27 February 2025
EMA/94274/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Retsevmo

International non-proprietary name: Selpercatinib

Procedure No. EMEA/H/C/005375/X/0031

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC0-24	area under the concentration versus time curve from time 0 to 24 hours
BID	twice daily
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMA	conditional marketing authorisation
Cmax	maximum drug concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CSR	clinical study report
DOR	duration of response
DCR	disease control rate
EC	European Commission
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
ERA	Environmental Risk Assessment
ERB	ethics review board
EUDRA	European Union Drug Regulatory Authorities
GCP	Good Clinical Practices
GMI	growth modulation index
HIPAA	health insurance portability & accountability act
ICF	informed consent form(s)
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	investigational new drug
INV	Investigator assessment
IRB	Institutional Review Board
IRC	Independent Review Committee
ISR	Incurred Sample Re-analysis
MA	marketing authorisation
MedRA	Medical Dictionary for Regulatory Activities
MTC	medullary thyroid cancer
NCA	noncompartmental
NCCN	National Comprehensive Cancer Network
NE	not estimable

NGS	next-generation sequencing
NSCLC	non-small cell lung cancer
ORR	objective response rate
NGS	next-generation sequencing
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBT	Persistent, bioaccumulative and toxic
PDTC	poorly differentiated thyroid carcinoma
PK	pharmacokinetics
PFS	progression-free survival
PI	principal investigator
PIP	paediatric investigation plan
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PT	preferred term
PTC	papillary thyroid cancer
QTcF	QT interval corrected for heart rate using Fridericia's formula
RANO	Response Assessment in Neuro-Oncology Criteria
RECIST	Response Evaluation Criteria in Solid Tumors
RET	REarranged during Transfection
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SMQ	Standardised MedDRA Queries
TC	thyroid cancer
TEAE	treatment-emergent adverse event (new or worsening AEs with date of onset during or after the date of first study intervention administration through the end of study); this is synonymous with "adverse event" for this report
TE-SAE	treatment-emergent SAE
Tmax	time to maximum plasma concentration
TTR	time to response
TTBR	time to best response
ULN	upper limit or normal
vPvB	very persistent and very bioaccumulative

1. Background information on the procedure

1.1. Submission of the dossier

Eli Lilly Nederland B.V. submitted on 8 March 2024 extensions of the marketing authorisation.

The MAH applied for an additional pharmaceutical form (film-coated tablets) associated with strengths 40 mg, 80 mg, 120 mg, and 160 mg of selpercatinib in addition to the existing 40-mg and 80-mg strengths capsule formulations.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(s) (c) (d) - Extensions of marketing authorisations

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The MAH did not receive Scientific advice from the CHMP on the current line extension.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau

Rapporteur appointed by the PRAC: Bianca Mulder

The application was received by the EMA on	8 March 2024
The procedure started on	28 March 2024
The CHMP Rapporteur's first Assessment Report was circulated to all	17 June 2024

CHMP and PRAC members on	
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 June 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 July 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	9 October 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	13 November 2024
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the MAH on	12 December 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	22 January 2025
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	13 February 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Retsevmo on	27 February 2025
The CHMP adopted a report on similarity of Retsevmo with name of the authorised orphan medicinal product(s) on (see Appendix on similarity)	27 February 2025

2. Scientific discussion

2.1. Problem statement

RETSEVMO (selpercatinib) has been granted a conditional MA in the European Union (EBD 11/02/2021) and is currently indicated as monotherapy:

- for the treatment of adults with:

– advanced RET fusion-positive non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor

– advanced RET fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted

- for the treatment of adults and adolescents 12 years and older with:

– advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate)

– advanced RET-mutant medullary thyroid cancer (MTC)

Retsevmo is currently available as 40mg and 80 mg-strength hard capsules. The recommended dosage is 120 mg twice daily for patients < 50 kg and 160 mg twice daily for patients > 50 kg.

This submission is an application for an extension of the marketing authorisation to introduce an additional pharmaceutical form film-coated tablets associated with strengths 40 mg, 80 mg, 120 mg, and 160 mg of selpercatinib in addition to the existing 40-mg and 80-mg strengths capsule formulations.

The objective of the new formulations and new strengths is to minimize the size of the dosage form as well as the quantity of dosage units compared to the capsule formulation and therefore to reduce the patient "tablet burden".

2.2. About the product

Selpercatinib is an inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase.

2.3. Type of Application and aspects on development

This is a line extension to introduce an additional pharmaceutical form (film-coated tablets associated with strengths 40 mg, 80 mg, 120 mg, and 160 mg of selpercatinib in addition to the existing 40-mg and 80-mg strengths capsule formulations.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as immediate release film-coated tablets containing 40 mg, 80 mg, 120 mg or 160 mg of selpercatinib.

The other ingredients are:

Tablet core: cellulose microcrystalline, mannitol, croscarmellose sodium, hydroxypropylcellulose, and sodium stearyl fumarate.

Film-coating agent: polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, black iron oxide (E172) (40 mg, 80 mg, and 120 mg), red iron oxide (E172) (80 mg, 120 mg and 160 mg).

The product is available in cold formable aluminium foil (CFAF) blisters sealed with aluminium foil lidding, in packs of 30, 56 or 60 film-coated tablets, as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name and structure of the active substance have not changed as compared to the currently approved manufacturing process. However, updates to the active substance manufacturing process have been submitted in this procedure. The active substance from this new process will be used for tablet manufacturing.

2.4.2.2. Manufacture, characterisation and process controls

The currently approved manufacturing process is used for capsule manufacturing. With the exception of the final active substance manufacturing step, the manufacturing process and controls remain largely unchanged.

1The starting materials and their manufacturing processes remain the same as the currently approved commercial process.

Adequate in-process controls are applied during manufacturing. In-process controls for active substance intermediates remain unchanged. The specifications and control methods for intermediate products, starting materials and reagents remain the same, with the exception of the specifications related to one intermediate.

A forced degradation study was performed, confirming that process-related and degradation impurities remain unchanged. Mutagenic impurities discussion remains unchanged. The only differences in the impurity profile are at the level of residual solvents, which are properly controlled in the active substance specification and by IPC.

Changes introduced have been presented in sufficient detail and have been properly justified. It was demonstrated that the changes did not have a significant impact on the quality of the product. The quality of the active substance produced for tablet manufacturing is considered comparable with active substance produced for capsule manufacturing.

2.4.2.3. Specification

The active substance specifications have been updated.1

Newly developed methods for assay and impurities are considered comparable to the current ones. Further evidence was provided during procedure. The newly developed analytical methods have been adequately described and appropriately validated in accordance with ICH guidelines.

Satisfactory information regarding the in-house primary reference standard for selpercatinib has been presented.

Batch analysis data (three batches produced at commercial scale) of the active substance are provided. The results are within the specifications and consistent from batch to batch. Furthermore, the results for the batches utilised in the bioequivalence study (capsules vs tablets) show a comparable quality profile.

2.4.2.4. Stability

Stability data from three commercial scale primary batches of active substance in the intended commercial package for up to 24 months under long term conditions (30 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches included in the stability program are representative of the commercial process although they were manufactured at a different manufacturer.

The novel analytical methods have been described and validated and are considered stability-indicating. All tested parameters were within the specifications. The stability data show that the active substance is stable at the long-term and accelerated storage conditions. No increase in impurities or decrease in assay has been observed at any storage condition. All tested parameters were within the specifications.

Photostability testing following the ICH guideline Q1B was performed on three batches. No degradation was observed. The results indicate that selpercatinib is stable when exposed to ambient lighting.

The stability results justify the proposed retest period of 36 months in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is an immediate-release film-coated tablet.

It is available as 40 mg, 80 mg, 120 mg and 160 mg tablets.

The finished product is presented as follows:

40 mg: a light grey, 6 mm round immediate-release film-coated tablet debossed with "Ret" over "40" on one side and "5340" on the other. The diameter of the tablet is approximately 6 mm.

80 mg: a dark red-purple, 7.3 mm round immediate-release film-coated tablet debossed with "Ret" over "80" on one side and "6082" on the other. The diameter of the tablet is approximately 7.3 mm.

120 mg: a light purple, 8.75 mm round immediate-release film-coated tablet debossed with "Ret" over "120" on one side and "6120" on the other. The diameter of the tablet is approximately 8.75 mm

160 mg: a light pink, 9.75 mm round tablet debossed with "Ret" over "160" on one side and "5562" on the other. The diameter of the tablet is approximately 9.75 mm.

The aim of the formulation development was to generate a formulation able to maximise the active substance concentration within the formulation and minimise the size of the dosage form and the number of units.

Excipients of the formulation are commonly used in solid oral dosage forms. All the excipients are of compendial quality, with the exception of the proprietary colour mixtures whose individual components meet pharmacopeial requirements. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Different experimental formulations have been studied during development and have been presented within the procedure. The final immediate release film-coated tablet formulation was the only one used in clinical studies. Bioequivalence studies were conducted using the higher dose of 160 mg. To support bioequivalence between the capsule and the tablet, comparative dissolution profiles of the bio-batches have been presented. To support the biowaiver of strengths, comparative dissolution profiles for the 40 mg, 80 mg, 120 mg and 160 mg tablet strengths have been presented. Similarity of in vitro dissolution profiles has been confirmed. This was considered satisfactory.

Adequate information on the development of the dissolution method and its condition has been provided, as well as comparison to in-vivo release behaviour. A rationale has been provided based on the in-vivo behaviour of selpercatinib dosage forms (tablet vs capsule) showing similar PK characteristics. Taking into account the justification based on the available in vivo clinical data, and the finished product control strategy, the proposed dissolution method can be accepted.

With respect to the manufacturing process development, the immediate release film-coated tablets are manufactured with a semi-continuous wet granulation, continuous direct compression (tableting), and batch-

mode coating (tablet coating) process. The development of the proposed commercial manufacturing process focused on product and process understanding through structured experimentation and the application of established scientific principles, including risk assessments. Risk assessment for each unit operation was conducted based on first principles understanding, published literature, previous experience with similar materials and prior knowledge derived from existing manufacturing platforms. Rationale for risk assessment and identification of variables further studied have been discussed in a detailed and comprehensive manner, showing good knowledge of the process and the relationship between variables and CQAs.

The development of the semi-continuous wet granulation process has been presented. The performance of the loss-in-weight (LIW) feeders was studied and challenged. The feeder mass tolerance limits are justified.

Models were developed to interpret the relationship between the formulation and the process and study the effect on granule and tablet properties. These models used for process development purposes are considered low-risk models. A model was used to understand the relationships among the different operating control variables that are important in defining the final operating space. Design space boundaries for granulation and drying parameters have been established in a multivariate manner. The methodology and presented conclusions have been agreed.

A model was used as part of the control strategy to set control limits predicting non-critical quality attribute. The model is considered low-risk in the context of use.

The development of the continuous compression step has been presented. The integrated direct compression platform consists of several individual LIW feeders, a continuous mixer, and a compression machine.

The target composition is maintained by continuously monitoring the relative mass flow rates of the individual LIW feeders according to the unit formula. Choice of equipment and configuration has been justified.

A Residence Time Distribution (RTD) model was developed using first principles in order to determine the downstream impact of upstream disturbances; in that context the RTD model is considered low-risk. Using the model, values of mean residence times were calculated as a function of mass flow rate. Considering the determined residence time distributions, performance of the individual feeders used in the compression platform was investigated. It was demonstrated that the system is capable of dampening potential variability arising from the incoming material.

An in-line feed-frame Near-Infrared (NIR) located at the tablet press is used as a Process Analytical Technology (PAT) tool in the process. The NIR is intended to be used as in-process control to determine collection or rejection of tablets and real-time release testing for content uniformity. The corresponding model is thus considered high-risk. The rationale for the control strategy for Uniformity of Dosage Unit (UDU) by implementing the NIR feed frame in conjunction with tablet weight limits, have been explained A high-level summary of the lifecycle activities planned to be performed on the NIR Feed Frame model has been provided.

The development of the batch-mode coating process has been presented. A mass and energy balance model of the tablet film coating process was developed to understand the role of different process parameters in generating the environment for coating application and drying. The model is considered low-risk. Based on the parametric control of the coating step, no IPC for coating weight gain is set in routine.

The final finished product design space has been presented. The proposed design space is considered to be valid and verified at full scale.

Sufficient supporting data have been provided to give confidence in the overall control strategy.

Performance of the process and control strategy have been verified at the established process boundaries during the technical transfer, where batches were manufactured within the final finished product manufacturing design space and following the established process control strategy. Process data have been reported which confirm process robustness and performance of the control strategy at the established process boundaries.

The primary packaging is cold formable aluminium foil (CFAF) blisters sealed with aluminium foil lidding. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured at Lilly del Caribe Inc., Puerto Rico, USA. Packaging and batch release are performed at Lilly S.A., Madrid, Spain. Satisfactory GMP documentation has been provided.

Selpercatinib tablets are manufactured with a semi-continuous wet granulation, continuous direct compression (tableting), and batch-mode coating (tablet coating) process. Design spaces have been proposed for the process.

IPC have been provided. The scope of the NIRS procedure (method and model) has been properly described.

In-process holding times and hold times for bulk coated tablets have been provided.

The batch size definition was determined to be acceptable for the process.

In line with EMA Guideline on Process Validation for finished product (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1), the applicant has provided a satisfactory justification supporting the fact that, based on the experience of the manufacturer, the process can be considered as standard. Substantial batch data are already available at commercial scale and using the commercial equipment (primary stability batches and technical transfer/clinical trial batches). During the line extension procedure, part of the process validation batches data have been provided, which was considered acceptable. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

2.4.3.3. Product specification

The finished product release and shelf-life specifications, includes appropriate tests for this kind of dosage form: description (visual), identification (HPLC), assay (HPLC), degradation products (HPLC), uniformity of dosage units by real-time release testing (NIR), dissolution (UV-Vis) and dye identity (by wet chemistry).

The finished product specifications have been properly justified.

Based on the assay results of primary stability batches and the clinical trial batches, the assay specification has been tightened during the procedure.

The specification limits for the unspecified and for the total degradation products have been justified in line with ICH Q3B.

The control of uniformity of dosage unit by real-time release testing has been extensively justified. The applicant proposes that future parallel testing by NIRS and HPLC will be performed on a periodic basis. The proposed plan for parallel testing is acceptable.

Justification for not performing the control of the crystal form, moisture, and microbial testing has been provided and considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Given the advanced cancer indication, the provided risk assessment was considered sufficient and no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Uniformity of dosage units is controlled by Real Time Release Testing through NIR spectroscopic method and model. Adequate description of the NIR spectroscopic method has been provided, as well as model development and validation summary. The NIR model characteristics have been justified. The applicant has justified that sufficient variability has been incorporated in NIRS model calibration and that sufficient data has been collected to date in commercial process conditions to support the robustness of the NIRS model. Fitness for purpose of the NIRS model has been demonstrated. The acceptance criteria for model validation, as set in the procedure scope, is considered justified with reference to the intended performance of the NIRS procedure.

Batch analysis results are presented for the primary stability batches (three batches per tablet strength) and two clinical trial batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three batches per each strength, manufactured at pilot and commercial scale, of finished product stored for up to 24 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The batches of the finished product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, identification, degradation products (any unspecified, total impurities) and dissolution. The analytical procedures used are stability indicating.

Results presented are compliant with specifications and do not show any trend.

The stability data generated were considered acceptable for establishing the shelf-life of the medicinal product. In addition, the applicant has provided a commitment to place on stability three batches at commercial scale of each tablet strength, for up to 36 months.

In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The tablets were shown to be photostable outside of the package.

Stress testing stability data have been presented. Finished product stored in an open-dish at elevated heat/moisture conditions showed no chemical degradation.

Bulk coated tablets stability data have been presented and support the bulk holding time. Start of shelf life in accordance with the Note for guidance on start of shelf-life of the finished dosage form has been confirmed.

Based on available stability data, the proposed shelf-life of 3 years without any special storage conditions as stated in the SmPC (section 6.3) are acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure no Major Objection and few Other Concerns have been raised. The applicant adequately addressed all questions raised.

Design spaces have been proposed for the manufacturing process of the finished product. The design spaces have been adequately verified.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

N/A

2.5. Non-clinical aspects

No new non-clinical data have been submitted as this line extension application concerns the addition of a new tablet formulation and two new strengths.

2.5.1. Ecotoxicity/environmental risk assessment

An ERA was not included in the dossier as there is no anticipated increase in the environmental exposure from this line extension.

2.5.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted, which is considered acceptable since this line extension application concerns the addition of a new tablet formulation and two new strengths without any changes to the posology or recommended dose.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study Name	J2G-MC-JZJZ	J2G-MC-JZPA
Report Location	Module 5.3.1.2	Module 5.3.3.4
Number of Sites	4 sites	1 site
Study Design	Phase 1, open-label, randomized, 2-period, 2-formulation, 2-sequence, 2-stage[a] adaptive crossover study	Phase 1, open-label, randomized, 2-period, 2-sequence crossover study in the fed and fasted states
Primary Objective	To evaluate bioequivalence of a single 160-mg dose of selpercatinib as the tablet formulation compared with 2 × 80-mg commercial capsule formulation	To assess the effect of food on the PK profile of selpercatinib after a high-fat meal
Status	Completed	
Dose(s) and Frequency	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, or • selpercatinib oral 160 mg as 1 × 160-mg tablet.	Participants received single oral dose of 160 mg selpercatinib on Days 1 and 8 in the fasted or fed state per randomization schedule. Each dose was administered as 1 × 160-mg tablet.
Participants Enrolled	224	46
Number Completed	196	44

2.6.2. Clinical pharmacology

Selpercatinib is an orally available, highly selective, adenosine triphosphate (ATP)-competitive small molecule inhibitor of the RET receptor tyrosine kinase.

In Europe, two strengths of selpercatinib hard capsules, 40 and 80 mg, are available.

Selpercatinib is orally given and the recommended dose is based on body weight:

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

In the current line extension, the MAH submitted the results from 2 studies:

- A bioequivalence study **J2G-MC-JZJZ** to support the registration of a new film-coated tablet in strengths of 40 mg, 80 mg, 120 mg and 160 mg developed to minimize the size of the dosage form as well as the quantity of dosage units the patient would be required to take relative to the commercial capsule formulation.
- Study **J2G-MC-JZPA** to investigate the effect of a high fat meal on the PK of 160 mg selpercatinib administered as a film-coated tablet.

2.6.2.1. Pharmacokinetics

Analytical Methods

The previous bioanalytical method developed for the quantification of selpercatinib used as part of the initial submission (please refer to EMEA/H/C/005375/0000) was revalidated to update the validation assay range. The bioanalytical method was developed at Altura Analytics, Inc (Moscow, Idaho, US). Selpercatinib and its deuterated isotope (D6-selpercatinib) as internal standard was extracted using a protein precipitation followed by a Liquid Chromatography-Tandem Mass Spectrometry (LC/MS-MS) detection.

The method has a calibration curve ranging from 10 to 10000 ng/mL (Lower Limit of Quantification (LLOQ) set at 10 ng/mL) and consisted of 8 concentration levels. Three Quality Control (QC) were considered, Low Quality Control (LQC), Medium Quality Control (MQC) and High-Quality Control (HQC) at 30, 500, and 8000 ng/mL. Inter-run and intra-run precision was below 10% and 4%, accuracy was less than 5%. Long term stability was demonstrated at 14 days stored at -70°C or -20°C.

For Study **J2G-MC-JZJZ** a total of 9764 samples were received from 24 Nov 2021 to 20 Jul 2022 and analysed from 14 Jan 2022 to 10 Aug 2022. Samples were received frozen (approximately at -70°C), and were analysed within 259 days of collection. 249 runs were performed from which 24 were considered as invalid for various documented reasons and all were re-runed, and 3 were rejected (2 for anomalous QC and 1 for a plate issue, all were re-runed). Incurred Sample Re-analysis (ISR) were performed on 541 samples with more than 93% provided satisfactory results.

For Study **J2G-MC-JZPA** a total of 1530 samples were received from 12 May 2022 to 20 Jun 2022 and analysed from 03 Jun 2022 to 28 Jun 2022. Samples were received frozen (approximately at -70°C), and were analysed within 55 days of collection. 29 runs were performed from which 3 were considered as invalid for various documented reasons and all were re-runed. ISR were performed on 135 samples with more than 92% provided satisfactory results.

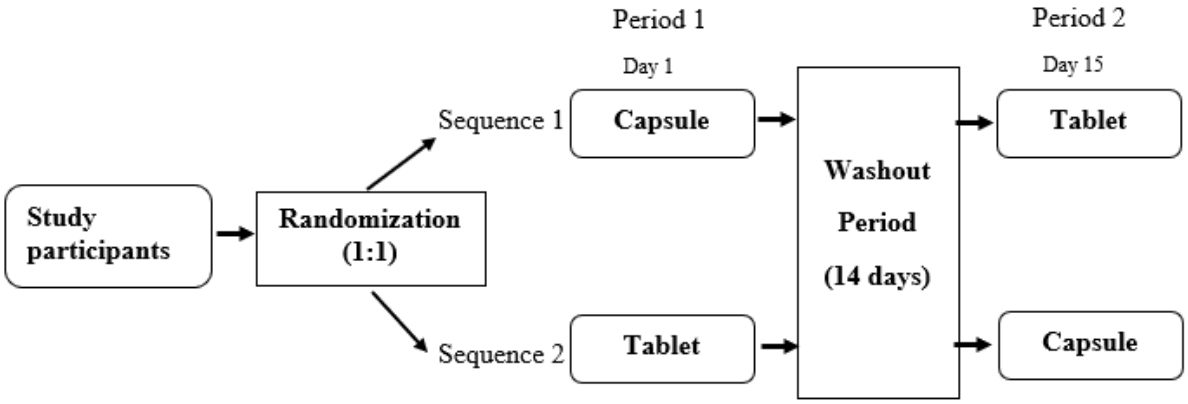
Bioequivalence

Study **J2G-MC-JZJZ**, was a Phase 1, open label, randomised, 2 period, 2-sequence, 2 formulations, 2-stage adaptive cross-over study in healthy adult male and female, to compare the pharmacokinetics (PK) of selpercatinib administered orally as a 1x160 mg tablet vs 2x80 mg capsule formulations under fasted conditions.

Design of the study

A 2-stage adaptive design is presented in Figure 1**Error! Reference source not found.**. Stage 1 PK results were used to establish the intra subject variability for both Cmax and AUC and to estimate the required sample size for Stage 2.

Figure 1: Study design applicable to Stage 1 and Stage 2



In Stage 1, up to approximately 60 participants were planned to be enrolled to ensure that at least 50 participants would complete the treatment and to ensured that a sufficient variation of gastric pH would be incorporated. Exploratory analysis of pH measurements (performed via Nasogastric tube insertion and aspiration of gastric secretions and testing via pH meter) were included to assess the pH dynamics and to determine whether the PK of each formulation were altered by initial pH. In Stage 2, pH was not required to be measured.

Number of Participants (planned and analysed):

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

Study Interventions, Dose, and Mode of Administration:

Subjects received in a cross-over design either the 2x80 mg capsule commercial formulation or 1x160 mg tablet formulation on Day 1. After a wash-out period of 14 days, subjects received their second single dose as capsules or tablet.

PK sampling consisted of pre-dose and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120 and 144 h post-dose.

Objectives, and Endpoints

Table 2: Objectives and Endpoints, Study J2G-MC-JZJZ

Objectives	Endpoints
Primary	
• To evaluate the bioequivalence of a single 160-mg dose of selpercatinib as the tablet formulation (test) compared to the commercial capsule formulation (reference)	• C_{max}, AUC(0-∞), and AUC(0-t_{last}) of selpercatinib
Secondary	
• To describe the safety and tolerability of a single 160-mg oral dose of selpercatinib as the tablet formulation (test) compared to the commercial capsule formulation (reference)	• Summary of the number of treatment-emergent AEs and serious adverse events

Abbreviations: AE = adverse event; AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; AUC(0-t_{last}) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; C_{max} = maximum observed drug concentration.

Study Period:

Study initiation date: 29 October 2021 (first participant signed informed consent form).

Study completion date: 19 July 2022 (last participant last visit).

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/m2.

Results

Plasma

A total of 224 subjects were enrolled from which 196 completed both periods as detailed in ***Table 2***. Twenty-eight participants discontinued the study for TEAEs (n=13) or any reason for withdrawal (n=15).

One deviation was considered notable. 11 participants on Day 15 (Period 2) did not have water restricted for a full hour prior to dose as per protocol instruction, but rather had water restricted only 6 to 46 minutes prior to dose. The impacted Period from these participants was excluded from the primary PK analysis but included in a sensitivity analysis.

Table 3: Summary of patient disposition

	160 mg selpercatinib (2 x 80 mg capsules) / 160 mg selpercatinib (1 x 160 mg tablet) (N=112) n (%)	160 mg selpercatinib (1 x 160 mg tablet) / 160 mg selpercatinib (2 x 80 mg capsules) (N=112) n (%)	Total (N=224) n (%)
Period 1			
Started	112 (100.0%)	112 (100.0%)	224 (100.0%)
Received at Least 1 Dose	112 (100.0%)	112 (100.0%)	224 (100.0%)
Completed	112 (100.0%)	111 (99.1%)	223 (99.6%)
Not Completed	0 (0.0%)	1 (0.9%)	1 (0.4%)
Withdrawal by Subject	0 (0.0%)	1 (0.9%)	1 (0.4%)
Period 1 Washout			
Started	112 (100.0%)	111 (99.1%)	223 (99.6%)
Completed	100 (89.3%)	104 (92.9%)	204 (91.1%)
Not Completed	12 (10.7%)	7 (6.3%)	19 (8.5%)
Adverse Event	3 (2.7%)	4 (3.6%)	7 (3.1%)
Lost to Follow-up	1 (0.9%)	0 (0.0%)	1 (0.4%)
Physician Decision	2 (1.8%)	0 (0.0%)	2 (0.9%)
Withdrawal by Subject	6 (5.4%)	3 (2.7%)	9 (4.0%)
Period 2			
Started	100 (89.3%)	104 (92.9%)	204 (91.1%)
Received at Least 1 Dose	100 (89.3%)	104 (92.9%)	204 (91.1%)
Completed	95 (84.8%)	101 (90.2%)	196 (87.5%)
Not Completed	5 (4.5%)	3 (2.7%)	8 (3.6%)
Adverse Event	4 (3.6%)	2 (1.8%)	6 (2.7%)
Lost to Follow-up	1 (0.9%)	0 (0.0%)	1 (0.4%)
Withdrawal by Subject	0 (0.0%)	1 (0.9%)	1 (0.4%)

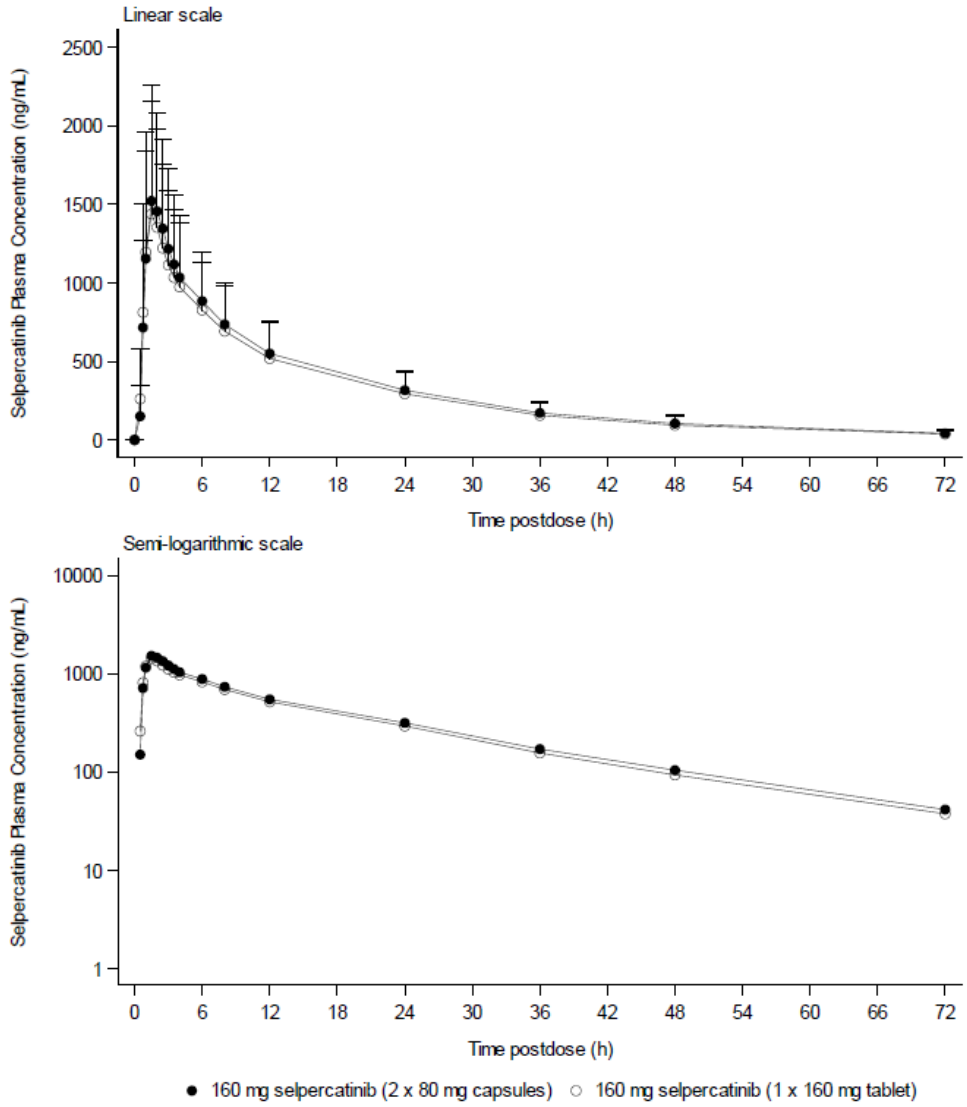
Abbreviations: N = number of participants studied
The washout period is defined as at least 14 days between doses of selpercatinib

The arithmetic mean (SD) plasma concentration-time profiles for selpercatinib following a single dose of 160 mg selpercatinib administered as the tablet vs capsule formulation are presented in Figure 2 , the associated PK parameters in *Table 3* and statistical bioequivalence analysis in *Table 4*

Table 4: Summary of PK parameters of selpercatinib

	Geometric mean (Geometric CV%) [n]	
Parameter	160 mg selpercatinib (2 x 80 mg capsules) (N=216)	160 mg selpercatinib (1 x 160 mg tablet) (N=212)
AUC(0-tlast) (ng.h/mL)	20200 (47%) [206]	18100 (65%) [204]
AUC(0-∞) (ng.h/mL)	20700 (45%) [206]	19300 (51%) [200]
%AUC(tlast-∞) (%)	1.75 (63%) [206]	1.88 (68%) [200]
Cmax (ng/mL)	1520 (61%) [209]	1350 (91%) [206]
tmax (h)#	1.50 (0.75-36.02) [209]	1.50 (0.75-36.00) [206]
t1/2 (h)~	15.5 (8.12-47.5) [209]	15.3 (8.83-42.7) [201]
CL/F (L/h)	7.73 (45%) [206]	8.28 (51%) [200]
Vz/F (L)	174 (48%) [206]	182 (55%) [200]
Vss/F (L)	164 (54%) [206]	170 (59%) [200]

Figure 2: Arithmetic mean plasma concentration profile of 160 mg selpercatinib when dosed at 2x80 mg capsules vs 1x160 mg tablet



Decreases in geometric least-squares mean AUC(0-tlast), AUC(0-∞), and Cmax of 10.9%, 7.3%, and 11.1%, respectively, were observed when selpercatinib was dosed as the 160-mg tablet compared to as 2 × 80-mg capsules (*Table 4*) The tablet and capsules were BE based on the 94.12% CIs of the ratios of the geometric least squares means which fell between the 80% to 125% limits.

There was no change in tmax observed when selpercatinib was dosed as the 160-mg tablet compared to as 2 × 80-mg capsules based on the 90% CI.

Table 5: Statistical analysis of the Pharmacokinetic parameters of selpercatinib

Parameter	Treatment	n	Geometric least squares mean	Ratio of geometric least squares means (Test/Reference)	94.12% CI for the ratio (Lower, Upper)
AUC(0-tlast) (ng.h/mL)	160 mg selpercatinib (2 x 80 mg capsules) (Reference)	206	20193		
	160 mg selpercatinib (1 x 160 mg tablet) (Test)	204	17982	0.891	(0.834, 0.951)
AUC(0-∞) (ng.h/mL)	160 mg selpercatinib (2 x 80 mg capsules) (Reference)	206	20707		
	160 mg selpercatinib (1 x 160 mg tablet) (Test)	200	19203	0.927	(0.882, 0.975)
Cmax (ng/mL)	160 mg selpercatinib (2 x 80 mg capsules) (Reference)	209	1515		
	160 mg selpercatinib (1 x 160 mg tablet) (Test)	206	1347	0.889	(0.810, 0.976)

Parameter	Treatment	n	Median	Median of differences (Test-Reference)	Approximate 90% CI for the difference (Lower, Upper)	P-value
tmax (h)	160 mg selpercatinib (2 x 80 mg capsules) (Reference)	192	1.50			
	160 mg selpercatinib (1 x 160 mg tablet) (Test)	192	1.50	0.00	(-0.07, 0.00)	0.0322

Similar results were obtained from the sensitivity analysis compared to the primary analysis. In the primary and sensitivity analysis, the 94.12% CIs of the geometric least squares mean ratios for AUC(0-tlast) and AUC(0-∞) fell between the 80% to 125% limits. In the sensitivity analysis, the lower bound of geometric least squares mean ratio for Cmax was below 80% limit, being 79.5%. Selpercatinib showed high intra-participant variability for Cmax of >50%.

Gastric pH

Gastric pH data was collected only in Stage 1. A similar trend towards decreased selpercatinib exposure with a higher baseline pH was observed when selpercatinib was dosed at 160mg tablet vs 2x80 mg capsules.

Food effect study

The effect of food on selpercatinib PK was evaluated in healthy volunteers in study **J2G-MC-JZPA.**

Study **J2G-MC-JZPA** was an open-label, randomized, two-period, two-sequence crossover study to investigate the effect of food on the PK of selpercatinib. The study was conducted at one center in Singapore that enrolled 46 participants.

Design

All participants were randomised to receive either a single dose of 160 mg in the fasted or fed state on Day 1 and were to have the alternate treatment on Day 8. A wash-out period of 7 days was considered.

Under the fed state, all participants were dosed 30 minutes after the start of the meal (high fat breakfast). An example of high fat breakfast consisted of 2 whole large eggs, 19 g of butter, 3 white bread slices, 50g frozen perdrix chicken cooked with 8g of butter, 250 g of yoghourt.

PK samples consisted pre-dose and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48, and 72 h post-dose.

Number of Participants (planned and analysed):

Number planned: 46

Number randomised: 46

Number treated: 46

Number completed the study: 44

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.

Objectives and Endpoints

Table 6 Objectives and Endpoints, Study J2G-MC-JZPA

Objectives	Endpoints
Primary	
To assess the effect of food on the PK of selpercatinib after a high-fat meal in healthy participants	$AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} of selpercatinib
Secondary	
To assess the safety and tolerability of 160 mg of selpercatinib	Summary of the number of treatment-emergent AEs and SAEs

Abbreviations: AE = adverse event; $AUC_{0-\infty}$ = area under the concentration versus time curve from time zero to infinity; AUC0-tlast = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; C_{max} = maximum observed drug concentration; PK = pharmacokinetics; SAE = serious adverse event.

Study Period:

Study initiation date: 19 April 2022 (first participant first visit).

Study completion date: 23 June 2022 (last observation from last participant).

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, 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

Forty-six patients were enrolled into the study, of these, 44 received all planned doses of selpercatinib, two withdrew.

The arithmetic mean (SD) plasma concentration-time profiles for selpercatinib following a single dose of 160 mg selpercatinib administered as the tablet in the fast and the fed state are presented *Figure 3*, the associated PK parameters in *Table 14* and statistical analysis in *Table 15*.

A statistically significant decrease in Cmax of 17.1%, as based on the 90% CI (that is, the 90% CI excluded 1 [0.744, 0.925]), was observed when selpercatinib was dosed in the fed state compared to in the fasted state.

A statistically significant increase in tmax, as based on the p-value (<.0001), was observed when selpercatinib was dosed in the fed state compared to in the fasted state. The median of paired differences was 1.00 hour.

Small decreases in AUC0-∞ and AUC0-tlast of 5.1% and 4.8%, respectively, were observed when selpercatinib was dosed in the fed state compared to in the fasted state, but are not considered to be statistically significant, based on the 90% CI.

Figure 3: Arithmetic mean plasma concentration profile of 160 mg selpercatinib when dosed at 1x160 mg tablet in the fed vs fast state

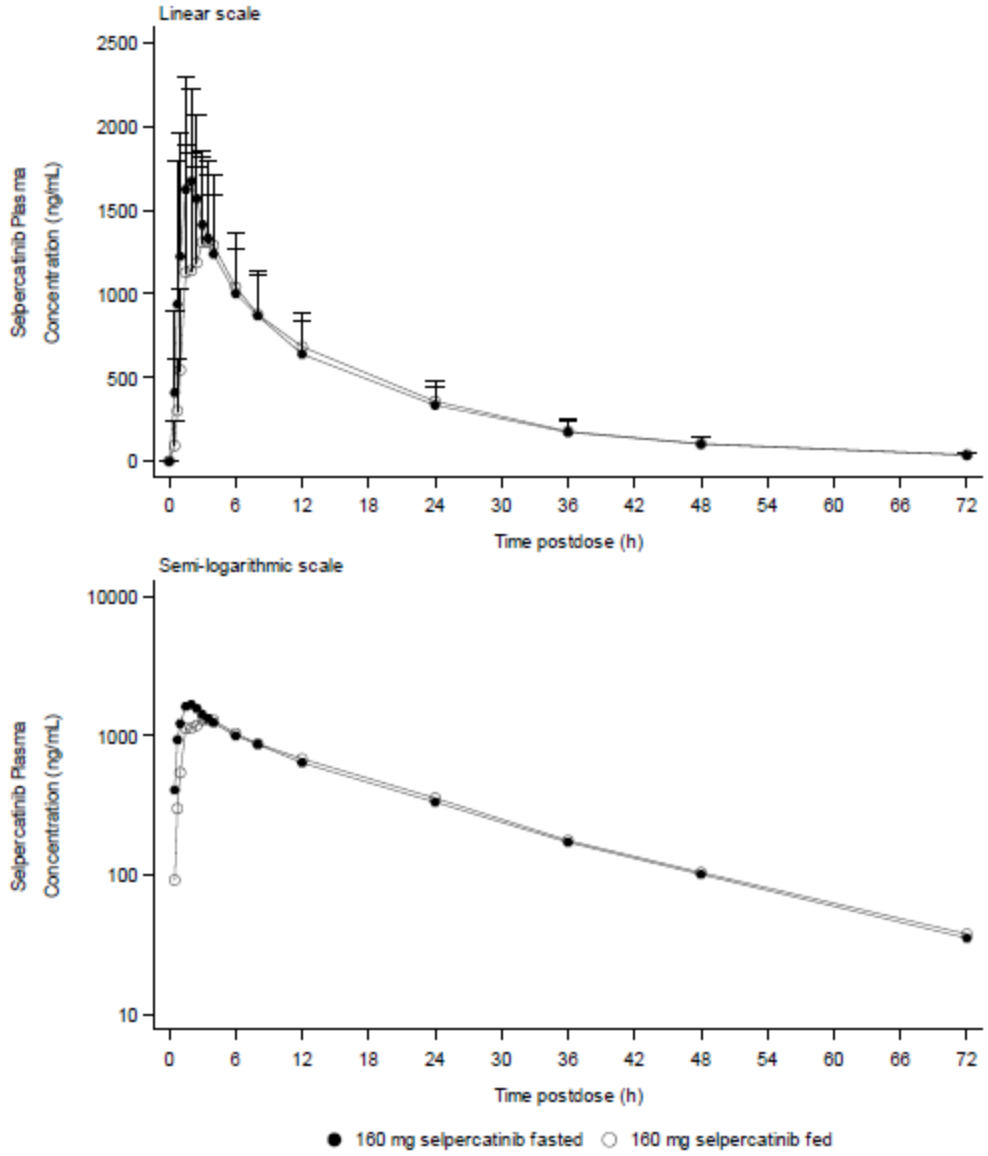


Table 7: Summary of PK parameters of selpercatinib (full dataset)

Parameter	Geometric mean (Geometric CV%) [n] 160 mg selpercatinib fasted (N=44)	160 mg selpercatinib fed (N=44)
AUC(0-tlast) (ng.h/mL)	22700 (32%) [44]	21700 (46%) [44]
AUC(0-∞) (ng.h/mL)	23400 (32%) [44]	22500 (44%) [44]
%AUC(tlast-∞) (%)	2.94 (54%) [44]	3.12 (55%) [44]
Cmax (ng/mL)	1840 (39%) [44]	1540 (45%) [44]
tmax (h)#	1.50 (0.75-4.00) [44]	2.75 (1.00-6.00) [44]
t1/2 (h)~	14.6 (9.01-21.2) [44]	14.9 (9.47-19.5) [44]
CL/F (L/h)	6.83 (32%) [44]	7.10 (44%) [44]
Vz/F (L)	144 (36%) [44]	152 (45%) [44]
Vss/F (L)	129 (35%) [44]	141 (44%) [44]

Table 8: Statistical analysis of the Pharmacokinetic parameters of selpercatinib (full dataset)

Parameter	Treatment	n	Geometric least squares mean	Ratio of geometric least squares mean (fed:fasted)	90% CI for the ratio (Lower, Upper)
AUC(0-tlast) (ng.h/mL)	160 mg selpercatinib fasted	44	22932		
	160 mg selpercatinib fed	44	21765	0.949	(0.869, 1.04)
AUC(0-∞) (ng.h/mL)	160 mg selpercatinib fasted	44	23737		
	160 mg selpercatinib fed	44	22603	0.952	(0.876, 1.03)
Cmax (ng/mL)	160 mg selpercatinib fasted	44	1863		
	160 mg selpercatinib fed	44	1545	0.829	(0.744, 0.925)
tmax (h)	160 mg selpercatinib fasted	43	1.50		
	160 mg selpercatinib fed	43	3.00	1.00	(0.50, 1.75) <.0001

2.6.1. Discussion on clinical pharmacology

As part of this variation, the MAH submitted the results from study **J2G-MC-JZJZ** investigating the BE between a new film-coated tablet formulation at four strengths (40, 80, 120 and 160 mg) vs the available commercial formulation, hard capsules supplied at two strengths 40 and 80 mg. In addition, the effect of a high fat meal on the PK of 160 mg selpercatinib administered as a film-coated tablet was investigated in study **J2G-MC-JZPA**.

Bionalytical method

The developed method for selpercatinib quantification in human plasma is adequate and comply with the ICHM10 Guideline on bioanalytical method validation and study sample analysis (EMA/CHMP ICH/172948/2019).

Long term stability was initially demonstrated at 14 days when stored at -70°C or -20°C, but was further extended at 391 days when stored at -70°C only (203 days when stored at -20°C). All the samples from both studies were received frozen approximately at -70°C, and all the samples were analysed within the demonstrated long term stability.

LLOQ was below 1/20 of average Cmax (LLOQ set at 10 ng/mL and average Cmax ≈1500-1800 ng/mL). ISR was performed with satisfactory results.

A sequential two-stage design was applied given the unknown intra-individual variability of selpercatinib and this design is acceptable based on the EMA Guideline of BE (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr).

BE study **J2G-MC-JZJZ**

For study **J2G-MC-JZJZ**, since the intra-individual variability (IAV) was unknown (which is generally needed to calculate the sample size to demonstrate BE) a two-stage design was performed, where in the first stage IAV was estimated at 59.1% on Cmax (data not shown). As part of the second stage, based on PK data from more than 200 subjects, bioequivalence between the two formulations was demonstrated, with 94.12% CIs of the ratios of the geometric least squares means which fells within the 80-125% limits for all three parameters. However the lower limit of the 94.12% CI was borderline for Cmax (0.81) and the entire CI for all three PK parameters did not contain 1 (0.83-0.95 for AUClast, 0.88-0.97 for AUCinf and 0.81-0.98 for Cmax). A stage effect was investigated as part of the ANOVA model and was found statistically significant without modifying the 94.12% CIs of PK parameters.

Food effect study **J2G-MC-JZPA**

The food effect study **J2G-MC-JZPA** was performed in Singapore, with a healthy subject population of Asian ethnicity. Based on the initial MAA (EMEA/H/C/005375/0000), although race was not found to have an effect on selpercatinib PK (based on a PopPK analysis), it was noted that Japanese subjects had a 1.4-fold and 1.2-fold increased Cmax and AUCtau compared to subjects of others ethnicity. This could explain the slightly higher PK parameters (Cmax and AUCt) between the two studies JZPA vs JZJZ (1840 vs 1340 ng/mL and 22700 vs 17800 ng.h/mL)

Results of the food effect study indicated a decreased Cmax by 17% (in line with the data in the initial MA where Cmax decreased by 14%) and a decrease of AUCtlast by 5% (different from the initial MAA where the AUCt increased by 8%), after the administration of a high fat breakfast. Tmax was delayed by 1.5h. Overall these results are considered not clinically relevant, and similar recommendation to the capsules with regards to food is supported.

2.6.2. Conclusions on clinical pharmacology

Results of the BE study (**J2G-MC-JZJZ**) showed that the tablet and the capsule formulations perform similarly and bioequivalence was established.

Results of the food effect study **(JZPA)** indicated that similar recommendation to the capsule with regards to food are supported (see SmPC 4.2).

2.6.3. Clinical efficacy

No new efficacy data have been provided as part of this submission. This is acceptable as the applicant is not seeking approval for any new indication.

2.6.4. Clinical safety

Safety data is provided from 224 healthy participant in Study JZJZ and 46 healthy participants in Study JZPA that were conducted using tablet formulation.

The safety evaluations in both studies were based upon the incidence, nature and severity of TEAEs reported throughout the study and on changes in clinical laboratory parameters and vital signs.

2.6.4.1. Patient exposure

Study JZJZ

In JZJZ BE study, participants received On Days 1 and 15, each of the following treatments once according to the randomisation scheme:

- selpercatinib oral 160 mg as 2 × 80-mg capsules, or selpercatinib oral 160 mg as 1 × 160-mg tablet.

Table 9: Summary of participant disposition

	160 mg selpercatinib (2 x 80 mg capsules) / 160 mg selpercatinib (1 x 160 mg tablet) (N=112) n (%)	160 mg selpercatinib (1 x 160 mg tablet) / 160 mg selpercatinib (2 x 80 mg capsules) (N=112) n (%)	Total (N=224) n (%)
Period 1			
Started	112 (100.0%)	112 (100.0%)	224 (100.0%)
Received at Least 1 Dose	112 (100.0%)	112 (100.0%)	224 (100.0%)
Completed	112 (100.0%)	111 (99.1%)	223 (99.6%)
Not Completed	0 (0.0%)	1 (0.9%)	1 (0.4%)
Withdrawal by Subject	0 (0.0%)	1 (0.9%)	1 (0.4%)
Period 1 Washout			
Started	112 (100.0%)	111 (99.1%)	223 (99.6%)
Completed	100 (89.3%)	104 (92.9%)	204 (91.1%)
Not Completed	12 (10.7%)	7 (6.3%)	19 (8.5%)
Adverse Event	3 (2.7%)	4 (3.6%)	7 (3.1%)
Lost to Follow-up	1 (0.9%)	0 (0.0%)	1 (0.4%)
Physician Decision	2 (1.8%)	0 (0.0%)	2 (0.9%)
Withdrawal by Subject	6 (5.4%)	3 (2.7%)	9 (4.0%)
Period 2			
Started	100 (89.3%)	104 (92.9%)	204 (91.1%)
Received at Least 1 Dose	100 (89.3%)	104 (92.9%)	204 (91.1%)
Completed	95 (84.8%)	101 (90.2%)	196 (87.5%)
Not Completed	5 (4.5%)	3 (2.7%)	8 (3.6%)
Adverse Event	4 (3.6%)	2 (1.8%)	6 (2.7%)
Lost to Follow-up	1 (0.9%)	0 (0.0%)	1 (0.4%)
Withdrawal by Subject	0 (0.0%)	1 (0.9%)	1 (0.4%)

Abbreviations: N = number of participants studied

The washout period is defined as at least 14 days between doses of selpercatinib

Study JZPA

In JZPA food-effect study, participants received single oral dose of 160 mg selpercatinib on Days 1 and 8 in the fasted or fed state per randomisation schedule. Each dose was administered as 1 × 160-mg tablet.

Forty-six participants were enrolled into the study; of these participants, 44 received all planned doses of selpercatinib, according to the randomization schedule.

Two participants did not complete the study and were excluded from the PK and statistical analyses:

- Participant 1: received 1 dose of selpercatinib in the fasted state on Day 1 of the study and withdrew due to personal issues unrelated to the trial.
- Participant 2: received 1 dose of selpercatinib in the fed state on Day 1 of the study and was withdrawn as, following their predose medical assessment consisting of physical examination, review of vital signs and ECGs, as per the investigator's clinical judgment, the participant was considered not suitable for dosing with the second dose of selpercatinib on Day 8

2.6.4.2. Adverse events

Table 10: Summary of treatment emergent adverse events in Study JZJZ

Treatment	All causalities			Related to study treatment		
	Number of participants [%] with adverse events	Number of adverse events and severity*		Number of participants [%] with adverse events	Number of adverse events and severity*	
160 mg selpercatinib (2 x 80 mg capsules) (N=216)	37 [17.1%]	Mild	49	7 [3.2%]	Mild	6
		Moderate	4		Moderate	3
		Severe	0		Severe	0
		Total	53		Total	9
160 mg selpercatinib (1 x 160 mg tablet) (N=212)	35 [16.5%]	Mild	48	6 [2.8%]	Mild	8
		Moderate	4		Moderate	0
		Severe	0		Severe	0
		Total	52		Total	8
Overall (N=224)	63 [28.1%]	Mild	97	12 [5.4%]	Mild	14
		Moderate	8		Moderate	3
		Severe	0		Severe	0
		Total	105		Total	17

* Only the maximum severity of each adverse event is reported

Abbreviations: N = number of participants studied

Table 11: Summary of treatment emergent adverse events (All causalities) by treatment in order of frequency -Study JZJZ

MedDRA preferred term	Number of adverse events* [number of participants with adverse events]		
	160 mg selpercatinib (2 x 80 mg capsules) (N=216)	160 mg selpercatinib (1 x 160 mg tablet) (N=212)	Overall (N=224)
Headache	7 [7]	13 [10]	20 [16]
COVID-19	7 [7]	6 [6]	13 [13]
Complication associated with device	3 [1]	2 [2]	5 [3]
Alanine aminotransferase increased	2 [2]	2 [2]	4 [4]
Blood creatine phosphokinase increased	1 [1]	3 [3]	4 [4]
Dysmenorrhoea	3 [3]	1 [1]	4 [4]
Cough	1 [1]	2 [2]	3 [3]
Urinary tract infection	2 [2]	1 [1]	3 [3]
Diarrhoea	1 [1]	2 [2]	3 [2]
Abdominal discomfort	1 [1]	1 [1]	2 [2]
Aspartate aminotransferase increased	1 [1]	1 [1]	2 [2]
Back pain	1 [1]	1 [1]	2 [2]
Constipation		2 [2]	2 [2]
Dermatitis contact	2 [2]		2 [2]
Muscle spasms	1 [1]	1 [1]	2 [2]
Neck pain		2 [2]	2 [2]
Skin abrasion	1 [1]	1 [1]	2 [2]
Skin laceration	2 [2]		2 [2]
Abdominal distension	1 [1]		1 [1]
Abdominal pain	1 [1]		1 [1]
Anxiety		1 [1]	1 [1]
Arthralgia		1 [1]	1 [1]
Contusion	1 [1]		1 [1]
Decreased appetite	1 [1]		1 [1]
Dry mouth		1 [1]	1 [1]
Dyspepsia	1 [1]		1 [1]
Early satiety		1 [1]	1 [1]
Fall	1 [1]		1 [1]
Fatigue		1 [1]	1 [1]
Folliculitis		1 [1]	1 [1]
Joint swelling		1 [1]	1 [1]
Musculoskeletal pain	1 [1]		1 [1]
Myalgia	1 [1]		1 [1]
Nausea		1 [1]	1 [1]
Non-cardiac chest pain	1 [1]		1 [1]
Pain in jaw	1 [1]		1 [1]
Presyncope		1 [1]	1 [1]
Rash maculo-papular	1 [1]		1 [1]
Rash papular		1 [1]	1 [1]
Rhinitis	1 [1]		1 [1]
Seasonal allergy	1 [1]		1 [1]
Tooth fracture	1 [1]		1 [1]

MedDRA preferred term	Number of adverse events* [number of participants with adverse events] 160 mg selpercatinib (2 x 80 mg capsules) (N=216)	160 mg selpercatinib (1 x 160 mg tablet) (N=212)	Overall (N=224)
Tooth injury	1 [1]		1 [1]
Vertigo positional		1 [1]	1 [1]
Vessel puncture site injury	1 [1]		1 [1]
Vomiting	1 [1]		1 [1]

* Adverse events with a change in severity are only counted one time at the highest severity

Abbreviations: N = number of participants studied.

Study JZPA

Table 12: Summary of Adverse events in Study JZPA

	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.

Table 13: Summary of Treatment-Emergent Adverse Events in Study JZPA

Treatment	All causalities: Number of participants [%] with adverse events	All causalities: Number of adverse events and severity*		Related to study treatment: Number of participants [%] with adverse events	Related to study treatment: Number of adverse events and severity*	
160 mg selpercatinib fasted (N=45)	32 [71.1%]	Mild	104	18 [40.0%]	Mild	48
		Moderate	1		Moderate	0
		Severe	0		Severe	0
		Total	105		Total	48
160 mg selpercatinib fed (N=45)	27 [60.0%]	Mild	85	11 [24.4%]	Mild	23
		Moderate	1		Moderate	0
		Severe	0		Severe	0
		Total	86		Total	23
Overall (N=46)	38 [82.6%]	Mild	189	23 [50.0%]	Mild	71
		Moderate	2		Moderate	0
		Severe	0		Severe	0
		Total	191		Total	71

Abbreviations: N = number of participants
* Only the maximum severity of each adverse event is reported

Table 14: Summary of treatment-Emergent Adverse Events (All Causalities) by treatment in order of frequency in Study JZPA

MedDRA preferred term	Number of adverse events* [number of participants with adverse events] 160 mg selpercatinib fasted (N=45)	160 mg selpercatinib fed (N=45)	Overall (N=46)
Catheter site erythema	12 [12]	14 [13]	26 [20]
Diarrhoea	11 [7]	13 [5]	24 [11]
Catheter site pain	12 [9]	8 [6]	20 [14]
Faeces soft	8 [2]	7 [1]	15 [2]
Catheter site bruise	7 [7]	4 [4]	11 [10]
Catheter site swelling	7 [3]	3 [3]	10 [6]
Headache	7 [6]	1 [1]	8 [7]
Fatigue	4 [4]	3 [3]	7 [6]
Vessel puncture site bruise	3 [3]	3 [3]	6 [5]
Abdominal distension	1 [1]	2 [2]	3 [3]
Lip dry	1 [1]	2 [2]	3 [3]
Erythema		3 [2]	3 [2]
Vomiting	3 [1]		3 [1]
Alopecia	2 [2]		2 [2]
Application site discolouration		2 [2]	2 [2]
Application site erythema	2 [2]		2 [2]
Constipation	1 [1]	1 [1]	2 [2]
Dry mouth	1 [1]	1 [1]	2 [2]
Flatulence	1 [1]	1 [1]	2 [2]
Somnolence	1 [1]	1 [1]	2 [2]
Vessel puncture site pain	1 [1]	1 [1]	2 [2]
Vessel puncture site swelling	1 [1]	1 [1]	2 [2]
Catheter site injury	2 [1]		2 [1]
Hiccups	2 [1]		2 [1]
Pruritus		2 [1]	2 [1]
Abdominal pain	1 [1]		1 [1]
Application site bruise		1 [1]	1 [1]
Back pain	1 [1]		1 [1]
Blood pressure increased		1 [1]	1 [1]
Catheter site discolouration	1 [1]		1 [1]
Catheter site haematoma	1 [1]		1 [1]
Catheter site rash	1 [1]		1 [1]
Chest discomfort	1 [1]		1 [1]
Cold sweat	1 [1]		1 [1]
Dehydration	1 [1]		1 [1]
Dizziness	1 [1]		1 [1]
Dry eye	1 [1]		1 [1]
Dry skin	1 [1]		1 [1]
Dry throat		1 [1]	1 [1]
Dysmenorrhoea		1 [1]	1 [1]
Faeces discoloured		1 [1]	1 [1]
Feeling hot		1 [1]	1 [1]
Insomnia		1 [1]	1 [1]
Nausea	1 [1]		1 [1]
Ophthalmic herpes simplex	1 [1]		1 [1]
Palpitations	1 [1]		1 [1]
Peripheral swelling	1 [1]		1 [1]
Pyrexia		1 [1]	1 [1]
Rash		1 [1]	1 [1]
Skin warm		1 [1]	1 [1]
Sleep disorder		1 [1]	1 [1]
Urge incontinence		1 [1]	1 [1]
Vessel puncture site erythema		1 [1]	1 [1]

2.6.4.3. Serious adverse event/deaths/other significant events

Study JZJZ

No events of death were reported in this study.

No SAEs were reported in this study.

Adverse Events of Special Interest

Five participants experienced TEAEs of special interest (liver function test abnormalities). There were no other AEs of special interest, that is, hypersensitivity, thrombocytopenia, or hypertension, reported in this study.

Study JZPA

No events of death were reported in this study.

No SAEs occurred during the study.

Adverse Events of Special Interest

One participant had an increase in blood pressure that was reported as a TEAE on Day 8, approximately 7 days after dosing with selpercatinib in the fed state. The event was mild in severity, considered as not related to study intervention by the investigator, and resolved after approximately 13 days.

There were no other AESIs, reported in this study.

Discontinuation due to adverse events

Study JZJZ

Participant discontinuations

A total of 196 participants completed the study. Twenty-eight participants discontinued the study, as follows:

- 13 participants discontinued from the study due to TEAEs
- 11 participants withdrew consent and discontinued from the study
- Two participants were withdrawn due to physician decision and 2 participants were lost to follow-up.

Study JZPA

There were no discontinuations from the study due to AE. Two participants discontinued the study due to personal issue and due to physician decision.

2.6.4.4. Laboratory findings

Clinical Laboratory Evaluation

Study JZJZ

Eight participants experienced clinically significant changes in clinical laboratory parameters that were subsequently reported as TEAEs:

- Two aspartate aminotransferase increased, considered to be not related to study treatment by the investigator, and resolved after approximately 3 weeks.
- Four blood creatine phosphokinase increased considered to be not related to study treatment by the investigator, and resolved after 3 weeks.
- Four Alanine aminotransferase increased. The TEAE was mild in severity, considered to be not related to study treatment by the investigator.

Study JZPA

There were no clinically meaningful changes in laboratory values during the study and were similar following dosing with selpercatinib in either the fasted or fed state. None of the increases for individual participants were reported as AEs or considered to be clinically significant.

Transient and small increases in mean liver function parameter values, ALT, ALP, AST, and bilirubin, were observed over the course of the study.

Other Safety Evaluations

Study JZJZ

The analyses detected no clinically meaningful findings in the vital sign measurements, ECGs, or other observations related to safety in this study. The assessments and observations were comparable across intervention groups.

Study JZJA

The analyses detected no clinically meaningful findings in the vital sign measurements, or other observations related to safety in this study. The assessments and observations were comparable across intervention groups.

2.6.5. Discussion on clinical safety

Safety data are limited in this submission, since both studies were PK studies, bioequivalence Study **JZJZ and** food effect study **JZPA**, in which single doses were administered. The safety assessment was targeted to ensure that the observed safety profile was consistent with the known safety profile of selpercatinib. Noting that the known safety profile of Retsevmo is mainly characterised in patients with various type of RET altered cancers while the provided data are in healthy volunteers.

The main TEAEs reported were headache or related to gastrointestinal toxicity and were mild in majority. There were no SAEs, nor deaths in either study. AESIs of mild liver enzymes increase occurred in study JZJZ and an AESI of hypertension considered not related to selpercatinib occurred in study JZPA.

Overall, data observed in both studies JZJZ and JZPA were consistent with the known safety profile of selpercatinib. The relevant sections of the SmPC (4.2, 4.3, 4.4 and 4.8) for tablets are consistent with those for capsules, which is considered acceptable.

Although an inclusion as ADR is not justified at this stage, cumulatively events of blood creatine phosphokinase increased reported with selpercatinib, will be provided in the next PSUR.

2.6.6. Conclusions on the clinical safety

Overall, no new safety concerns have been identified.

2.7. Risk Management Plan

The MAH submitted an updated RMP version 13.1.

2.7.1. Safety concerns

Table 15: Summary of Safety Concerns

• **Summary of Safety Concerns**	
• **Important identified risks**	• None
• **Important potential risks**	• Liver injury • Cardiac arrhythmia due to QT prolongation • Reproductive and developmental toxicities • Growth plate abnormalities in paediatric patients
• **Missing information**	• Exposure and safety in patients with severe hepatic impairment • Exposure and safety in patients with cardiac impairment

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Table 16: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Liver injury	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4. **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None
Cardiac arrhythmia due to QT prolongation	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4. **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None
Reproductive and developmental toxicity	**Routine risk minimisation measures:** SmPC Section 4.6 **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Pregnancy and Breastfeeding follow-up forms **Additional pharmacovigilance activities:** Study: None
Growth plate abnormalities in paediatric patients	**Routine risk minimisation measures:** SmPC Sections 4.2 and 5.3 **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Exposure and safety in patients with severe hepatic impairment	**Routine risk minimisation measures:** A clinical pharmacology study assessing the effect of hepatic impairment on the pharmacokinetics of selpercatinib is completed. SmPC is updated based on the safety and pharmacokinetic data. **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None
Exposure and safety in patients with cardiac impairment	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None

Abbreviation: SmPC = Summary of Product Characteristics.

2.7.4. Conclusion

Safety concerns, pharmacovigilance plan and risk minimization measures remain unchanged in this procedure. The CHMP considered that the risk management plan version 13.1 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The proposed text modifications to the package leaflet does not include text that is significantly different from previous user tested.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Retsevmo (Selpercatinib) is included in the

additional monitoring list as it is approved under a conditional marketing authorisation [REG Art 14-a].

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The purpose of this submission is to add two new strengths of 120 and 160 mg of selpercatinib and a new pharmaceutical form (film-coated tablets) associated with all strengths (40 mg, 80 mg, 120 mg and 160 mg).

Two PK studies have been conducted in support of this application:

-**Study J2G-MC-JZJZ (JZJZ)**, a bioequivalence (BE) study to evaluate bioequivalence of a single 160-mg dose of selpercatinib as film-coated tablet formulation compared with 2 × 80-mg commercial capsule formulation in healthy volunteers.

The primary objective was to evaluate the bioequivalence of a single 160-mg dose of selpercatinib as the film-coated tablet formulation (test) compared to the commercial capsule formulation (reference).

The secondary objective was to describe the safety and tolerability of a single 160-mg oral dose of selpercatinib as the film-coated tablet formulation (test) compared to the commercial capsule formulation (reference).

- Study J2G-MC-JZPA (JZPA), a food-effect study to assess the effect of food on the PK profile of selpercatinib (160 mg film-coated tablet single dose) after a high fat meal.

The primary objective was to assess the effect of food on the PK of selpercatinib after a high-fat meal in healthy participants.

The secondary objective was to assess the safety and tolerability of 160 mg film-coated tablet of selpercatinib. This application refers to a line extension with no change in approved indications.

3.2. Favourable effects

Bioequivalence was demonstrated with study **J2G-MC-JZJZ**, showing that the tablet formulation and capsule formulations perform similarly. Bioequivalence was established.

Results of the food effect study **(JZPA)** indicated that similar recommendation to the capsule with regards to food are supported (see SmPC 4.2).

3.3. Uncertainties and limitations about favourable effects

None.

3.4. Unfavourable effects

Although information is limited by the single dose and by the population (healthy volunteers vs cancer patients), TEAEs observed with selpercatinib tablet formulation in both studies JZJZ and JZPA were consistent with the known safety profile of selpercatinib.

The main TEAEs reported were headache or related to gastrointestinal toxicity and were mild in majority. There were no SAE, nor death in either study. AESIs of mild liver enzymes increase occurred in study JZJZ and an AESI of hypertension considered not related to selpercatinib occurred in study JZPA.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The benefits of the new strengths and the new formulation are acknowledged.

3.6.2. Balance of benefits and risks

As bioequivalence has been demonstrated, a positive B/R balance comparable to the reference strength can therefore be concluded.

3.7. Conclusions

The overall benefit/risk balance of Retsevmo is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Retsevmo is not similar to cabozantinib (Cometriq), sorafenib tosylate (Nexavar), Lutathera, Onivyde pegylated liposomal, Zejula, Pemazyre, Kimmtrak, Xermelo, Qarziba, Ayvakyt, Koselugo, Somakit, Qinlock, Crysvita, Tibsovo, Finlee, Spexotras, Zynyz, Vyloy, Elahere and Hetronifly within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

Outcome

Based on the CHMP review of data on quality, safety and pharmacokinetics, the CHMP considers by consensus that the benefit-risk balance of Retsevmo 40 mg, 80 mg, 120 mg and 160 mg, film-coated tablets is favourable in the following indications:

Retsevmo as monotherapy is indicated for the treatment of adults with:

- advanced *RET* fusion-positive non-small cell lung cancer (NSCLC) not previously treated with a *RET* inhibitor
- advanced *RET* fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted (see sections 4.4 and 5.1)

Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with:

- advanced *RET* fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate)
- advanced *RET*-mutant medullary thyroid cancer (MTC)

The CHMP therefore recommends the extension(s) of the marketing authorisation for Retsevmo subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive thyroid cancer, the MAH should submit the final data from the study LIBRETTO-121.	30 June 2025
In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with systemic treatment naïve RET fusion-positive thyroid cancer, the MAH should submit the final data from the cohort 2 of the pivotal study LIBRETTO-001.	31 December 2025
In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive solid tumours other than NSCLC and thyroid cancer, the MAH should submit the final data from patients with RET-fusion positive solid tumours other than NSCLC and thyroid cancer enrolled in the pivotal study LIBRETTO-001.	31 December 2025