5. Summary of Adverse Events

	Number of events [number of participants with events] (% of participants with events)	
	160 mg selpercatinib fasted (N = 45)	160 mg selpercatinib fed (N = 45)
All TEAEs	105 [32] (71.1%)	86 [27] (60.0%)
Mild	104 [32] (71.1%)	85 [27] (60.0%)
Moderate	1 [1] (2.2%)	1 [1] (2.2%)
Severe	0	0
Treatment-related AEs	48 [18] (40.0%)	23 [11] (24.4%)
Fatal AEs	0	0
SAEs	0	0
Treatment-related SAEs	0	0
AEs leading to discontinuation from study	0	0

Abbreviations: AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Following administration of selpercatinib in with high-fat meal, 27 (60.0%) participants reported 86 TEAEs. Eleven (24.4%) of these participants reported 23 TEAEs that were considered to be related to study treatment.

The most frequently reported TEAEs following dosing with high-fat meal were general disorders and administration site conditions. The majority of TEAEs were considered to be mild in severity, with 1 TEAE considered to be of moderate severity. The majority of TEAEs resolved by the end of the study.

No events of death were reported, and no serious adverse events (SAEs) occurred in this study. There were no discontinuations from the study due to adverse events.

Participant (b) (6) had an adverse event of special interest (AESI) of blood pressure increased (approximately 7 days after dosing with selpercatinib with high-fat meal) that was mild in severity and considered as not related to study intervention.

[2] catheter site conditions were as a result of the catheter placed for blood draws, that is, were not a result of administration of study drug

The incidence of treatment-related TEAEs reported was approximately double (48 versus 23 events) when selpercatinib was administered in the fasted state compared to with high-fat meal; this increase was attributed to higher incidences of diarrhoea, headache, and vomiting reported overall.

Single oral doses of 160 mg as an oral tablet were well tolerated in healthy male and female participants when dosed in the fasted or with high-fat meal. There were no clinically significant findings in the vital signs or 12-lead ECG data during this part of the study.

Clinical Pharmacology Reviewer's assessment of food effect study:

PK of the food effect study:

The high-fat meal was consistent (Total Kcal: 800-1000, Fat Kcal: 500-600, ≥50 %) with the meal described in the FDA food effect guidance.

The administration of selpercatinib in tablet form at a dosage of 160 mg, with food, led reduction in Cmax by 17.1%; however, given the high variability in selpercatinib absorption, this decrease was deemed clinically not significant.

Minor reductions of 5.1% and 4.8% were noted in the AUC0-∞ and AUC0-tlast, respectively, when the drug was administered with high-fat meal as compared to the fasted state.

The magnitude of the food effect was similar to the food effect that was previously observed with the capsule formulation when administered with a high-fat meal (See clinical pharmacology review[3], Original NDA 213246, selpercatinib capsules), and are not considered clinically significant. Based on the original NDA 213246 review, selpercatinib capsules may be administered with or without food, unless coadministered with a PPI, and similarly selpercatinib tablets should be administered with or without food, unless coadministered with a PPI.

Though the data are limited, throughout the study, there were no fatalities or serious adverse events reported. Additionally, no clinically significant observations were noted in the vital signs.

3. **Interaction with gastric acid-reducing agents**

Coadministration of the selpercatinib capsule formulation with a PPI[4] decreases selpercatinib plasma concentrations when administered in a fasted state. When administered with food, food mitigates the decrease in selpercatinib exposure in the presence of a PPI.

The Sponsor claimed that based on the following scientific rationale a consistent PPI-mitigating effect of food when the drug is administered in tablet form is anticipated.

[3] DARRTS: NDA213246, REV-SUMMARY-11 (Office Director Review): 05/08/2020: ZACK-TAYLOR, AUTUMN D

[4] Proton pump inhibitors

- BE between the tablet (160 mg) and the capsule (2 × 80-mg) formulations.
- No clinically significant effect was observed when the tablet formulation was administered with food, which is consistent with the effect observed with capsule formulation.
- The ratio of the intrinsic solubilities of (b) (4) (b) (4) demonstrating that the (b) (4) are very similar in terms of solubility. Similarity of solubilities of (b) (4) suggests that reduction of gastric acidity should have very similar impact on in vivo performance and that the change in (b) (4) will have minimal impact on absorption across the potential range of gastric pH.
- Dissolution data across physiological pH showed in vitro comparability of the 40, 80, and 120-mg tablet strengths with the 160-mg tablet strength.
- Effects of gastric acid-reducing agents are expected to be the largest for the 160-mg strength, with the 40, 80, and 120-mg strengths exhibiting similar or lesser effects.
- Neither the tablet nor the capsule formulation contains any excipients that would be anticipated to affect gastric emptying rates or intestinal motility.

Clinical Pharmacology Reviewer's assessment:

As presented above the approved selpercatinib capsule and new tablet formulations are shown to be bioequivalent and no clinically significant differences in selpercatinib tablet AUC and Cmax were observed following administration of a high-fat meal in healthy subjects.

The Division of Biopharmaceutics Review states that selpercatinib exhibits high solubility at gastric pH in both (b) (4) (approved capsule formulation) and (b) (4) (proposed tablet formulation). Similarity of solubilities of (b) (4) suggests that reduction of gastric pH by co-administration of acid reducing agents, might have similar impact on the in vivo performance of the drug product. In addition, change in (b) (4) will have minimal impact on the absorption of selpercatinib across the potential range of gastric pH as evident through the BE study for the proposed 160 mg selpercatinib tablet (b) (4) and the approved (2 ×80-mg) selpercatinib capsule (b) (4)

Based on the pH-solubility studies conducted on both (b) (4) and dissolution profile data at different pH conditions provided solely for the tablet dosage form it is likely that this new dosage form (tablet) would have a potential DDI with the acid-reducing agents. However, the risk is expected to be same for the tablets as that of the approved capsule dosage form and no additional risk for the proposed formulation is identified.

The Clin pharm review concludes that based on the above biopharmaceutics information, as well as the clinical pharmacology data showing bioequivalence between the approved capsule and proposed tablet formulations, the food effect study showing no significant food effect, and the previously reviewed drug interaction study with proton pump inhibitors (PPIs) (Original NDA 213246 review), selpercatinib tablets should be administered similarly to the approved capsule

formulation. Selpercatinib tablets should be administered without regard to food, unless administered with a PPI, in which case it should be administered with food.

III. LABELING REVIEW

The following changes are proposed in the labeling (underlined edits by Applicant, purpose edits by FDA).

Labeling Section	Proposed Changes
	(b) (4)

IV. RECOMMENDATION

The Office of Clinical Pharmacology has reviewed the Clinical studies 2G-MC-JZJZ (JZJZ) and J2G-MC-JZPA (JZPA) submitted in this NDA, in support of a new immediate release tablet formulation of Retevmo® (Selpercatinib Tablets, 40 mg, 80 mg, 120 mg, and 160 mg). This NDA is approvable from a clinical pharmacology perspective.

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

/s/

OM ANAND
03/11/2024 05:30:08 PM

JEANNE FOURIE ZIRKELBACH
03/11/2024 05:31:28 PM

NICOLE L DREZNER
03/12/2024 08:15:57 AM

NAM ATIQUR RAHMAN
03/25/2024 11:11:58 AM